Guideline 12-9 REQUIRES UPDATING

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Treatment of Acute Myeloid Leukemia (AML)

Members of the Acute Leukemia Advisory Committee

Guideline 12-9 was reviewed in February 2019 and the Acute Leukemia Advisory Committee determined that it REQUIRES UPDATING.
(See Section 6: Document Assessment and Review for details)

Guideline 12-9 is comprised of 6 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/28266

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original version February 2016	2006 to Aug 2015	Full Report	Web publication	NA
Current Version February 2019	2015 to Mar 2018	New data found in Section 6: Document Assessment and Review	Updated web publication	2016 recommendations REQUIRE UPDATING

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

6MP, 6-mercaptopurine (mercaptopurine)
ACR, aclarubicin
ADE, AraC + DNR + etoposide
A-HAM, ATRA + HAM = all-trans retinoic acid + high-dose cytarabine + mitoxantrone
A-ICE, ATRA + ICE
AML, acute myeloid (myelogenous) leukemia
ANLL, acute non-lymphoid leukemia
AMSA, amsacrine
AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside
ATRA, all-trans retinoic acid
AZA, azacitidine
BHAC, N^4-behenoyl-1-ß-D-arabinosylcytosine
CBF, core-binding factor
CI, continuous iv infusion
CN-AML, cytogenetically normal AML
COAP, cyclophosphamide, vincristine, AraC, prednisone
CPX-351, a liposomal formulation of cytarabine and daunorubicin (5:1 molar ratio)
CR, complete remission (complete response)
CRi, complete remission with incomplete recovery
CRp, complete remission without full platelet recovery
CsA, cyclosporin A (cyclosporine)
DA, DNR + AraC
DAT, DNR +AraC + 6-thioguanine (TG)
DClo, DNR + clofarabine
DFS, disease-free survival
DNR, daunorubicin
DNX, DaunoXome, a liposomal formulation of daunorubicin
EFS, event-free survival
ELN, European LeukemiaNet
EMA, etoposide + MTZ + AraC
FAI, fludarabine + AraC + IDA
FLAG, fludarabine + high dose AraC + GCSF
FLAI, fludarabine + AraC + IDA
FLAM, flavopiridol + AraC + MTZ
GCSF, granulocyte-colony stimulating factor
GM-CSF, granulocyte-macrophage colony-stimulating factor
GO, gemtuzumab ozogamicin
HAA, homoharringtonine + AraC + ACR
HAD, homoharringtonine + AraC + DNR
HAM, high-dose cytarabine + mitoxantrone
HCT, hematopoietic cell transplantation
HDAC, high-dose cytarabine
HR, hazard ratio
HSCT, hematopoietic blood stem cell transplantation

ICE, idarubicin + cytarabine + etoposide
IDA, idarubicin
IEiv, IDA + etoposide, iv
IEpo, IDA + etoposide, orally
IFN, interferon
IL-2, interleukin-2
ITT, intention to treat
iv, intravenously
KRN, KRN8602 (3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin hydrochloride)
LFS, leukemia-free survival
MAC, MTZ + AraC
MACE, amsacrine + AraC +etoposide
MAE, MTZ + AraC + etoposide
MICE, MTZ + AraC + etoposide
MDS, myelodysplastic syndromes
MidAC, MTZ + AraC
MTZ, mitoxantrone
NR, not reported
ns, not significant (not statistically significant)
OR, odds ratio
OS, overall survival
po, oral administration (per os)
PR, partial response/remission
RAEB-t, refractory anemia with excess of blasts in transformation
RD, remission duration
RFI, relapse-free interval (after induction)
RFS, recurrence-free survival
s-AML, secondary AML arising from MDS or myeloproliferative disease
S-HAM, sequential HAM: 2nd course after three days, i.e., HDAC (d 1+2, 8,9) + MTZ (d 3, 4, 10, 11)
SAE, severe adverse effect
sc, subcutaneously
SCT, stem cell transplant
std, standard
t-AML, therapy-related AML following treatment of primary malignant disease
TAD, thioguanine + cytarabine + daunorubicin
TG, 6-thioguanine
TTF, time to treatment failure
VPA, valproic acid
TRM, treatment-related mortality
TSC, timed-sequential chemotherapy
VCR, vincristine
WBC, white blood cell

LIST OF FIGURES

LIST OF TABLES

Systemic Treatment of Acute Myeloid Leukemia (AML)

Section 1: Recommendations Summary

The 2016 recommendations

REQUIRE UPDATING

This means that the guidance document needs updating to ensure that the recommendations reflect current evidence and practice. The existing recommendations remain relevant and it is still appropriate for this document to be available while the updating process unfolds.

GUIDELINE OBJECTIVES

The primary objective was to make recommendations regarding the most effective intensive systemic treatment of acute myeloid leukemia (AML) in adult patients. A secondary objective was to make recommendations regarding use of patient characteristics to determine appropriate treatment.

TARGET POPULATION

The target population is adult patients with AML (excluding acute promyelocytic leukemia) who are deemed suitable for intensive treatment.

INTENDED USERS

The intended users are hematologists, oncologists, nurses, and pharmacists.

RESEARCH QUESTIONS

1. What is the most effective systemic induction treatment for adults with previously untreated AML who can tolerate intensive treatment?

2. What is the most effective systemic post-remission treatment (consolidation and/or maintenance, excluding stem cell transplant) for adults with previously untreated AML?

3. What is the most effective systemic treatment (reinduction, consolidation, maintenance; not including stem cell transplant) for adults with relapsed or refractory AML who can tolerate intensive treatment?

4. Which patient characteristics are most important when making treatment decisions?

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Preamble

After reviewing the literature to arrive at these recommendations there are two important background issues that will affect their implementation:

1. Fitness or frailty is a key determinant in assessing whether a patient should be offered induction chemotherapy with curative intent because of the potential toxicity of this approach. The selection criteria for entry into most of the studies mentioned do not explicitly address this issue other than age and performance status. In studies specifying young or elderly patients, the cut-off is often 60 years of age, but 50 to 65 years have been used in some trials. It is becoming clear that age alone is not an accurate way of determining treatment tolerability and other tools are emerging that may refine the evaluation of this important factor. These types of studies are either in progress or in design and will hopefully better define the target population for these recommendations (1).

2. Due to the complex nature of treatment of AML and the heterogeneous way in which it is treated in different countries, these recommendations must be considered in the broader context of the jurisdiction in which the treatments were administered. For example, comparing the outcomes of different induction regimens may depend on when bone marrow evaluations were performed to confirm treatment response, and the number of induction courses that are considered standard (one versus two). Dosing of agents may also be influenced by the other agents used in the regimen. Similarly, the outcomes of consolidation regimens may be influenced by the preceding induction regimen, which is not uniform.

Question 1. Induction for Previously Untreated AML

Recommendation 1

• Cytarabine (cytosine arabinoside, AraC) plus an anthracycline (or anthracenedione) is recommended as standard induction treatment for AML.
  • Conventional-dose AraC at 100-200 mg/m^2/day for seven days is recommended for routine use
  • High-dose AraC (HDAC) (1-3 g/m^2/day) may be considered in younger patients and those with poor-risk factors*.
  • Idarubicin (IDA), daunorubicin (DNR), and mitoxantrone (MTZ), are the recommended anthracyclines (anthracenediones) for use with AraC.
  • The recommended dose for DNR is 60 mg/m^2/day.
  • It is recommended that IDA or DNR be administered for three days. Various regimens with MTZ have been used and are considered acceptable.
 	
*See Preamble above for age considerations and Background (Section 2) for a summary of the European LeukemiaNet subgroups (2)

Recommendation 2
Addition of gemtuzumab ozogamicin (GO) at 3 mg/m^2 to 7+3 regimens is recommended.

Qualifying Statements for Recommendation 2

- Increase in veno-occlusive disease (more recently designated sinusoidal obstructive syndrome [SOS]) has been reported with GO at 6 mg/m^2 (3,4). This was not evident

with doses at 3 mg/m^2. The risk of SOS needs to be weighed against the benefit of receiving GO in patients who are destined to receive an allogeneic cell transplant.
- While the ALFA-0701 trial (5) suggested greater benefit in patients with cytogenetically normal or with favourable/intermediate genetics, there was insufficient evidence to restrict the recommendation based on cytogenetics or other defined subgroups.
- While evidence indicates GO may improve OS and RFS, it is currently not approved for use in Canada.

Recommendation 3
The purine analogues cladribine, fludarabine, and clofarabine cannot be recommended for routine use at this time. There may be a role in relapsed/refractory AML (see Question 3).

Qualifying Statements for Recommendation 3

- Some fludarabine regimens have been found effective but not directly compared with the same regimens without fludarabine, nor to standard 3+7 treatment. The MRC AML15 trial (6,7) and Russo et al (8,9) found benefit of FLAG-IDA (fludarabine + AraC + granulocyte colony-stimulating factor [GCSF] + IDA) and FLAI (fludarabine + AraC + IDA), respectively. The fludarabine arms contained high-dose AraC and the control arms used standard-dose AraC. The relative effect of AraC dose and fludarabine in these trials is unknown.
- FLAG is among the regimens recommended by (10) for relapsed/refractory AML based on non-randomized trials. A small Chinese study of induction (11) found FLAG (fludarabine + AraC + GCSF) and IDA + AraC to result in similar complete remission (CR). While evidence from the literature review is considered insufficient to make a recommendation, FLAG may be an option in cases where an anthracycline is contraindicated.

Recommendation 4
• Addition of etoposide to AraC plus DNR induction is not recommended.

Recommendation 5
• Induction chemotherapy adjuvants such as GCSF or granulocyte-macrophage (GM)-CSF, interleukin-11, or multidrug resistance modulators such as cyclosporine A, PSC-833 (valspodar), and zosuquidar are not recommended.

Question 2. Post-Remission Treatment

It is considered standard practice to give consolidation treatment to patients who achieve CR after induction treatment. Transplantation was outside the scope of the review and other guidelines should be consulted concerning appropriate selection of patients for transplant. All patients that may be transplant candidates should receive early referral to a transplant centre. While transplant may take place immediately after induction (without any

consolidation), due to delays prior to transplant, most patients scheduled for transplant will receive consolidation treatment.

Recommendation 6
Two or three courses of consolidation are recommended.

Qualifying Statements for Recommendation 6

- Regimens for consolidation may be the same as used for induction and the distinction between these two phases of treatment is sometimes somewhat arbitrary. The total number of courses of induction plus consolidation combined may be the most important consideration.

Recommendation 7
• For patients with core-binding factor (CBF)-AML receiving consolidation with AraC alone, HDAC at 1-3 g/m^2/day is recommended. HDAC may be considered for other patients. • Patients with CBF-AML should receive three cycles of consolidation, of which at least two contain HDAC.

Qualifying Statements for Recommendation 7

- HDAC at 1-3 g/m^2/day is considered appropriate; however, there is insufficient evidence to recommend an optimal dose within this range.
- The benefit of HDAC is greatest for CBF-AML. The relative benefit of HDAC compared with adverse effects is less clear for other subtypes of AML.

Recommendation 8
• HDAC or standard-dose AraC may be used in combination chemotherapy. Standard-dose combination chemotherapy should be considered for patients determined to be unsuitable for HDAC consolidation.

Qualifying Statements for Recommendation 8

- Effectiveness may be influenced by age and/or prior treatment.
- There is insufficient evidence to recommend an optimal dose of HDAC.
- The benefit of adding anthracycline to HDAC is unclear.

Recommendation 9
• There is insufficient evidence to make any recommendations for or against the use of maintenance chemotherapy in patients who received consolidation therapy. • Use of maintenance treatment alone is not routine, but may be considered for those unable to tolerate consolidation.

Qualifying Statements for Recommendation 9

- We did not consider there to be sufficient evidence to make a recommendation at this time. Based on past experience there is no evidence maintenance therapy after consolidation is useful as it currently exists; however, there are ongoing studies examining this issue (see Table 4-17). Ongoing trials with new drugs with different mechanisms of action and targeted therapy may find a benefit.

Question 3. Relapsed or Refractory AML

While the intent in the treatment of relapsed or refractory AML is to allow subsequent transplant for responding patients, the decisions regarding transplant eligibility and procedures are beyond the scope of this document. The Program in Evidence-Based Care/Cancer Care Ontario report on Stem Cell Transplant (12) and recent provincial guidelines should be consulted. All patients that may be transplant candidates should receive early referral to a transplant centre.

Recommendation 10

• For patients with refractory disease or relapse, a more intensive or non-cross-resistant treatment is recommended. The following list is not meant to be inclusive of all reasonable therapies, but highlights a few with good response in the included randomized controlled trials (RCTs):
  • HDAC + MTZ
  • AraC (500 mg/m^2/day continuous infusion)* + MTZ + etoposide ± GM-CSF
  • AraC (100 mg/m^2 q12h) + DNR + etoposide
  • Low-dose CAG: AraC (10 mg/m^2 q12h) + ACR + GCSF ± etoposide
*See qualifying statement regarding dose

• Clofarabine, fludarabine (FLAG, FLAG-IDA), and cladribine regimens should be considered when alternative or additional agents are required.

Qualifying Statements for Recommendation 10

- There is no clear consensus about the length of CR duration that indicates re-treatment with the same induction chemotherapy would be as effective as an alternate regime. The National Comprehensive Cancer Network (NCCN) suggests CR duration of >12 months (10), while others use two to five years, or never. It has been suggested that AML recurring after a long CR may actually be new disease. With more detailed characterization of the genetic architecture of AML this distinction may become more evident in the near future. Re-treating with an ineffective regimen delays effective treatment while increasing risk of adverse events and treatment-related mortality.

- FLAG is among the regimens recommended by the NCCN (10) for relapsed/refractory AML based on non-randomized trials (13). While evidence from the literature review is considered insufficient to make a recommendation, FLAG may be an option in cases where an anthracycline is contraindicated.
- AraC at 1 g/m^2/day or 1.5 g/m^2/day has also been widely used (e.g., (14-16)) but not directly compared. Several trials, both randomized and retrospective, report a large variation in response rates (17-22).
- A small case-series reported experience using high-dose etoposide and cyclophosphamide with modest benefit (23), although evidence appears weak.

Question 4. Which patient characteristics are most important when making treatment decisions?

During the planning stages of the systematic review it was decided to focus on RCTs, while acknowledging that RCTs might not provide the best source of evidence on patient characteristics. Some treatments were found to be of benefit in only a subset of patients (age, cytogenetic risk or subtype); however, the trials were usually not powered to detect differences in subgroups. The RCTs were not designed to directly determine which of these factors should guide treatment. The accompanying literature review, while commenting on some characteristics related to treatment, was not sufficient to address this question and no recommendations are being made. Several guidelines on treatment of AML have included sections on patient factors including age, comorbidities, cytogenetic abnormalities and associated risk category, and response to previous treatment. The most recent are the NNCN guideline (10), the Canadian consensus guideline for older patients (24), and the European Society for Medical Oncology (ESMO) guideline for diagnosis, treatment, and follow-up (25). Older but comprehensive management guidelines from Britain (26), Italy (27), and the European LeukemiaNet (2) are also relevant. The reader is referred to these documents for further details. Some of this information may arise from studies that are currently ongoing.

Systemic Treatment of Acute Myeloid Leukemia (AML)

Section 2: Guideline – Recommendations and Key Evidence

The 2016 recommendations

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BACKGROUND

Intensive systemic treatment of AML toward a potential cure requires accurate diagnosis and prognostication using cytogenetic and molecular markers as described in recent guidelines from the National Comprehensive Cancer Network (NCCN) (10), the European Society for Medical Oncology (ESMO) (25), the European LeukemiaNet (2), Britain (26), Italy

(27), and Canada (24). The American Society of Hematology and the College of American Pathologists are jointly preparing a guideline for the initial work-up of acute leukemia (http://www.hematology.org/Clinicians/Guidelines-Quality/4340.aspx).

AML is a disease with an extremely poor prognosis, and generally leading to death within a few months. Intensive treatments are required to induce complete remission (CR) but are very toxic and are associated with relatively high early mortality rates, especially in elderly patients with poor performance status or comorbidities. Patients who are considered unable to tolerate intensive treatment may be offered supportive care or low-intensity therapy; these are outside the scope of the current guideline. Even patients with good response to induction will relapse within a few months (early relapse) or a few years. To increase survival, through decreasing relapse, induction (if resulting in CR) may be followed by stem cell transplant (allogeneic if there is a suitable donor) or further chemotherapy (consolidation ± maintenance). Issues regarding transplant are also outside the scope of the current guideline and other guidelines or reviews should be consulted (10,12,24,28,29). All patients that may be transplant candidates should receive early referral to a transplant centre.

As with other cancers, AML is a heterogeneous disease with prognosis and response to treatment influenced by the genetic changes involved. AML is divided into three to four risk groups, based on cytogenetic findings, with corresponding rates of obtaining a complete remission (<5% blasts in the bone marrow) and duration of disease-free survival (DFS) and overall survival (OS). One of the more recent classifications is by the European LeukemiaNet (2)[1]. APL has a different prognosis and treatment than other subtypes and is excluded from recent randomized controlled trials (RCTs) evaluating AML treatments. As such, it is also not covered in this guideline; the reader may consult the NCCN AML guideline (10) or others specifically on APL (30-33). Due to the high rate of serious adverse events (including death) of intensive therapy, the relative benefit of therapy versus risk has to be considered. As discussed in the literature review (see Section 3), some chemotherapy regimens may also work better for specific subtypes of AML. Most trials were neither designed nor powered to distinguish treatment effectiveness for specific molecular subgroups, although retrospective analysis suggests some differences that may be explored in further trials. Core-binding factor (CBF)-AML is an example of a subtype with favourable prognosis with certain chemotherapeutic regimens (34-36).

We acknowledge there are ongoing studies investigating targeted agents such as the kinase inhibitors sorafenib and midostaurin with preliminary results that are not included in the current recommendations. These and other agents currently being studied may have a role in the future.

As alluded to above, the genetic subtype or profile of AML is very important and complex diagnostic techniques may be required. Due to the acute nature of the disease, treatment is often started prior to obtaining all prognostic information. Patient monitoring and management during treatment is crucial. Patients are often exhibiting hematological

[1] **Favourable** [t(8;21)(q22;q22); RUNX1-RUNX1T1; inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11; mutated NPM1 without FLT3-ITD (normal karyotype); mutated CEBPA (normal karyotype], **Intermediate-I** [all AML with normal karyotype except those in the favourable group: mutated NPM1 and FLT3-ITD (normal karyotype); wild-type NPM1 and FLT3-ITD (normal karyotype); wild-type NPM1 without FLT3-ITD (normal karyotype)], **Intermediate-II** [t(9;11)(p22;q23); MLLT3-MLL; other cytogenetic abnormalities not classified as favourable or adverse], or **Adverse** [inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1; t(6;9)(p23;q34); DEK-NUP214; t(v;11)(v;q23); MLL rearranged; -5 or del(5q); -7; abnl(17p); complex karyotype].

effects prior to treatment, and most treatments will have hematological and other toxicities. Infections are a major cause of early mortality. Improvement in management of infection and other aspects of supportive care probably accounts for the lower treatment-related mortality and better survival in more recent studies, even when comparing the same chemotherapy regimens (37,38). Treatment at specialized centres with appropriate physical facilities including infection control, and with highly-trained teams including hematologists and hematopathologists with specialization in AML is essential. Due in part to the above factors, results of clinical trials by different centres and in different time periods may be difficult to compare.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Preamble

After reviewing the literature to arrive at these recommendations there are two important background issues that will affect their implementation:

1. Fitness or frailty is a key determinant in assessing whether a patient should be offered induction chemotherapy with curative intent because of the potential toxicity of this approach. The selection criteria for entry into most of the studies mentioned do not explicitly address this issue other than age and performance status. In studies specifying young or elderly patients, the cut-off is often 60 years of age, but 50 to 65 years have been used in some trials. It is becoming clear that age alone is not an accurate way of determining treatment tolerability and other tools are emerging that may refine the evaluation of this important factor. These types of studies are either in progress or in design and will hopefully better define the target population for these recommendations (1).

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Question 1. Induction for Previously Untreated AML

Recommendation 1

- Cytarabine (cytosine arabinoside, AraC) plus an anthracycline (or anthracenedione) is recommended as standard induction treatment for AML.
  - Conventional-dose AraC at 100-200 mg/m^2/day for seven days is recommended for routine use
  - High-dose AraC (HDAC) (1-3 g/m^2/day) may be considered in younger patients and those with poor-risk factors*.
  - Idarubicin (IDA), daunorubicin (DNR), and mitoxantrone (MTZ), are the recommended anthracyclines (anthracenediones) for use with AraC.
    - The recommended dose for DNR is 60 mg/m^2/day.
    - It is recommended that IDA or DNR be administered for three days. Various regimens with MTZ have been used and are considered acceptable.

*See Preamble above for age considerations and Background for a summary of the European LeukemiaNet subgroups (2)

Key Evidence for Recommendation 1

- Standard treatment for AML in most countries is a 7+3 regimen, consisting of AraC at 100-200 mg/m^2/day for seven days plus an anthracycline for three days and this is reflected in other guidelines (2,10,24,26,27,39). While studies summarized in the literature review (see Table 4-1) used conventional-dose AraC at 100-400 mg/m^2/day, there was insufficient evidence to specify the optimal dose of AraC within this range and therefore no change in practice is suggested.
- Most trials in this systematic review used an anthracycline for three days, either days 1, 3, and 5 (British and European Organisation for Research and Treatment of Cancer [EORTC] trials), days 3 to 5 (German trials), or days 1 to 3 (most others).

- EORTC/GIMEMA AML-12 (40) is the largest and most recent trial studying HDAC. It found improved CR (78.7% versus 72.0%, p<0.01) with HDAC (3 g/m^2 every 12 h [q12h]) compared with standard-dose AraC (100 mg/m^2/day) in patients age 15 to 60 years receiving DNR + etoposide. OS was also improved (six-year OS 42.5% versus 38.7%, p=0.06, p=0.009 adjusted by multivariate analysis), with similar trends for DFS (overall, 44.7% versus 41.6%, p=0.27, adjusted p=0.08; DFS age <46 years 52.8% versus 46.4%, p=0.07, adjusted p=0.02) and event-free survival (EFS, 43.6% versus 35.1%, p=0.003 for age <46 years). There was no difference in survival for patients age >46 years (DFS 35.5% versus 35.8%, p=0.73; EFS 26.6% versus 24.8%, p=0.44). Patients with secondary AML, very-bad-risk cytogenetic abnormalities, and/or FLT3-ITD (internal tandem duplication) mutation benefited with HDAC. There was no difference in induction deaths or non-hematologic toxicities (except conjunctivitis). Older trials found increased adverse events with HDAC, especially in older patients. More recent trials found neither benefit nor increased risk in elderly patients.

- ECOG E1900 (41-43) and Lee et al (44) compared DNR at 90 mg/m^2/day and 45 mg/m^2/day in patients age ≤60 years, while the HOVON 43 (45,46) made this comparison in patients age >60 years. These RCTs found the higher dose improved response rate (70.6% versus 57.3%, p<0.001; 82.5% versus 72.0%, p=0.014; 54% versus 54%, p=0.002) and survival (median 23.7 m versus 15.7 months, p=0.001; five-year OS 46.8% versus 34.6%, p=0.030; two-year OS 31% versus 26%, p=0.16 but p=0.001 for age

60-65 subgroup).

- National Cancer Research Institute (NCRI) AML17 (47) found no benefit in using DNR at 90 mg/m^2/day compared with 60 mg/m^2/day as there were no difference in CR (73% versus 75%), two-year OS (59% versus 60%), or two-year recurrence-free survival (RFS) (51% versus 48%). Furthermore, the trial was closed early due to higher 60-day mortality with 90 mg/m^2/day DNR (10% versus 5%, p=0.001). The study was initially powered to detect differences in five-year DFS and these data are not yet available.

- DNR is the most studied and commonly used anthracycline for AML induction.
- A recent mixed-treatment comparison meta-analysis (48) including both direct and indirect effects found higher CR and OS with IDA compared with conventional-dose DNR (defined as cumulative dose of 90-180 mg/m^2 per cycle), but no significant difference between IDA and high-dose DNR (based on only two trials).
- A meta-analysis performed as part of this systematic review found that IDA compared with DNR resulted in higher rates of CR (odds ratio [OR]=0.80, 95% confidence interval 0.70-0.93, p=0.003), with IDA better compared with either standard or high-dose DNR. IDA was also found to result in better OS (hazard ratio [HR]=0.91, confidence interval 0.84-0.98, p=0.009), although the difference in the subset of studies using higher-dose DNR was not significant (HR=0.92, confidence interval 0.82-1.05, p=0.14). The EORTC/GIMEMA AML-10 trial (49) used AraC + etoposide in both arms; with this combination there was no difference in CR between IDA and DNR (66.9% versus 68.7%, p=0.49). Reports of differences in adverse events between IDA and DNR are inconsistent. Three trials (GIMEMA (50), JALSG AML201 (51), and Rubio Borja (52)) found higher rates of early deaths with IDA (38% versus 22%, 4.7% versus 2.1%, and 30% versus 20%), while ALFA-9803 (9% versus 10%) (53) and EORTC/GIMEMA AML-10 (3.3% versus 3.2%) (49), which was the largest trial, did not.
- Meta-analysis of studies comparing MTZ and DNR (mostly 45 mg/m^2/day) found better CR with MTZ (OR=0.72, p=0.002 for studies without confounding agents). No significant differences in survival were reported and there were no consistent differences in adverse events. There were no studies comparing MTZ with doses of DNR >50 mg/m^2/day.
- Results of a small number of trials suggest that aclarubicin (ACR) may be an alternative to DNR. The Danish Society of Hematology Study Group on AML (54,55) reported a higher CR rate with ACR + AraC compared with DNR + AraC (DA) in patients up to age 60 years (CR 66% versus 50%, p=0.043), with similar rates of survival (four-year OS 29% versus 20%, p=0.26, ten-year OS 24% versus 16%, p not significant [ns]). Jin et al (56) found both HAA (homoharringtonine + AraC + ACR) and HAD (homoharringtonine + AraC+ DNR) superior to DA, with stronger benefit for HAA (CR 73% HAA, 67% HAD, 61% DA; p=0.011 HAA versus DA, p=0.20 HAD versus DA, p=0.22 HAA versus HAD; for three-year EFS and three-year RFS HAA and HAD were better than DA alone). ACR and DNR were not directly compared.

Interpretation of Evidence for Recommendation 1

- The Working Group concluded there was no evidence to suggest that other treatments were better than standard treatment with AraC plus an anthracycline, and that the beneficial and adverse effects of DNR, IDA, and MTZ were comparable; any of these is an acceptable choice.
- The Working Group acknowledged that HDAC may have a role for specific subgroups of

patients but carries a risk of increased toxicity and should not be used routinely. Adverse events are more frequent at higher doses, and HDAC at 6 g/m^2/day was considered too toxic to include in the recommendation.

- Direct comparison of DNR at 60 mg/m^2/day and 45 mg/m^2/day is limited, however indirect comparison (see Key Evidence) of other doses suggests 60 mg/m^2/day is better. While both 45 mg/m^2/day and 60 mg/m^2/day were used many of the trials, the authors consider 45 mg/m^2/day to be too low and patients would be undertreated.
- The data suggest outcomes with MTZ and IDA are better than DNR at 45 mg/m^2/day. IDA resulted in better CR but not OS compared with DNR at 60 mg/m^2. MTZ was not compared with DNR at higher doses, and the doses tested are now considered sub-optimal. While there was not complete consensus, overall the authors believed the evidence was not sufficient to recommend either IDA or MTZ over DNR at the recommended DNR dose of 60 mg/m^2/day and all are acceptable. There may be differences in cost and eligibility criteria for clinical trials that would influence the selection for specific patients.
- There is evidence for use of ACR; however, the Working Group considered it insufficient to make a recommendation at this time.

Recommendation 2

Addition of gemtuzumab ozogamicin (GO) at 3 mg/m^2 to 7+3 regimens is recommended.

Qualifying Statements for Recommendation 2

- Increase in veno-occlusive disease (more recently designated sinusoidal obstructive syndrome [SOS]) has been reported with GO at 6 mg/m^2 (3,4). This was not evident with doses at 3 mg/m^2. The risk of SOS needs to be weighed against the benefit of receiving GO in patients who are destined to receive an allogeneic cell transplant.
- While the ALFA-0701 trial (5) suggested greater benefit in patients with cytogenetically normal or with favourable/intermediate genetics, there was insufficient evidence to restrict the recommendation based on cytogenetics or other defined subgroups.
- While evidence indicates GO may improve OS and RFS, it is currently not approved for use in Canada.

Key Evidence for Recommendation 2

- Meta-analysis found that survival benefit was significant for patients with favourable and intermediate cytogenetics (five-year OS 77.5% versus 55.0%, p=0.0006 and 40.7% versus 35.5%, p=0.005, respectively) and unclear for adverse cytogenetics (six-year OS 9.1% versus 7.9%, p=0.9) (57).
- Meta-analysis indicated that GO did not influence CR (see (57) and Systematic Review Figure 4-7).
- Published meta-analyses based on data from the Medical Research Council (MRC) AML15 and NCRI AML16 trials found GO at 3 mg/m^2 on day 1 resulted in improved OS and RFS (57-59). The ALFA-0701 trial administered GO at 3 mg/m^2 (maximum dose 5 mg) on days 1, 4, and 7 and found three-year EFS benefit (31% versus 19%, p=0.0026) and two-year OS benefit (53.2% versus 41.9%, p=0.0368) although with longer follow-up the OS difference was no longer significant (three-year OS 44% versus 36%, p=0.18)

(5,60,61).

- The NCRI AML17 found GO at 6 mg/m^2 (day 1) resulted in no CR or survival benefit compared with GO at 3 mg/m^2 (CR 91.6% versus 86.5%, ns; three-year OS 53% versus 48%, ns) and resulted in higher 30-day and 60-day mortality (7% versus 3%, p=0.02 and 9% versus 5%, p=0.01 respectively) and other adverse events (62). SOS occurred with 6 mg/m^2 but not 3 mg/m^2 GO.
- GO at 6 mg/m^2 added to other chemotherapy resulted in higher rates of early deaths compared with control arms in all trials using this dose (3,63,64).

Interpretation of Evidence for Recommendation 2

- The Working Group concluded that the OS and RFS benefits outweighed the adverse events (early death) at 3 mg/m^2 but not 6 mg/m^2.
- While the magnitude of benefit was greater in subgroups with favourable or intermediate cytogenetics, benefit was found in the overall population. The evidence was considered insufficient to exclude patients with adverse cytogenetics and therefore the recommendation is not based on cytogenetic risk category.

Recommendation 3

The purine analogues cladribine, fludarabine, and clofarabine cannot be recommended for routine use at this time.

There may be a role in relapsed/refractory AML (see Question 3).

Qualifying Statements for Recommendation 3

- Some fludarabine regimens have been found effective but not directly compared with the same regimens without fludarabine, nor to standard 3+7 treatment. The MRC AML15 trial (6,7) and Russo et al (8,9) found benefit of FLAG-IDA (fludarabine + AraC + granulocyte colony-stimulating factor [GCSF] + IDA) and FLAI (fludarabine + AraC + IDA), respectively. The fludarabine arms contained high-dose AraC and the control arms used standard-dose AraC. The relative effect of AraC dose and fludarabine in these trials is unknown.
- FLAG is among the regimens recommended by NCCN (10) for relapsed/refractory AML based on non-randomized trials. A small Chinese study of induction (11) found FLAG (fludarabine + AraC +GCSF) and IDA + AraC to result in similar CR. While evidence from the literature review is considered insufficient to make a recommendation, FLAG may be an option in cases where an anthracycline is contraindicated.

Key Evidence for Recommendation 3

- The Polish Adult Leukemia Group (PALG) (65) compared DA + cladribine with DA and found improved CR (62% versus 51%, p=0.02 for one course; 68% versus 56%, p=0.01 for two courses) and three-year OS (45% versus 33%, p=0.02), with no significant difference in adverse events.
- Juliusson et al (66) added cladribine to AraC + IDA. The cladribine arm had better CR after one cycle (51% versus 35%, p=0.014 after one course; 63% versus 60% after two courses), and no difference in adverse events. The trial was too small to measure differences in survival outcomes.
- In the PALG study (65), cladribine improved CR and survival when added to AraC +

DNR, whereas benefits with fludarabine were not statistically significant (CR 59% fludarabine + DA versus 56% DA, p=0.47; three-year OS 35% versus 33%, p=0.98).

- Two trials published as abstracts suggest clofarabine may be of benefit. Clofarabine + DNR resulted in similar outcomes to AraC (100 mg/m^2 q12h) + DNR in the NCRI AML16 trial (67). The EORTC/Gimema AML-14A trial (68) found 84% response rate (CR + complete remission with incomplete recovery [Cri]) for clofarabine added to AraC + IDA in patients with intermediate/bad-risk AML. Confirming evidence from full publications of the NCRI AML16 or other trials is required.

Interpretation of Evidence for Recommendation 3

- Cladribine, fludarabine, and clofarabine have shown to be of benefit in some trials, but the evidence is not sufficient to make any recommendations.
- While the PALG trial is of much interest and suggests additional benefit for cladribine, there has been controversy about the results. The authors are aware of unpublished results of additional studies that were not able to confirm the PALG observation. The validity of the PALG results is currently being examined in ongoing studies.

Recommendation 4

- Addition of etoposide to AraC plus DNR induction is not recommended.

Key Evidence for Recommendation 4

- The MRC AML11 trial (69) compared DNR + AraC + etoposide (ADE) with DNR + AraC + thioguanine (DAT) in patients age >55 years (changed to age >60 years in the later part of study) and found five-year OS better with DAT than with ADE (12% versus 8%, p=0.02). Other trials did not deal specifically with older patients.
- The MRC trials AML10 (70) and AML15 (6,7) were the largest trials examining etoposide and found no survival difference with its addition but more grade 3 and 4 gastrointestinal toxicity. The AML15 trial found higher response with ADE compared with DA (CR+CRi after one cycle, 70% ADE versus 63% DA, p=0.002; CR, 82% ADE versus 78% DA, p=0.06).
- Several other trials (see systematic review Table 4-8) varied multiple components in the treatment arms such that the effect of etoposide could not be evaluated.

Interpretation of Evidence for Recommendation 4

While etoposide may have a small benefit on response rates, this did not translate to improved survival. Trials have not shown sufficient benefit to warrant routine use.

Recommendation 5

- Induction chemotherapy adjuvants such as colony stimulating factor (CSF) (GCSF or granulocyte-macrophage [GM]-CSF), interleukin-11, or multidrug resistance modulators such as cyclosporine A, PSC-833 (valspodar), and zosuquidar are not recommended.

Key Evidence for Recommendation 5

- Meta-analysis by Sung et al (71) concluded CSF priming should not be used in routine

clinical care. Meta-analysis by Heuser et al (72) concluded CSF administered concurrently or after chemotherapy did not improve CR, DFS/EFS, or OS.

- Interleukin-11 was not found to have CR or survival benefit (73).
- While cyclosporine A was found to have benefit in the Hellenic trial (74) and SWOG 9126 trial (75), these trials were small and included narrow subgroups of patients. Later studies with more specific inhibitors of drug efflux such as PCS-833 (valspodar) (76-80) and zosuzuidar (81) did not confirm these results.

Interpretation of Evidence for Recommendation 5

- The meta-analysis provides high quality evidence against the routine use of CSF as part of induction chemotherapy. CSF may have a role for supportive care during or subsequent to treatment. This use is outside the scope of the current guideline. Evidence for use of other chemotherapy adjuvants was considered weak and insufficient to justify their routine use for induction therapy.

Question 2. Post-Remission Treatment

It is considered standard practice to give consolidation treatment to patients who achieve CR after induction treatment. Transplantation was outside the scope of the review and other guidelines should be consulted concerning appropriate selection of patients for transplant. All patients that may be transplant candidates should receive early referral to a transplant centre. While transplant may take place immediately after induction (without any consolidation), due to delays prior to transplant, most patients scheduled for transplant will receive consolidation treatment.

Recommendation 6

Two or three courses of consolidation are recommended.

Qualifying Statements for Recommendation 6

- Regimens for consolidation may be the same as used for induction and the distinction between these two phases of treatment is sometimes somewhat arbitrary. The total number of courses of induction plus consolidation combined may be the most important consideration.

Key Evidence for Recommendation 6

- MRC AML14 trial found that there was no difference between one and two courses of consolidation after two courses DA induction (76,77).
- The GOELAM BGMT-95 trial found no difference between one course of consolidation with standard-dose AraC + IDA (same as induction) or with this consolidation followed by a cycle of HDAC, with both groups receiving maintenance (82,83). Patients had received one planned course of induction, with an additional course given to patients that had not achieved CR.
- Elonen et al found no difference between two cycles induction plus two cycles consolidation including HDAC and the same regimen with four additional cycles of consolidation (84).
- The MRC AML11 trial found no difference between two courses induction with followed

by either one or four courses consolidation (69). Induction had been randomized to either DAT [DNR + AraC + thioguanine], ADE [AraC + DNR + etoposide], or MAC [MTZ + AraC].

Interpretation of Evidence for Recommendation 6

- Additional cycles of consolidation increase the cost and the incidence of adverse events (including death) and this must be balanced with any survival benefit. While the optimal number of cycles is not determined and likely depends on both the induction and consolidation regimens used, there is no evidence to support routine use of more than three cycles of consolidation. In most trials patients received two courses of induction and one to four courses of consolidation. Adverse events including death increase with additional cycles, and the studies summarized in Key Evidence found no benefit to using more than one or two courses consolidation. One to two courses of consolidation is standard practice in many institutions. However, the SWOG protocol is to give three cycles consolidation after a single induction with DNR + AraC; as evidence was not found showing that outcomes are either better or worse using the SWOG protocol, the Working Group believed the recommendation needed to be broad enough to include this practice.

Recommendation 7

- For patients with CBF-AML receiving consolidation with AraC alone, HDAC at 1-3 g/m^2/day is recommended. HDAC may be considered for other patients.
- Patients with CBF-AML should receive three cycles of consolidation, of which at least two contain HDAC.

Qualifying Statements for Recommendation 7

- HDAC at 1-3 g/m^2/day is considered appropriate; however, there is insufficient evidence to recommend an optimal dose within this range.
- The benefit of HDAC is greatest for CBF-AML. The relative benefit of HDAC compared with adverse effects is less clear for other subtypes of AML.

Key Evidence for Recommendation 7

- HDAC (1-3 g/m^2 q12h) resulted in better survival outcomes compared with standard-dose AraC (100-400 mg/m^2/day) but with more adverse events in some trials (34,85).
- The Cancer and Leukemia Group B (CALGB) 8525 trial (34,35) compared four courses consolidation with AraC at 100 mg/m^2/day, 400 mg/m^2/day, and 3 g/m^2 q12h. There was a dose-response relationship, with HDAC resulting in best OS and DFS for patients age <60 years, while there was no difference between doses for patients age >60 years. The majority (71%) of patients age >60 years could not tolerate the high dose and 32% of this group had serious central nervous system abnormalities. The benefit of HDAC regarding continuous CR at five years was significant for CBF-AML and normal karyotype AML; it was less clear for other subtypes (21% HDAC versus 13% low-dose AraC). Patients administered HDAC required more hospitalization and more courses required platelet transfusion.
- Recent induction trials (see Recommendation 1) did not find unacceptable adverse events with HDAC.

- The MRC AML15 trial (6,7) found no statistically significant OS and RFS benefit with AraC at 3 g/m^2 q12 h (days 1, 3, and 5) compared with 1.5 g/m^2 q12h (days1, 3, and 5) (OS 53% versus 47%, p=0.6, RFS 42% versus 34%, p=0.06). There were modest differences in hematologic toxicity but more supportive care and hospitalization with the higher dose.
- In studies where AraC was given together with anthracycline, the effect of AraC dose was inconsistent. The JALSG AML201 trial compared HDAC at 2 g/m^2 q12h to standard-dose combination chemotherapy with AraC at 100 mg/m^2/day (four courses: MTZ + AraC, DNR + AraC, ACR + AraC, etoposide + vindesine + AraC) (86). They found both were tolerated with no OS difference, although HDAC resulted in better DFS in the subgroup with favourable cytogenetics) (86).

Interpretation of Evidence for Recommendation 7

- The Working Group believed the benefits of HDAC outweighed the harm associated with it, especially for patients with CBF-AML. Although some trials found more adverse events with HDAC compared with AraC, more recent induction trials did not find unacceptable adverse events with HDAC. These later trials are judged to include better patient management including supportive care and are more applicable to current practice.

Recommendation 8

- HDAC or standard-dose AraC may be used in combination chemotherapy. Standard-dose combination chemotherapy should be considered for patients determined to be unsuitable for HDAC consolidation.

Qualifying Statements for Recommendation 8

- Effectiveness may be influenced by age and/or prior treatment.
- There is insufficient evidence to recommend an optimal dose of HDAC.
- The benefit of adding anthracycline to HDAC is unclear.

Key Evidence for Recommendation 8

- The JALSG AML201 trial compared three courses of HDAC at 2 g/m^2 q12h to four courses of standard-dose AraC at 100 mg/m^2/day, each combined with different agents (MTZ, DNR, ACR, etoposide + vindesine) (86). They found both were tolerated with no overall survival difference, although HDAC resulted in better DFS in the subgroup with favourable cytogenetics.
- The Australasian LLG AML7 trial (87) found that for patients with ICE induction (AraC [3 g/m^2 q12h, days 1, 3, 5, 7] + IDA [9 mg/m^2/day, days 1 to 3] + etoposide [75 mg/m^2/day, days 1 to 7]) there was no addition benefit to consolidation with one cycle ICE compared with an attenuated regimen with two cycles of standard AraC (100 mg/m^2/day, five days) + IDA (two days) + etoposide (five days).
- A trial by the SAKK found one course of HDAC (3 g/m^2 q12h) given with DNR (45 mg/m^2/day) resulted in better four-year OS, (45% versus 34%, p=0.07), as well as DFS and EFS, compared with AraC at 100 mg/m^2/day plus DNR in patients age 15 to 65 years (85). There were more grade 3 adverse events with HDAC (58% versus 21%).

Results were similar to those for OS and DFS in the CALGB 8525 trial (34,35) in which four courses HDAC but without anthracycline was administered. These trials suggest anthracycline provides no additional benefit with multiple cycles of HDAC; however, it is unclear whether there is benefit for inclusion with a single cycle of consolidation.

- SAL AML96 (88) found no difference between AraC at 1 g/m^2 q12h compared with 3 g/m^2 q12h, both given with MTZ.
- An abstract of the NCRI AML16 trial (67) reported no difference in OS or RFS with AraC (100 mg/m^2 q12h) + DNR (50 mg/m^2/day) versus no consolidation in older patients (most age >60 years). However, these patients had received two cycles of the same regimen (with longer cycle duration) for induction.
- The MRC AML15 trial (7) found MACE→MidAC* resulted in outcomes similar to HDAC alone (OS 52% versus 52%, RFS 41% versus 40%) although with more adverse events. Subgroup analysis found a strong survival benefit for MACE→MidAC in patients with high-risk disease/unfavourable cytogenetics (OS 39% versus 0%, p=0.0004); however, this important result is based on only 54 patients and needs to be confirmed.

  *MACE: AMSA (100 mg/m^2/day, days 1 to 5) + AraC (200 mg/m^2/day, continuous infusion days 1 to 5) + etoposide (100 mg/m^2/day, days 1 to 5) → MidAC: MTZ (10 mg/m^2/day slow iv days 1 to 5) + AraC (1 g/m^2 by 2h iv infusion q12h, days 1 to 3).

- The German SAL AML 2003 (89) and CALGB 9222 (90) trials found multi-agent regimens including HDAC did not improve outcome and had more adverse events than HDAC alone.

Interpretation of Evidence for Recommendation 8

- Trials suggest that both standard-dose AraC with anthracycline and HDAC with or without anthracycline are effective. The relative benefit may be influenced by number of courses received, induction therapy received, and disease cytogenetics. One course HDAC + DNR was found to be better than one course standard-dose AraC + DNR, but one cycle ICE (with HDAC) was similar to two cycles of attenuated ICE (with 100 mg/m^2/day AraC). The Working Group considered the evidence insufficient to recommend a specific AraC dose or regimen.
- Complex regimens adding several agents to AraC + anthracycline or using non-anthracycline regimens were found to have no or very little additional benefit and usually more adverse events. The added complexity of administration and patient management was judged to greatly outweigh any benefit.

Recommendation 9

- There is insufficient evidence to make any recommendations for or against the use of maintenance chemotherapy in patients who received consolidation therapy.
- Use of maintenance treatment alone is not routine, but may be considered for those unable to tolerate consolidation.

Qualifying Statements for Recommendation 9

- We did not consider there to be sufficient evidence to make a recommendation at this time. Based on past experience there is no evidence maintenance therapy after

consolidation is useful as it currently exists; however, there are ongoing studies examining this issue (see Table 4-17). Ongoing trials with new drugs with different mechanisms of action and targeted therapy may find a benefit.

Key Evidence for Recommendation 9

- Trials evaluating maintenance therapy with interleukin-2 alone found small and inconsistent effects. The MP-MA-0201 trial (91-94) found improved leukemia-free survival (LFS) (six-year LFS 30% versus 22%, p=0.015) for patients in first CR receiving interleukin-2 plus histamine dihydrochloride compared with no maintenance. LFS and OS were not improved for patients in subsequent CR.

Interpretation of Evidence for Recommendation 9

- Several trials studied various maintenance regimens; however results are weak or inconsistent and are insufficient to make specific recommendations on maintenance regimens.
- As indicated in the preamble to this question, consolidation therapy is considered standard practice for patients who can tolerate it. The question of how to treat patients in CR but who are judged not suitable for consolidation treatment was not specifically addressed by the studies in the literature review.

Question 3. Relapsed or Refractory AML

While the intent in the treatment of relapsed or refractory AML is to allow subsequent transplant for responding patients, the decisions regarding transplant eligibility and procedures are beyond the scope of this document. The Program in Evidence-Based Care/Cancer Care Ontario report on Stem Cell Transplant (12) and recent provincial guidelines should be consulted. All patients that may be transplant candidates should receive early referral to a transplant centre.

Recommendation 10

- For patients with refractory disease or relapse, a more intensive or non-cross-resistant treatment is recommended. The following list is not meant to be inclusive of all reasonable therapies, but highlights a few with good response in the included RCTs:
  - HDAC + MTZ
  - AraC (500 mg/m^2/day continuous infusion)* + MTZ + etoposide ± GM-CSF
  - AraC (100 mg/m^2 q12h) + DNR + etoposide
  - Low-dose CAG: AraC (10 mg/m^2 q12h) + ACR + GCSF ± etoposide

  *See qualifying statement regarding dose
- Clofarabine, fludarabine (FLAG, FLAG-IDA), and cladribine regimens should be considered when alternative or additional agents are required.

Qualifying Statements for Recommendation 10

- There is no clear consensus about the length of CR duration that indicates re-treatment with the same induction chemotherapy would be as effective as an alternate regime. The NCCN suggests CR duration of >12 months (10), while others

use two to five years, or never. It has been suggested that AML recurring after a long CR may actually be new disease. With more detailed characterization of the genetic architecture of AML this distinction may become more evident in the near future. Re-treating with an ineffective regimen delays effective treatment while increasing risk of adverse events and treatment-related mortality.

- FLAG is among the regimens recommended by NCCN (10) for relapsed/refractory AML based on non-randomized trials (13). While evidence from the literature review is considered insufficient to make a recommendation, FLAG may be an option in cases where an anthracycline is contraindicated.
- AraC at 1 g/m^2/day or 1.5 g/m^2/day has also been widely used (e.g., (14-16)) but not directly compared. Several trials, both randomized and retrospective, report a large variation in response rates (17-22).
- A small case-series reported experience using high-dose etoposide and cyclophosphamide with modest benefit (23), although evidence appears weak.

Key Evidence for Recommendation 10

- Most information exists for use of the anthracyclines MTZ and DNR.
- Low-dose CAG (AraC at 10 mg/m^2 q12h + ACR + GCSF) + etoposide gave better CR than CAG alone (71% versus 51%, p=0.0002) while five-year OS was similar (27% versus 24%) (95). It was not compared with other regimens such as standard-dose AraC with MTZ or DNR and, therefore, relative effectiveness is uncertain (95).
- Most trials used etoposide; however, other than for low-dose CAG, studies evaluating the role of etoposide when added to AraC + anthracycline have not been reported. Etoposide added to HDAC had marginal benefit but increased adverse events in a SECSG study (96).
- The following regimens have been found effective, but were not compared with standard treatment and therefore the evidence is not sufficient to recommend a particular regimen. The evidence summarized for Question 2 found HDAC to be more effective than standard-dose AraC in consolidation therapy for de novo AML.
  - HDAC (3 g/m^2/day) + MTZ: CR of 58% and median survival of 12 months in a trial by Martiat et al (97)
  - HDAC (3 g/m^2 q12h as a 3-hour infusion, days 1,2,8,9) + MTZ compared with HDAC (1 g/m^2) + MTZ in patients age <60 years: higher CR (52% versus 45%, p=0.01) but more early deaths in a German AMLCG study (98)
  - AraC (500 mg/m^2/day continuous infusion) + MTZ + etoposide ± GM-CSF: CR 65% versus 59% (51% versus 46% refractory, 89% versus 81% relapsed) in the EMA91 trial (99)
  - AraC (100 mg/m^2 q12h) + DNR + etoposide (ADE): 54% CR, three-year OS 12%, three-year DFS 22% in the UK MRC AML-R trial (100) and 63% CR, four-year OS 27%, four-year DFS 29% in the UK MRC AML-HR trial (101)
  - Low-dose CAG: AraC (10 mg/m^2 q12h) + ACR + GCSF ± etoposide: CR 71% versus 51%, five-year OS 27% versus 24% (95)

- In the Classic I trial (102), clofarabine (40 mg/m^2/day for five days) + AraC (1 g/m^2/day for 5 days) compared with AraC alone improved CR rate (35.2% versus 17.8%, p<0.01) and EFS but not OS, with higher rates of serious adverse events (60%

versus 49%, primarily infections and deaths). In a non-randomized trial (103), clofarabine + HDAC (2 g/m^2/day) after GCSF priming resulted in a CR rate of 46% and median OS of nine months. Treatment-related mortality was 12%, with all cases due to infections.

- The German AMLCG trial (104) found fludarabine added to AraC + IDA resulted in small improvements in CR (44% versus 35%, ns), median time to treatment failure (3.4 months versus 2.0 months, p<0.05), non-response rate (26% versus 37%, p=0.054 overall; 24% versus 40%, p<0.05 age <60 years). A non-randomized trial (13) is the basis of the NCCN (10) recommendation for fludarabine use.
- Two MD Anderson trials (105,106) [abstracts only] compared clofarabine and fludarabine when added to IDA + AraC. CR was 43% versus 30% (ns) in the first trial and 32% versus 25% in the second trial (ongoing). Clofarabine resulted in worse four-week mortality (16% versus 4%), and possibly more infections (47% versus 35%, ns), but less grade 3 and 4 toxicities in survivors.
- Cladribine used in the regimen cladribine + AraC +GCSF ± MTZ or IDA has been recommended by the NCCN (10) based on non-randomized trials (107,108). Cladribine use is supported by the review by Robak and Wierzbowska (109), as well as trials in de novo AML patients as reviewed in Question 1 (65,66).

Interpretation of Evidence for Recommendation 10

- Because trials did not compare the experimental arm to a standard regimen the Working Group was unable to conclude that one regimen was superior. Those listed appear to be the most effective in this context based on the literature review and may be considered for initial use. As mentioned in the discussion for post-remission therapy in Question 2, appropriate selection depends on prior therapy.

Question 4. Which patient characteristics are most important when making treatment decisions?

During the planning stages of the systematic review it was decided to focus on RCTs, while acknowledging that RCTs might not provide the best source of evidence on patient characteristics. Some treatments were found to be of benefit in only a subset of patients (age, cytogenetic risk or subtype); however, the trials were usually not powered to detect differences in subgroups. The RCTs were not designed to directly determine which of these factors should guide treatment. The accompanying literature review, while commenting on some characteristics related to treatment, was not sufficient to address this question and no recommendations are being made. Several guidelines on treatment of AML have included sections on patient factors including age, comorbidities, cytogenetic abnormalities and associated risk category, and response to previous treatment. The most recent are the NNCN guideline (10), the Canadian consensus guideline for older patients (24), and the ESMO guideline for diagnosis, treatment, and follow-up (25). Older but comprehensive management guidelines from Britain (26), Italy (27), and the European LeukemiaNet (2) are also relevant. The reader is referred to these documents for further details. Some of this information may arise from studies that are currently ongoing.

IMPLEMENTATION CONSIDERATIONS

While evidence indicates GO may improve OS and RFS, it is currently not approved for use in Canada.

RELATED GUIDELINES

- Zaretsky Y, Crump M, Haynes AE, Stevens A, Imrie K, Meyer RM, Hematology Disease Site Group. Treatment of acute myeloid leukemia in older patients. Toronto (ON): Cancer Care Ontario; 2008 Dec 18 [ARCHIVED 2013 Nov]. Program in Evidence-based Care Evidence-based Series No.: 6-14 ARCHIVED 2013.

- Kouroukis CT, Rumble RB, Walker I, Bredeson C, A. S. Stem cell transplantation in myelodysplastic syndromes and acute myeloid leukemia. PEBC recommendation report SCT-3. 2012 [cited 2014 Oct 16]: Available from: https://https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/976.

Systemic Treatment of Acute Myeloid Leukemia (AML)

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

While commonly used induction therapies lead to remission in a substantial portion of AML patients, long-term survival is poor. Mortality due to induction is high with some regimens. The choice of subsequent consolidation and maintenance therapy is less clear and there appears to be no consensus on which regimens to use. For patients whose disease is refractory to initial induction or who later relapse, there is also no standard. Many trials in patients with AML have been published and it was the goal to determine whether there was sufficient evidence to recommend standardization of treatment in the various disease stages overall or for specific subgroups of patients in order to improve response and survival.

GUIDELINE DEVELOPERS

This guideline was developed by the Systemic Treatment of Acute Myeloid Leukemia GDG (Appendix 1), which was convened at the request of the Systemic Treatment Group of CCO.

The project was led by a small Working Group of the Systemic Treatment of Acute Myeloid Leukemia GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in acute leukemia and health research methodology. Other members of the Systemic Treatment of Acute Myeloid Leukemia GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 2, and were managed in accordance with the PEBC Conflict of Interest Policy

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle (110,111). This process includes a systematic review, interpretation of the evidence, and draft recommendations by the Working Group; internal review by content and methodology experts; and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework (112) as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

SEARCH FOR EXISTING GUIDELINES

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following databases were searched for existing guidelines that addressed the research questions: SAGE Directory of Cancer Guidelines, National Guideline Clearing House, and the Canadian Medical Association (CMA) Infobase. Websites of the following guideline developers were also searched: European Leukemia Net, European Hematology Association, National Institute for Health and Care Excellence (NICE) (UK), Scottish Intercollegiate Guidelines Network (SIGN) (UK), American Society for Clinical Oncology (ASCO) (US), National Comprehensive Cancer Network (NCCN) (US), National Health and Medical Research Council (Australia), and the New Zealand Guidelines Group. MEDLINE and Embase were searched for guidelines for the period 1990 to October 17, 2014 (see Appendix 3). Guidelines were considered as potentially relevant if they were based on a systematic review and were on the topic of systemic treatment of AML in adults. A search for existing guidelines for adaptation or endorsement did not yield an appropriate source document for the full project, although existing guidelines would be referred to especially for the final question dealing with patients characteristics influencing treatment decisions. A search of the primary literature was required (see Section 4 Evidence Review).

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP

members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

ACKNOWLEDGEMENTS

The Systemic Treatment of Acute Myeloid Leukemia GDG would like to thank the following individuals for their assistance in developing this report:

- Joseph Brandwein, Melissa Brouwers, Jeannine Kassis, Sarah Kellett, Sheila McNair, Donna Maziak, Hans Messersmith, Thomas Nevill, Mary Lynn Savoie, John Storring, Emily Vella, and Eric Winquist for providing feedback on draft versions.
- Kristy Yiu, Crystal Su, and Umangjot Bharaj for conducting a data audit.
- Sara Miller for copy editing.

Systemic Treatment of Acute Myeloid Leukemia (AML)

Section 4: Systematic Review

INTRODUCTION

Acute myeloid leukemia (AML) has an incidence rate in Canada of 3.6 cases/100,000 (2010 data; Canadian Cancer Society, http://www.cancer.ca/en/cancer-information/cancer-type/leukemia-acute-myelogenous-aml/statistics/?region=on) and 4.0/100,000 in the United States (2008 to 2010, National Cancer Institute, seer.cancer.gov/statfacts/html/amyl.html). Incidence increases with age, while survival decreases.

The Working Group of the Systemic Treatment of Acute Myeloid Leukemia Guideline Group developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1. What is the most effective systemic induction treatment for adults with previously untreated AML who can tolerate intensive treatment?

2. What is the most effective systemic post-remission treatment (consolidation and/or maintenance, excluding stem cell transplant) for adults with previously untreated AML?

3. What is the most effective systemic treatment (reinduction, consolidation, maintenance; not including stem cell transplant) for adults with relapsed or refractory AML who can tolerate intensive treatment?

4. Which patient characteristics are most important when making treatment decisions?

METHODS

The standard induction regimen consisting of cytarabine (cytosine arabinoside, AraC) plus an anthracycline was established over 25 years ago (113-115), based largely on studies by the Cancer and Leukemia Group B (CALGB) (116). Since that time, different doses, variations and derivative of anthracycline used, and use of additional agents have been studied in attempts to improve response and survival. Several guidelines and reviews included specific comparisons, but we were unaware of comprehensive and current systematic reviews that covered all trials. It was therefore deemed necessary to conduct a literature review covering a broad period going back to the time when current treatment was established.

A literature search strategy (see Appendix 3 for search strategy) was developed and conducted using the MEDLINE and Embase databases for the period 1990 to October 17, 2014; it was rerun on August 18, 2015 to find recent publications. The search included guidelines, systematic reviews, and randomized controlled trials (RCTs). Systematic reviews were evaluated based on their clinical content and relevance prior to screening of primary studies. The intent was to determine whether there were reviews that could form the literature base for this guideline instead of conducting a new systematic review. Reviews on subgroups of patients or treatments were identified that might supplement our analysis, and these are referred to later in interpretation of the results. It was determined that none of the

systematic reviews were comprehensive and current enough to form the basis of this guideline. A full review of the primary RCT literature was therefore required. Abstracts from conferences of the American Society for Clinical Oncology (ASCO), American Society for Hematology (ASH), and European Hematology Association (EHA) were searched for years 2009 to 2014 using Embase and the conference websites. As a result of external review comments, the ASH 2015 conference abstracts were also searched; however, as this was subsequent to the formal systematic literature review, these results are indicated as such and have not been fully integrated into the review.

Study Selection Criteria and Process

A review of the titles and abstracts and subsequent full-text review (if warranted) was conducted by one reviewer (GGF).

Inclusion Criteria:

- Adult patients with AML randomized to systemic treatment versus other systemic treatment (including different schedule/dose) or placebo
- For induction therapy, at least one arm consisted of systemic therapy including a combination of a cytarabine and an anthracycline (or derivative such as the anthracenedione mitoxantrone)
- RCTs could include a mixture of leukemias/myelodysplastic syndromes (MDS) as long as at least 50% of patients had AML or outcomes of AML patients were reported separately.
- Reported outcomes related to disease control (complete remission rate) and/or survival.

Exclusion Criteria:

- Studies focussed on stem cell transplantation, supportive care (e.g., transfusions, prevention or treatment of infections or iron overload). Granulocyte colony-stimulating factor (GCSF) or related agents were not excluded when it appeared use was being evaluated as part of the systemic therapy to treat AML (instead of complications/side effects).
- RCTs of systemic treatment compared with transplantation.
- Retrospective studies, prospective cohort studies, case control studies, case series studies.
- Studies focussed on patients with acute promyelocytic leukemia (APL), acute lymphoblastic leukemia, non-acute leukemias, or MDS.

Data Extraction and Assessment of Study Quality and Potential for Bias

Ratios, including hazard ratios (HR), were expressed with a ratio <1.0 indicating benefit of the investigational treatment compared to the control or placebo. All extracted data and information were audited by an independent auditor.

Important quality and completeness of reporting features for randomized trials, such as sample size calculations, number of patients, statistical significance of outcomes, and whether analysis was on an intent-to-treat (ITT) basis were extracted for each study. Studies in which effectiveness of randomization is suspect due to unequal group characteristics have a notation added. Blinding of outcome assessment was rare and therefore not used as criteria for assessment. Extraction of data on adverse events was generally limited to significant differences between treatment arms in severe (grade 3+) adverse events.

Synthesizing the Evidence

When clinically homogeneous results from two or more trials were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.3 provided by the Cochrane Collaboration (117). For time-to-event outcomes, the HR, rather than the number of events at a specific time, is the preferred statistic for meta-analysis, and is used as reported. If the HR and/or its standard error were not reported, they have been derived from other information reported in the study, using the methods described by Parmar et al (118). For all outcomes, the generic inverse variance model with random effects, or other appropriate random effects models have been used. Statistical heterogeneity was calculated using the X^2 test for heterogeneity and the I^2 percentage. A probability level for the X^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% was considered indicative of statistical heterogeneity.

RESULTS

The original literature search from MEDLINE and Embase, after removal of duplicates, resulted in 7367 citations. Of these, 1678 dealt only with MDS and were excluded. Of the remaining citations, preliminary sorting resulted in 4219 RCTs, 451 systematic reviews or meta-analyses, and 1019 guidelines. The abstract search resulted in a further 36 citations. An additional five guidelines were located from websites (see Section 3). The search update of August 2015 found 1373 publications.

Search for Existing Systematic Reviews

Of the 451 systematic reviews or meta-analyses found in the literature search, 29 remained after application of inclusion/exclusion criteria. The review by the Swedish Council on Technology Assessment in Health Care (119-121) was the only one to cover the full range of treatments and all adult patients but only included literature published to 1998, plus some key publications until September 2000. Other reviews were located on specific chemotherapy agents (clofarabine (122), cytarabine (123,124), hematopoietic growth factors (71,72,125-130), gemtuzumab ozogamicin (GO) (57,59,131,132), homoharringtonine (133,134), idarubicin and daunorubicin (48,135,136) or anthracyclines generally (137), interleukin-2 (IL-2) (138,139)] or on specific subgroups of patients [older patients (140), adolescents and young adults (141,142), or patients with core-binding factor [CBF] AML (143,144)).

As the reviews were either outdated or too narrow in scope to allow their use as the basis for a new set of recommendations it was decided to perform a full systematic review of RCTs. The above reviews were consulted for specific sub-questions and evaluated along with the individual RCTs.

Literature Search Results

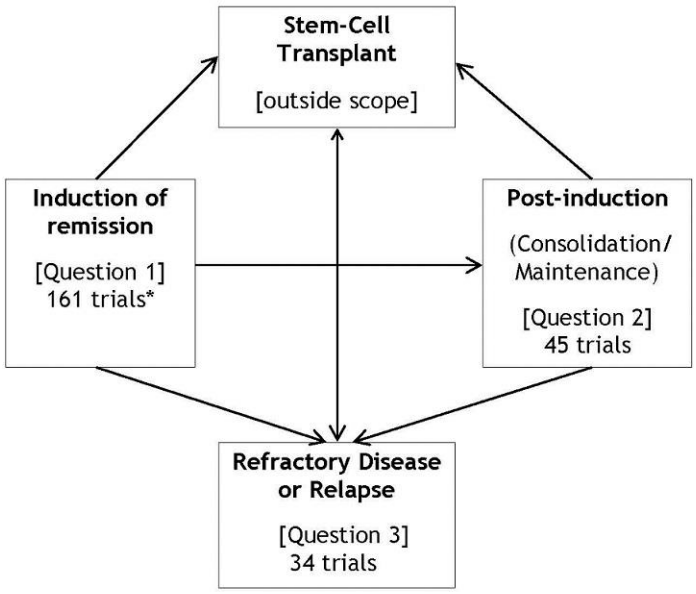
Initial screening of the RCTs primarily by reviewing titles and abstracts resulted in 524 publications (488 from MEDLINE/Embase, 36 from abstract search). Approximately 26 additional references were added based on reference lists or targeted searches to find additional details about included trials or full publications of abstracts.

Publications were excluded in the second stage (full-text evaluation) for the following reasons: induction without anthracycline + cytarabine (n=57), retrospective molecular or prognostic analysis (n=32), have later or more complete publication (n=90), duplicate abstracts/publications (n=22), pilot/dose-finding/phase I/II trials (n=14), reports of trial design (n=14), not RCTs or not AML (n=12), reviews (n=6), supportive care (n=5), transplants (n=4), economics (n=3), childhood AML (n=2), no results (n=1), and pharmacokinetics (n=1). Following full-text screening there remained 287 publications representing 240 trials.

The search update of August 2015 found 57 publications of RCTs; of these, 42 were already included (36 of these from the original searches and six other abstracts contained no additional relevant data beyond that already in other included publications). The new publications represented three new trials (145-148) and additional information for four already included trials (ALFA-0107 (5), and the UK Medical Research Council [MRC]/National Cancer Research Institute [NCRI] AML15, AML16, AML17 trials (149-152)).

Results from induction studies are given in Table 4-1 to Table 4-12 (3-9,11,36,40-47,49-56,58,60-70,73-83,86,87,116,145-147,149,150,152-298) with ongoing studies reported in Table 4-13 (106,299-305). Results from post-remission studies are given in Table 4-14 to Table 4-16 (6,7,34,35,40,45,46,51,53,58,63,67,69,76,77,79,82-94,151,153,156,161,162,165,168,172,176,177,181,185,192,194,196,198,199,207,208,213,233, 234,245,246,261,262,270,275-279,297,306-342), with ongoing studies in Table 4-17 (47,152,343-347). RCTs involving patients with refractory or recurrent disease are given in Table 4-18 (17,18,47,75,95-102,104-106,148,152,348-373). Some trial results appear in more than one set of tables due to multiple randomizations (see next subsection). Trials in which randomization is to both induction and post-induction treatment at the start, with post-induction treatment determined by the induction randomization group are considered to be primarily studies of induction, although more specifically are evaluation of a treatment pathway. These trials are included only in the induction tables (Tables 4-1 to 4-13). The relationship of the various stages of AML treatment, research questions, and number of trials located is illustrated in Figure 4-1.

Figure 4-1. Interrelationship of AML stages and research questions



* Includes 27 trials with secondary randomization to consolidation and/or maintenance

Study Design and Quality

Trial Descriptions

Details on the trials are included in the data extraction tables (see Tables 4-1 to 4-12 and Tables 4-14 to 4-18). Following induction, subsequent treatment varied for patients in complete remission (CR). In some trials no further treatment was given or it was not specified (to be decided by the attending physicians and patients). Other trials gave post-remission treatment which depended on which induction had been received (i.e., initial randomization led to a pathway of treatment), or conducted a second randomization (consolidation, maintenance, or both) of all patients with CR willing to continue in the trial. A small number of trials randomized patients at three stages (induction, consolidation, maintenance). Most studies in relapsed or refractory patients randomized patients to reinduction treatment; a few randomized patients (who had CR to reinduction therapy) to post-induction treatments.

The total number of participants is given for each study; where there is a second randomization of interest the number of patients for this randomization is also noted. Almost all trials had approximately equal numbers per arm. Exceptions such as trials with 2:1 or other unequal randomizations have been noted. As age has often been considered a major factor in determining treatment, and trials and guidelines are often for either older or younger patients, the age range as defined by the trial inclusion criteria along with actual median age of patients enrolled has been extracted. In a limited number of trials, the age range for inclusion was not stated; in these cases the actual age range for patients has been reported.

Randomization and Prospective Design

As part of the literature review design, only prospective RCTs were included in the literature search.

Allocation Concealment

Of the induction trials publications, approximately one-third gave details of the randomization process suggesting allocation concealment. The proportion was higher for consolidation trials (67%) and lower for maintenance trials (15%). Of the other studies, details on the method of randomization were not reported. Even the largest research groups conducting numerous multicentre and international trials (with the exception of CALGB and the European Organisation for Research and Treatment of Cancer [EORTC]) did not consistently report on method of randomization, suggesting that there the issue may be of reporting as opposed to trial design. There was no indication that allocation was not concealed or that researchers influenced the treatment received. The treatment arms were generally balanced with respect to patient and disease characteristics. As abstracts reported fewer details they were also less likely to report on methods of randomization. This was not considered a large enough concern to require downgrading the overall assessment of the quality of evidence.

Blinding

Most trials appeared to be of open design without blinding of investigators or participants. Thirty-two trials indicated they were open-label design and twenty trials indicated they were double-blind; of the latter group nine involved evaluation of colony-stimulating factors (CSFs). An additional five trials indicated blinding in some aspect of the trial. A few trials indicated they were unblinded at some point during data analysis,

suggesting they had blinding in the design, but this was not mentioned explicitly. Due to the extreme toxicity and known differences in adverse effect profiles of some of the regimens, knowledge of treatment may have been essential in order to provide appropriate supportive care. Differences in modes of administration would also have made it difficult to have blinding of participants and researchers. Trials of GCSF or granulocyte-macrophage (GM)-CSF were much more likely to be double-blind, possibly because they are routinely used in supportive care. In the included trials, GCSF or GM-CSF were given as a chemotherapy adjuvant to modify effect of the active agents and therefore less likely to have large serious adverse effects. Lack of blinding for assessment of adverse effects may be a major source of bias, and may play a role in other non-survival outcomes. Due to the extremely poor prognosis of AML, we were mainly concerned with death or severe (grade 3 and 4) adverse events, which are more likely to be noted objectively compared with less severe toxicities. It is considered highly unlikely that blinding or lack of blinding would influence assessment of death or overall survival (OS) outcomes. The overall assessment is that while blinding was not routinely reported, or was not part of the RCT design, this is not a significant enough source of bias to downgrade our assessment of the quality of evidence.

Power and Sample Size Calculations

Sample size and power calculations, when reported in the original publications, are indicated in the data extraction tables. The majority of trials did not include sample size and power calculations. Many of the trials were too small to be able to find statistically significant results. In general, studies that included power calculations were designed only to detect relatively large (20% to 30%) improvements in CR for induction studies or in survival for post-remission studies. Few studies were sufficiently powered to detect small differences in survival, and this applied especially to induction studies that were designed with CR as the primary outcome. The lack of many statistically significant differences was therefore not unexpected. Where sample size calculations were provided, these are a factor in determining whether to consider a lack of statistically significant differences to indicate there is likely no difference, or just that no conclusions could be reached. There were some very large multicentre trials (>1000 patients) by large leukemia research groups, as well as some relatively small trials that found significant differences in outcomes. Due to the extremely large number of comparisons made in the various trials, it was considered inappropriate to give a summary evaluation of the potential bias due to sample size. Related issues are included with the results and discussion of various regimen comparisons in the following sections of this review.

Appropriate and Complete Outcome Assessment

Patients with AML generally have very poor prognosis, with survival limited to a few months. Deaths during, or even prior to treatment, are common. Treatments also have many adverse effects and very high-level infection control and supportive care are required. Likely due to these factors, short-term outcomes were usually appropriately and completely assessed. CR rates were reported for all trials, although in a small portion of publications the authors stressed the overall CR rate and stated there was no difference between arms, instead of clearly stating the results by treatment. Early mortality or induction-related mortality were also well assessed. Both the disease itself and the treatments received induce hematologic effects and susceptibility to severe infections; these were also well-reported. Non-hematological adverse events were less consistently reported; gastrointestinal effects were the most common. While a concern, most of these effects were not life-threatening and could be managed, and were not designated as primary or secondary outcomes in the study design.

Survival data were not well reported for many of the trials, especially the smaller ones, and often only median values (or none) were given. This may be a limitation due to the very short survival and small number of patients, such that in small trials there may be no long-term survivors, or too few to allow meaningful between-group comparisons. Survival data, when available, were extracted and appear in the data tables. For studies large enough to calculate survival rates, two to three years appears sufficient, and only a few studies have follow-up beyond four to five years. The lack of survival data is considered a limitation to the body of evidence in this review. As for the previous discussion of power and sample size, it is considered more appropriate to discuss for individual comparisons in the following sections.

Source of Funding

Many trials, especially those evaluating newer agents in phase II/III trials, were funded at least in part by pharmaceutical companies. This may have influenced what agents were evaluated and whether larger follow-up studies were conducted. The larger trials tended to receive funding from governments and research institutes or cancer societies, with pharmaceutical companies sometimes also providing support (especially provision of the drugs being evaluated). Many trials did not report sources of funding, possibly with costs covered by the participating institutions. Recent publications generally included a statement about funding. While a potential source of bias, especially at the earlier stages of drug development, it is considered minor for the larger phase III multicentre trials.

Appropriate Analysis

Most studies with full publications included details on assessment of response in the methods as well as a section on statistical analysis. This was especially true for the more recent trials. Over time, patient management and assessment of response has improved, such that assessment and analysis used in some earlier studies may be considered inappropriate by today's standards. This is not a weakness of the study design, but rather a reflection of changes in knowledge. Several studies noted that patients died prior to treatment commencement or patients refused assigned (or any) treatment. While this is unavoidable due to the severity of the disease and toxicity of treatment, it complicates ITT analyses. Only approximately 30% of the trials indicated an ITT analysis.

Overall Quality and Bias Assessment

The quality of trials including the elements summarized in this section was considered in the interpretation of study results in the subsequent sections of this review. Due to the large number of trials and comparisons made, of which extremely few found statistically significant differences, a table of formal study-by-study and element-by-element assessment of each trial is not included in this review. Some limitations of studies that may affect their interpretation or validity are noted for specific comparisons.

Overall, the large phase III trials were conducted by established multicentre (and often multi-country) leukemia research groups, were well-designed, and methods and results were well reported. Methods and results of these trials were reported in detail. These were evaluated as of high quality and low-moderate risk of bias. Some of the most recent trials have been published only as abstracts because data just became available or longer-term follow-up is ongoing. While likely to be of similar quality as other trials by the same research groups, this could not be assessed.

Several studies conducted by leukemia research groups in Japan, China, Russia, Poland, and Germany were published primarily in non-English languages, with only English abstracts available. While some of these are likely high-quality studies, many of the quality/bias elements could not be evaluated and the risk of bias is high. It should be noted

that the larger trials with positive (significant) results are often presented at English-language conferences or published in English at a later date.

Some (but not all) of the smaller phase II/III RCTs, especially those conducted at single centres, were of a more exploratory nature and the conclusions were to either conduct more trials based on promising results, or cease investigation of the experimental regimen. This is reflected both in the data tables and the discussion in the text of the review. Trial details were often not as fully reported. Several of the smallest trials (<100 patients) were reported only as abstracts, even if completed many years ago. The funding source is more likely to have an influence. Overall, these trials are judged to have moderate to high risk of bias.

Outcomes

CR, OS, and other survival outcomes such as event-free survival (EFS), disease-free survival (DFS), or recurrence-free survival (RFS) were the key outcomes for this review. Data on these have been extracted if reported in the publications. CR or a variation such as CR + CRp (complete remission without full platelet recovery) or CR + CRi (complete remission with incomplete recovery) was given for all induction studies and is the primary measure of induction response. CR rates for each arm of the induction trials are noted in the tables except as indicated otherwise. Patients without CR generally had extremely low rates of survival and were usually excluded from any interventions subsequent to induction. All patients were in included in calculations of OS; however, only patients with CR were included in other survival outcomes. For post-remission studies, a single CR rate reflective of the entire induction population is generally reported in the data tables, and this can be considered a characteristic of the population being randomized to post-remission treatment.

Survival outcomes were reported less consistently than CR and often were missing due to preliminary reporting or insufficient follow-up. Several publications only reported median survival data. Hematologic outcomes and adverse events were reported in varying levels of detail and in no standardized manner. These have been summarized in the data tables only when there were major or significant differences noted between the treatment arms.

1. What is the most effective systemic induction treatment for adults with previously untreated AML?

Standard induction treatment has involved an anthracycline (primarily daunorubicin [DNR]) plus cytarabine (cytosine arabinoside = arabinofuranosyl cytidine; AraC). Within this framework, trials can be broadly classified as those evaluating AraC dose or comparing AraC with other nucleoside analogues (Table 4-1 and Table 4-2), anthracycline dose or schedule (Table 4-3), or comparison of anthracyclines. Idarubicin (IDA) and DNR are compared in Table 4-4, mitoxantrone (MTZ) versus DNR in Table 4-5, other comparisons to DNR in Table 4-6, and other anthracycline comparisons in Table 4-7. Other trials either added on an additional agent to the cytarabine/anthracycline or compared an entirely different multi-agent regimen to cytarabine/anthracycline. Studies with etoposide are indicated in Table 4-8, all-trans retinoic acid (ATRA) in Table 4-9, gemtuzumab ozogamicin (GO) in Table 4-10, GCSF or GM-CSF in Table 4-11, and other agents in Table 4-12.

Induction, Cytarabine Dose or Comparison

Of the RCTs in Table 4-1, nine (36,40,76,77,116,153,154,157,161-164,166) directly compared dosage of AraC, which was administered intravenously (iv) over 30-120 minutes or iv by continuous infusion (CI). The CALGB 8321 study found no overall difference comparing

200 mg/day versus 100 mg/day, but found a benefit of the higher dose in patients <60 years of age (116). Two studies comparing 400 mg/day versus 200 mg/day (MRC AML12 in patients age <60 years (153,154) and MRC AML14 in patients age >60 years (76,77)) and one study comparing 1 g/day versus 200 mg/day (157) found no difference. Four trials compared high-dose AraC (HDAC; 2-6 g/day) to standard-dose AraC (100-200 mg/day). ALSGM4 used 6 g versus 100 mg and found no difference (163) while SWOG 8600 found 4 g versus 200 mg improved DFS but neither CR nor OS (161,162). The largest (n=1942) and most recent study, EORTC/GIMEMA AML-12, compared 6 g/day versus 100 mg/m^2/day in patients receiving DNR + etoposide and found improved CR overall (age 15 to 60 years) and improved OS and DFS in the subset age <46 years (40). A study by Sabty et al had similar design but was much smaller (n=128) and did not find a difference (166). A study in patients with CBF-AML administered DNR together with AraC found extremely high CR rate (99%) and no difference in survival between AraC at 500 mg/m^2/day (days 1 to 3) then 1 g/m^2 every 12 hours (q12h) (days 8 to 10) compared with AraC at 200 mg/m^2/day (days 1 to 7) (36).

One trial compares DNR to N^4-behenoyl-1-ß-D-arabinosylcytosine (BHAC, widely used in Japan instead of AraC) and found BHAC 200 mg resulted in worse CR and EFS than AraC 80 mg, although dosages may not have been optimal (168). One RCT varied both BHAC and DNR dose (167) while three varied both AraC and anthracycline (155,156,159). It is difficult to determine whether any differences are due to variation in AraC or anthracycline.

The systematic review on HDAC by Li et al (123) included two of the above studies plus three German studies which were confounded by differences in anthracyclines as well. It did not include the EORTC/GIMEMA AML-12 study. They concluded HDAC compared with standard-dose AraC was beneficial for RFS but not CR or OS.

Induction, Nucleoside Analogues other than Cytarabine

Three Polish Adult Leukemia Group [PALG] studies (65,169,170) explored the addition of cladribine to DNR + AraC and the trial by Juliusson et al (66) added cladribine to IDA + AraC (see Table 4-2). CR was improved by addition of cladribine; however, survival benefit was noted in only the two larger studies. One study found improvement in three-year OS (45% versus 33%, p=0.02; p=0.005 for age 50 to 60 years but not significant in younger patients) (65) and the other found benefit in EFS for patients age 40 to 60 years but not age <40 years (170).

The NCRI AML16 trial (67) and EORTC/GIMEMA AML-14A (68) found clofarabine and AraC resulted in similar adverse events, CR, and survival outcomes. Both are published only as abstracts. The systematic review on clofarabine in older adults (122) may be referred to for a summary of trials outside the scope of the current review (non-randomized trials, induction with clofarabine + AraC).

Fludarabine was studied in five trials. The PALG study (65) added fludarabine to DNR + AraC and the GOELAM SA4 trial (83,171) added fludarabine to IDA + AraC. Both trials found increased rates of CR and survival with fludarabine, but the differences were not statistically significant. The MRC AML15 trial (6,7) found that fludarabine + AraC + GCSF (FLAG) + IDA is effective but the contribution of fludarabine in this combination cannot be ascertained as comparison was only made to DRN + AraC + etoposide. Russo et al (8,9) found fludarabine + AraC + IDA (FLAI) to be better than IDA + AraC + etoposide (ICE) but effect cannot be attributed to fludarabine due to addition of etoposide and use of different AraC doses. A Chinese study (11) found FLAG and IDA + AraC to result in similar and high CR (92% versus 87%).

A small study (n=34) substituting troxacitabine for either IDA or AraC found these combinations were not superior to IDA + AraC (173).

Induction, Anthracycline Dose or Schedule

Trials comparing anthracycline dose or schedule are given in Table 4-3 (41-47,76,77,155,156,167,174-185). DNR doses of 30-90 mg/m^2/day for three days together with a fixed dose of AraC (generally 100-400 mg/m^2/day for seven to ten days) were compared in various studies. MRC AML14 found no difference between 35 mg and 50 mg DNR (76,77). The German AMLCG found 60 mg superior to 30 mg while the Russian AML-95 found no difference between 45 mg and 60 mg (176-179). ECOG E1900 (41-43) and Lee et al (44) compared 90 mg and 45 mg in patients age ≤60 years, while the HOVON 43 (45,46) made this comparison in patients age >60 years. These RCTs found the higher dose improved response rate and survival. Subgroup analysis by Lee et al found significant OS benefit in intermediate-risk subgroup but not others. ECOG found benefit in all risk subgroups; benefit was greatest for those age <50 years (p=0.002), while the difference was non-significant for patients age 50 to 60 years (p=0.12). The HOVON trial found significant two-year OS benefit of the higher dose for patients age 60 to 65 years but not age >65 years. For patients with CBF abnormalities p=0.09 for benefit of the higher dose. NCRI AML17 (47) found no difference between 90 and 60 mg/m^2/day but more adverse events in the 90 mg arm.

Other trials varied both AraC and anthracycline dose. MRC AML9 (156) found DNR (50 mg/m^2/day) + AraC (100 mg/m^2 q12h) + thioguanine (DAT) more effective when given 3+10 days than for 1+5 days. ECOG (180) found that an attenuated schedule/dosage DNR 50 mg/m^2/day for one day versus 60 mg/m^2/day for three days and reduced AraC) was found to result in less hospitalization and early deaths in patients age ≥70 years. This is in contrast trials reported by Parovichnikova et al (155) and Mori et al (167) that found standard doses (DNR 40-45 mg/m^2/day + either AraC 100 mg/m^2 q12h or BHAC 200 mg/m^2/day) could be used in patients age >60 years and age 60 to 75 years, respectively.

The ALFA-9801 trial (181) found no significant difference between three and four courses of IDA (12 mg/m^2/day). Feldman et al (183) compared MTZ at 80 mg/m^2 (day 2 only) compared with 12 mg/m^2/day (days 1-3) and found CR of 57% versus 42% and median survival of nine months versus six months. The differences were not statistically significant as the study was designed only to detect or exclude a very large difference. A small study comparing MTZ bolus versus CI (182) found both were effective, with significant differences (favouring the bolus group) only for patients age <40 years.

Induction, Anthracycline Comparison: IDA versus DNR

Sixteen trials as detailed in Table 4-4 compared IDA versus DNR (with AraC in both arms)[2]. Most common doses were IDA at 12 mg/m^2/day for three days and DNR at 45 mg/m^2/day for three days, but other dosages were also used, complicating the interpretation. Two trials (186,187) with DNR at 25 and 30 mg/m^2/day found IDA equally or more effective but this may be due to DNR being at too low a dose (see previous subsection). The remaining trials used DNR at 40 mg/m^2/day or more.

A meta-analysis performed as part of this systematic review (see Figure 4-2) found that IDA resulted in higher rates of CR (OR=0.80, 95% confidence interval 0.70-0.93, p=0.003). This held both for studies which used standard-dose DNR (defined as three doses of 40-50

[2] An additional trial conducted by Lee et al is summarized under ongoing trials. Results have been reported in an abstract presented, subsequent to external review of this document, at the December 2015 ASH conference (300). Results have been added to Table 4-13 (ongoing trials) but not included in the meta-analysis. The trial compared IDA (90 mg/m^2/d for three days) versus IDA (12 mg/m^2/d for three days), with AraC in both arms and did not find statistically significant differences.

mg/m^2/day, total 120-150 mg/m^2) and high-dose DNR (total 180-250 mg/m^2), p=0.02 and p=0.03, respectively. The EORTC/GIMEMA AML-10 trial (49) was the largest trial and found no significant difference in CR (66.9% IDA versus 68.7% DNR, p=0.49). This trial was different than all the others comparing IDA with DNR in that an additional agent, etoposide, was used in both arms in addition to AraC and IDA/DNR. When this trial is excluded the results favour IDA more strongly (p=0.0001 overall, p=0.0006 for standard-dose DNR). Several trials were conducted in elderly patients or reported these patients as a subgroup. Meta-analysis for patients age ≥55 years also found CR benefit for IDA compared with DNR (OR=0.77, confidence interval 0.63-0.94, p=0.01). The ALFA 9801 and ALFA 9803 trials were the most recent and accounted for over one-half of the patients.

In the JALSG AML201 study (51) the MAB M6 subgroup had significantly better CR with three days IDA than with five days DNR (78% versus 38%, p=0.037), while there were no differences for other subgroups.

Figure 4-2. Meta-analysis of trials comparing complete remission rates with idarubicin versus daunorubicin

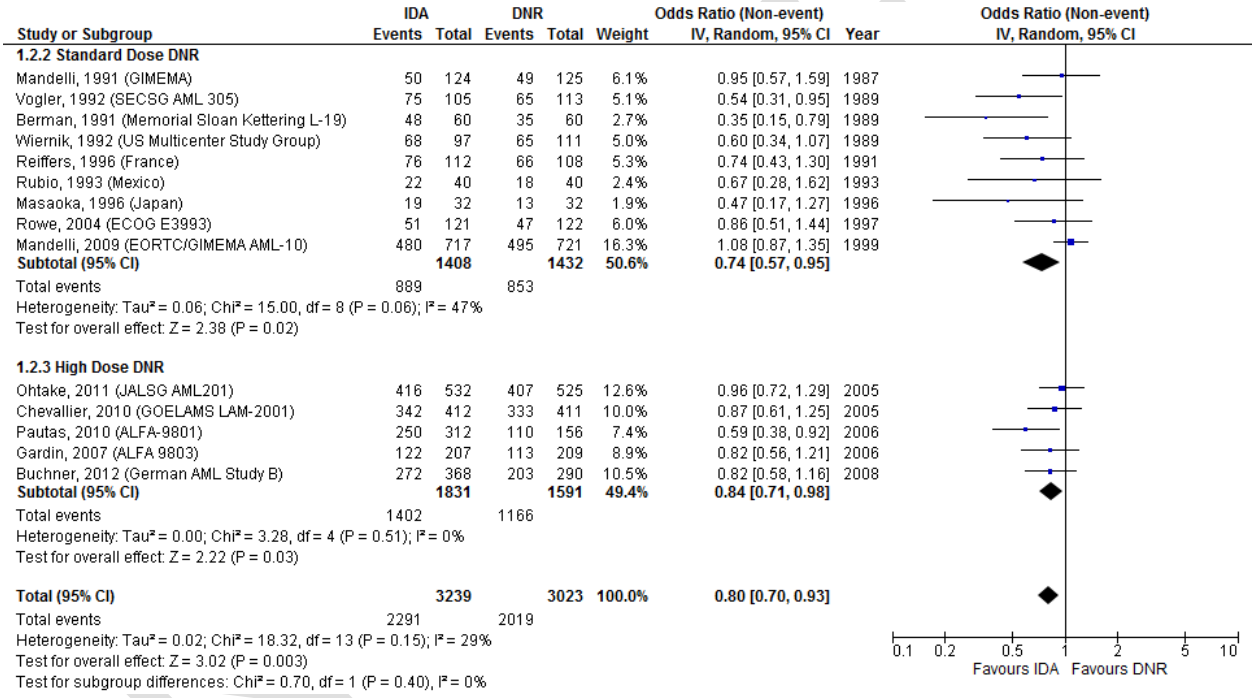
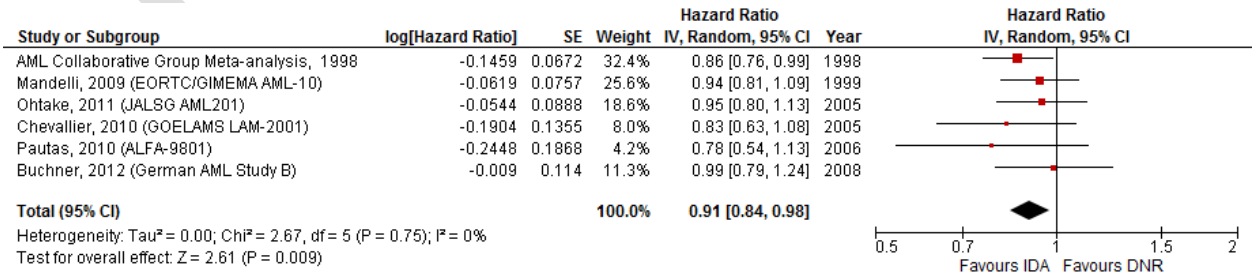


Figure 4-3. Meta-analysis of trials comparing overall survival (four-year OS or five-year OS) with idarubicin versus daunorubicin



An individual patient meta-analysis of five small older trials by the AML Collaborative Group (135) concluded both CR and five-year OS were significantly better with IDA compared with DNR. For studies in the current review survival data are not reported in a consistent manner. Outcomes reported include OS (12 studies), DFS (4 studies), EFS (3 studies) or RFS (3 studies) and these are given as median times or at two, four, or five years. Five studies reported four-year or five-year OS. When these more recent studies with four to five-year OS are added to the AML Collaborative Group meta-analysis (see Figure 4-3), there is small but significant OS benefit for IDA compared with DNR (HR=0.91, 95% confidence interval 0.84-0.98, p=0.009). A recent mixed treatment comparison meta-analysis (48) including both direct and indirect effects found higher CR and OS with IDA compared with conventional-dose DNR (defined as cumulative dose of 90-180 mg/m^2 per cycle). It did not find a significant difference between IDA and high-dose DNR (relative risk [RR]=1.00 for CR, RR=1.01 for OS), although only two studies were included for the direct comparison.

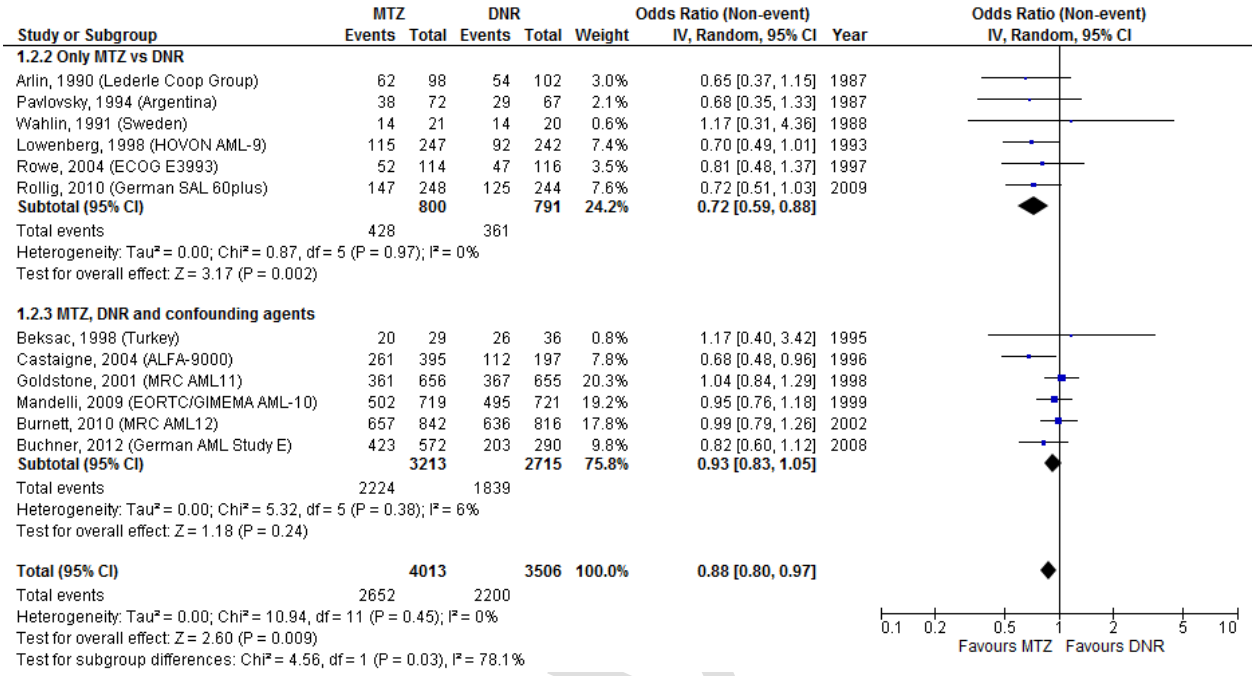
GIMEMA (50), JALSG AML201 (51), and Rubio Borja (52) found higher rates of early deaths with IDA (38% versus 22%, 4.7% versus 2.1%, 30% versus 20%, respectively), while ALFA-9803 (53) found similar induction deaths (9% versus 10%). Many trials reported adverse effects to be similar or were inconsistent. In the two largest trials (which included over 1000 patients each), the EORTC/GIMEMA AML-10 (49) reported similar grade 3 and 4 adverse events after induction, although less severe infections and other toxicities with DNR after consolidation, while the JALSG AML201 (51) reported higher rates of sepsis (8.7% versus 4.9%, p=0.02) with IDA.

Induction, Anthracycline Comparison: MTZ versus DNR

Trials comparing MTZ and DNR are included in Table 4-5. Six trials (159,190,198,200-202) directly compared MTZ + AraC with DNR + AraC, two trials made the same comparison but with etoposide in both arms (49,153,154), and one additional trial compared DNR + AraC to the same followed by MTZ + AraC (203). Three trials (69,196,204) compared MTZ with DNR but varied other agents as well (etoposide or amsacrine [AMSA] in one arm, different durations of AraC). A meta-analysis of the results for CR is shown in Figure 4-4. In studies comparing only MTZ + AraC with DNR + AraC, MTZ was found to give a better CR rate (OR=0.72, 95% confidence interval 0.59-0.88, p=0.002). Typically doses were 45 mg/m^2/day DNR and 12 mg/m^2/day MTZ.

Median survival was less than one year in most studies, with no consistent pattern regarding MTZ versus DNR. No significant survival differences were reported. There were no differences in adverse events that were found consistently among various trials.

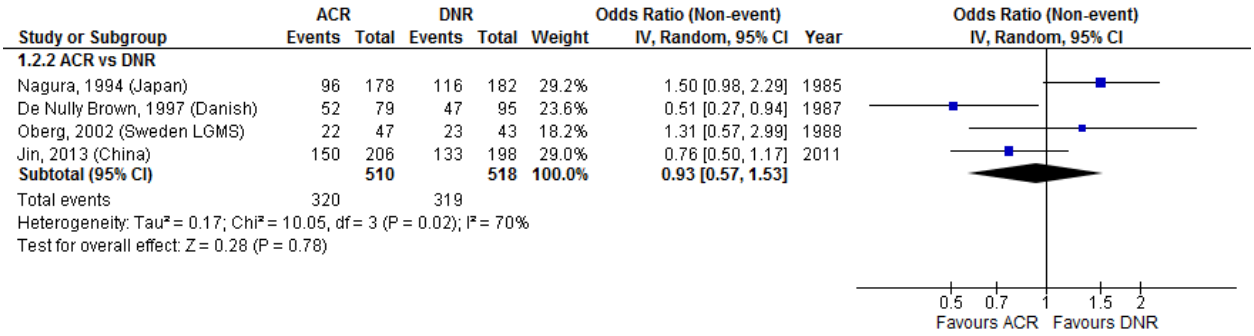
Figure 4-4. Meta-analysis of trials comparing complete remission rates with mitoxantrone versus daunorubicin



Induction, Anthracyclines other than IDA or MTZ compared with DNR

Trials comparing anthracyclines (other than IDA or MTZ) to DNR are reported in Table 4-6. Three trials compared aclarubicin (ACR) versus DNR (with AraC or BHAC in both arms) (54,55,205,206), and one additional trial compared ACR versus DNR (with AraC and homoharringtonine in both arms) (56). ACR was given at 14-80 mg/m^2/day. As seen from the meta-analysis displayed in Figure 4-5, the studies by The Danish Society of Hematology Study Group on AML (54) and Jin et al (56) showed better CR with ACR. The Sweden LGMS study (206) was conducted in an older group of patients (age ≥60 years) and found more early deaths with ACR (36% versus 16%). In contrast, the Danish study on AML found no difference in early deaths (24% versus 22%). They reported better CR with ACR for patients age 17 to 60 years (p=0.02) but not age 61 to 65 years, but they had reduced the dose by 33% in the latter group and suggested the dose may have been too low. No significant differences in survival were reported. The study by Nagura et al (205) is limited by the low dose of ACR (14 mg/m^2/day) and use of BHAC (which has been reported as inferior to AraC (168)). ACR appears to be effective but the optimal dose is not determined. A meta-analysis of CAG (cytarabine, aclarubicin, and GCSF) (374) found CR rates for CAG were 57.9% overall, 56.7% for de novo AML and 60.1% for relapsed/refractory AML. In seven trials which had comparison to historic results with non-CAG regimen (generally anthracycline + AraC), CR was 63% CAG versus 44% non-CAG (OR=2.43, confidence interval 1.52-3.88).

Figure 4-5. Meta-analysis of trials comparing complete remission rates with aclarubicin versus daunorubicin



Other anthracyclines compared with DNR included amsacrine (AMSA) (207), DaunoXome® (DNX; a liposomal formulation of daunorubicin) (208), and KRN8602 (KRN) (210). AMSA was found to result in more adverse events than DNR and there was no evidence of additional benefit compared to DNR. DNX compared with DNR in elderly patients (age >60 years) resulted in higher incidence of early deaths mainly due to infections (early deaths 12.5% versus 2.6% at six months, p=0.053) but better longer-term OS and DFS due to lower incidence of relapse beyond six months (59% versus 78% at two years, p=0.064). KRN was found to be of similar effectiveness (but not statistically significant due to the small number of patients, n=58) but with more central nervous system and gastrointestinal adverse events and fewer cardiotoxic adverse reactions.

Induction, Other Anthracycline Comparisons

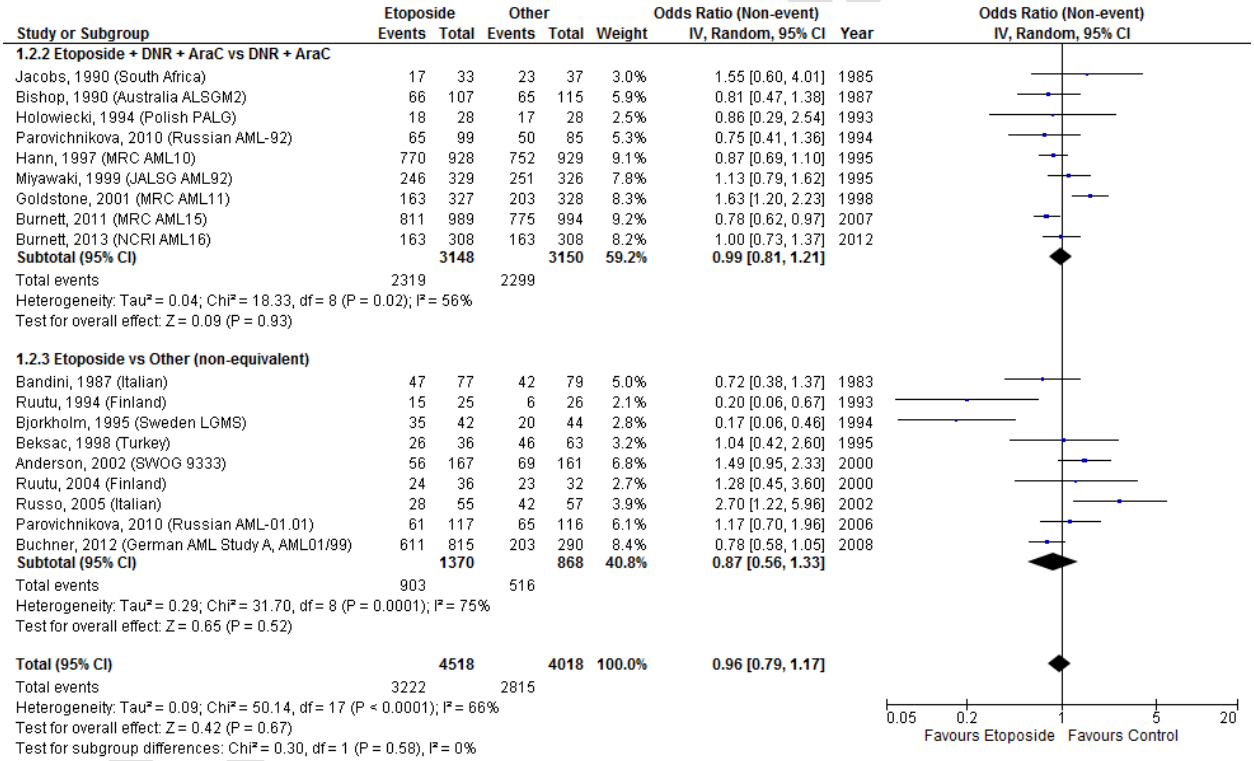
Trials that compared anthracyclines other than DNR are summarized in Table 4-7. Earlier studies (213-215,217) evaluated rubidazone, doxorubicin, and zorubicin compared with each other or IDA; lack of recent trials suggests they are no longer of interest. Studies comparing IDA and MTZ were inconclusive (190,204,216). A small trial suggested CPX-351, a liposomal formulation of cytarabine and daunorubicin (5:1 molar ratio) may be better than AraC + DNR (219), especially for secondary AML (s-AML) patients, and a larger phase III trial is planned. German AMLCG trials AMLCG 1985 (220,221), AMLCG 1999 (196,222), and AMLCG 2008 (230) compared various combinations for two courses of TAD [thioguanine + AraC + DNR] and HAM [high-dose AraC plus MTZ] and found no statistically significant differences. Survival data for the AMLCG 2008 trial are not yet available.

Induction, Etoposide

Nine trials evaluated the addition of etoposide to DNR + AraC (or BHAC in one trial) (see Table 4-8). Results of the meta-analysis for CR are shown in Figure 4-6. When all trials are included, the composite result is that etoposide has no effect on CR (p=0.93). However, the MRC AML10 and AML11, which are companion trials in patients ages <56 years and ≥56 years, respectively, reported opposing results. None of the other studies focussed on elderly patients. When the AML11 trial is removed, the meta-analysis shows a small but significant CR benefit for etoposide (OR=0.88, p=0.05). The AML11 trial in patients age ≥56 years found five-year OS better with DNR + AraC + thioguanine (DAT) than with DNR + AraC + etoposide (ADE). The Australia ALSGM2 trial found survival benefit for etoposide in the younger patients (age <55 years) but not older patients, although this was no longer noted with 10-year results. The MRC trials AML10 and AML15 were the largest trials and found no survival difference with the addition of etoposide.

Nine other trials included etoposide; however, there were also other differences in the arms so that the effect of etoposide alone is unclear. These are summarized in Table 4-8 and the second portion of the meta-analysis in Figure 4-6. Most showed no significant differences for the regimens tested. A small study by Ruutu et al (240) found oral etoposide + thioguanine + IDA to be better than intravenous DNR + AraC + oral thioguanine (CR 60% versus 23%, p=0.007; RFS median 9.9 months versus 3.7 months, p=0.042); however, the benefit may be due to IDA instead of etoposide. DNR was only given on day 5 compared with IDA on days 1 to 3. A small study by the Sweden LGMS found MTZ + etoposide + AraC much better than doxorubicin-DNA + AraC + thioguanine + vincristine + prednisolone (CR 83% versus 45%, p<0.001, median OS 28 months versus 13 months, p<0.03), but again this may be due to the choice of anthracycline (243). Fludarabine + AraC + IDA was found to result in higher CR rates (74% versus 51%, p=0.01) than IDA + AraC + etoposide and with fewer adverse effects; long-term survival was not significantly different (8).

Figure 4-6. Meta-analysis of trials comparing complete remission rates with etoposide versus other treatments



Induction, ATRA

Table 4-9 includes five trials that evaluate ATRA. The trial by Estey at MD Anderson (244) and two trials by Burnett et al (MRC AML12, NCRI AML16) (153,154,249) found no benefit for ATRA, while two trials by Schlenk et al (AMLSG AML HD98B (245,246), AMLSG 07-04 (247,248)) found benefit for ATRA. MRC AML12 was conducted in patients age <60 years, while AML16 was conducted in older patients (53 to 82 years, median 67 years). HD98B, conducted in older patients (age ≥61 years) reported significantly better CR, OS, EFS, and RFS with ATRA. When analyzed by subgroups, the OS and RFS benefit was found only for patients

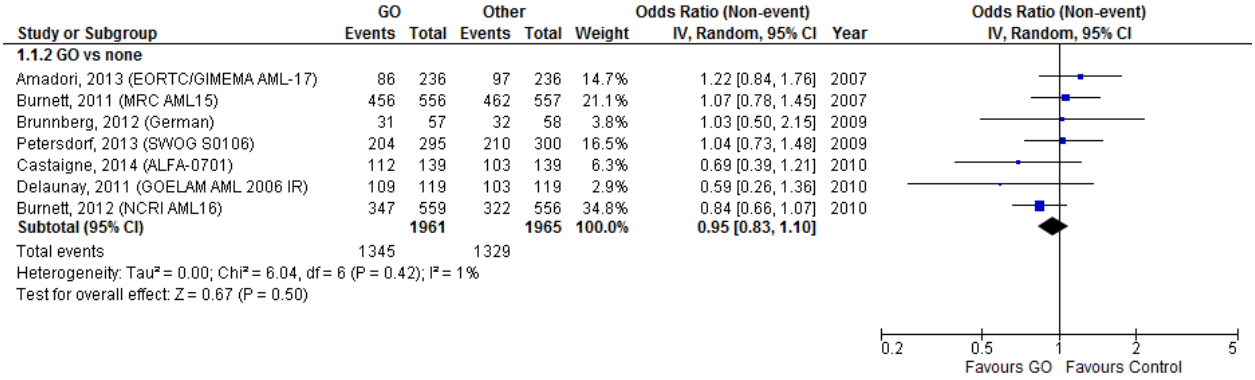
with mutant *NPM1*. The subsequent and larger AMLSG 07-04 trial in younger patients (age 18 to 60 years) found improved OS with ATRA, mainly attributed to ELN-favourable subtypes. The subgroup with *NPM1* mutation had improved CR and EFS in the ATRA arm, while ATRA resulted in no difference for the wild-type *NPM1* subgroup. The AML16 trial included 73 patients with *NPM1* mutants (ITD WT) compared with 289 patients with *NPM1* mutations in the German AMLSG 07-04 trial; the AML16 trial did not find differences with ATRA for subgroups and was likely underpowered for this. Both these trials are recent and not yet fully published.

Induction, Gemtuzumab Ozogamicin

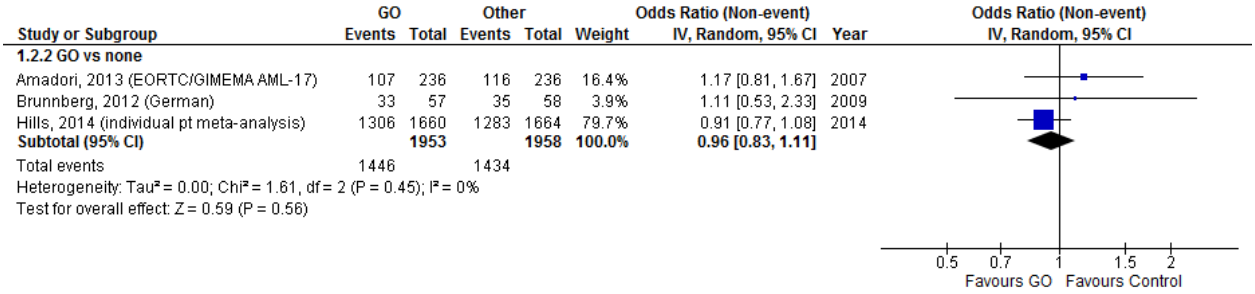
Trials evaluating the use of GO are summarized in Table 4-10. The NCRI AML17 trial compared GO 6 mg/m^2 (day 1) versus GO 3 mg/m^2 (62) and found no benefit of the higher dose compared with the lower dose. Six trials, namely ALFA 0701 (60), EORTC/GIMEMA AML-17 (64), GOELAM AML 2006 IR (3), MRC AML15 (6), NCRI AML16 (58), and SWOG S0106 (63), compared chemotherapy with or without GO, while a German study (4) compared AraC + GO with AraC + DNR. A recent individual patient data meta-analysis by Hills et al (57) included five of these trials, omitting the EORTC/GIMEMA AML-17 trial (64) and the trial by Brunnberg et al (4) (the latter because GO was compared with DNR instead of being added to AraC + DNR). A meta-analysis by Kharfan-Dabaja et al (59) included all of the seven trials. The meta-analysis by Loke et al is the most recent and included six trials (132). It included fewer patients for some of the trials than did the individual patient meta-analysis and did not subgroup by dose, and therefore will not be discussed further. While longer-term follow-up (three-year instead of two-year data) is now available for the ALFA 0701 trial, this is not expected to make a large difference in the overall analysis. Published meta-analyses are evaluated as being high quality and will be referred to instead of conducting new meta-analyses for survival outcomes. For the current review, meta-analysis was conducted for CR outcome, as indicated in Figure 4-7a. Hills et al used CR with or without complete peripheral count recovery (CR + CRp) instead of CR; however, as indicated in Figure 4-7b which is based on data from the review by Hills et al plus the two other studies, there was no significant difference in CR (or CR + CRp) with or without GO. Kharfan-Dabaja et al did not report on CR as an outcome.

Figure 4-7. Meta-analyses of trials comparing complete remission rates with and without GO

a) CR in all trials



b) CR + CRp as reported in the Hills et al meta-analysis plus additional trials



The review by Hills et al included individual patient data not available from the publications, while Kharfan-Dabaja et al calculated outcomes from survival curves. Hills et al reported 30-day mortality to be worse with GO (OR=1.28, p=0.08). Kharfan-Dabaja et al reported early therapy-related deaths (induction death or 30-day mortality) to be worse (HR=1.60, P=0.02). For the two large trials AML15 and AML16, which used a single dose of GO at 3 mg/m^2, there was no difference in 30-day mortality (HR=1.09, p=0.6), while 6 mg/m^2 GO (SWOG S0106 and GOELAM AML 2006 IR) resulted in much worse 30-day mortality (HR=2.79, p=0.007). Both meta-analyses found GO improved RFS (OR=0.84; p=0.0003 and p=0.04). The individual patient meta-analysis calculated five-year OS as 35.6% GO versus 32.2% control (p=0.01) and six-year OS as 34.3% versus 30.6%. Overall, they found HR=0.90 (confidence interval 0.82-0.98), with benefit for the subgroup at 3 mg/m^2 (p=0.02) but not 6 mg/m^2 (p=0.9). In contrast, Kharfan-Dabaja et al found no significant difference in OS (HR=0.95, confidence interval 0.83-1.08, p=0.42). The difference is mainly due to the inclusion of the EORTC/GIMEMA AML-17 trial which used GO at 6 mg/m^2 (days 1 and 15) and resulted in worse OS overall and for patients age ≥70 years. This trial found GO improved survival in patients with s-AML age <70 years. Hills et al looked at OS in subgroups with favourable, intermediate, and adverse cytogenetics and found five-year OS of 77.5% versus 55.0% (p=0.0006), 40.7% versus 35.5% (p=0.005), and 9.1% versus 7.9%, p=0.9, respectively. Projected numbers for six-year OS were 75.5% versus 54.8%, 39.6% versus 33.9%, and 8.9% versus 6.7%.

A prognostic factor analysis of CBF-AML patients from the MRC/NCRI trials (250) found use of GO induction (HR=0.40, p<0.0001), performance status, and age to be significant factors in multivariate analysis of survival. FLT3 and NPM1 mutation status had no effect. The ALFA-0701 trial (5) found stronger GO benefit in patients with cytogenetically normal AML, and in patients with genetics that were favourable/intermediate.

Induction, GCSF or GM-CSF

Twenty-seven trials evaluating CSF are included in Table 4-11. Of these, three were included in a meta-analysis by Sung et al (71), eight in a meta-analysis by Heuser et al (72), and thirteen in both. While these reviews were published in 2009 and 2011, only three small trials from the current literature search (253,256,257) were not included in these other reviews. As the reviews by Sung et al and Heuser et al were found to be comprehensive and evaluated to be of high quality, additional meta-analysis was not conducted. Table 4-11 includes data for all the trials, including some additional details not reproduced in the other reviews. Sung concluded CSF priming does not improve outcome and should not be used in routine clinical care. The review by Heuser et al included more studies primarily because it included both trials with CSF given prophylactically after chemotherapy and those with CSF administered concurrently with chemotherapy. While these two subsets were reported

separately, both analyses found no differences in CR rates, DFS/EFS, or OS. Prophylactic CSF reduced neutrophil recovery time and length of hospitalization but not survival. The Cochrane Collaboration (130) prepared a recent systematic review on CSF in AML with a focus on prevention and treatment of infectious complications and included 19 trials; as such, they specifically excluded nine studies of CSF priming (before and/or only for the duration of chemotherapy). They found CSF added to chemotherapy gave no difference in all-cause 30-day mortality (RR=0.97), OS (HR=1.00), DFS (HR=1.00), or CR (RR=1.03). An individual patient meta-analysis (referred to in an analysis of MRC AML11 and AML12 trials (254) but not published) found neither benefit nor harm for endpoints of CR, DFS, or OS.

Induction, Agents not in other Tables

Table 4-12 contains data from 30 randomized trials of induction that do not readily fit into the previous subsections. Many of these are recent trials of promising agents, and as such do not appear in older reviews or guidelines.

One trial (285) compared one cycle of FLAM (flavopiridol + AraC + MTZ) to AraC + DNR (two cycles allowed for patients without CR, but only given to approximately one-half the patients in this category) and found significantly better CR in the flavopiridol arm (70% versus 46%, p=0.003 overall); FLAM resulted in higher CR than one cycle AraC + DNR for all subgroups. Differences were less when evaluating after two cycles AraC + DNR, although still suggestive of FLAM benefit. Toxicities were similar in both arms and a phase III trial is planned.

Homoharringtonine and the related semi-synthetic derivative omacetaxine have been studied and widely used in China. Many of the studies are published in Chinese, are not indexed in MEDLINE or Embase, and English-language reports are not readily available. The reader is referred to two recent reviews (133,134) that cover this literature. The meta-analysis of Chinese studies published from 2006 to 2013 included five RCTs, 13 single-arm retrospective trials and three retrospective trials comparing two regimens (133,134). It concluded that homoharringtonine is effective, with overall CR rate of 65% (69% in randomized trials, 63% in retrospective studies, 47% in studies exclusively with elderly patients). The other review (133) gives a comprehensive background although does not appear to include a systematic review. It included three RCTs prior to 2006 and therefore not included in the meta-analysis, plus one recent RCT (also found in the current literature search) which is described below. Both reviews suggested large phase III RCTs are warranted.

While homoharringtonine has been studied and used in China, results are now available for a large randomized multicentre study (56) comparing homoharringtonine + AraC + ACR (HAA) versus homoharringtonine + AraC+ DNR (HAD) versus DNR + AraC (DA). HAA was significantly better than DA for CR, EFS, and RFS; differences between HAD and DA were smaller and not statistically significant (CR 67% versus 61%, p=0.20; EFS 32.7% versus 23.1%, p=0.08). Adverse events were similar except for more early deaths in the homoharringtonine arms (5.8% HAA, 6.6% HAD, 1% DA). Benefit was greatest in the subgroup with favourable cytogenetics.

Lomustine, a multi-kinase inhibitor, was studied in the GOELAM BGMT-95 trial (82,83) in patients age ≥60 years. The trial was only powered to detect 15% increase in CR and 20% increase in OS and therefore most results are not statistically significant. It suggested improvement in CR (p=0.055 after one course; p=0.104 overall), especially in patients with adverse cytogenetics (p=0.074 adverse cytogenetics subgroup; p=0.286 favourable/intermediate subgroup). Median OS was longer (12 months versus 7 months, p=0.05), although the improvements in two-year OS and EFS were not statistically significant

(31% versus 24% and 22% versus 18%, respectively). A trial of lomustine during induction plus consolidation (LAMSA 2007, NCT00590837) is completed but not yet published[3].

Another multi-kinase inhibitor, midostaurin, is being evaluated in patients age 18 to 60 years with FLT3 mutations in the CALGB 10603/RATIFY trial; results have not yet been reported.[4]

Lestaurtinib was evaluated in NCRI AML15 and AML17 trials (286) in FLT3-mutated AML. No differences in CR or survival were found and there were minimal differences in toxicity compared with the control group. Stratified subgroup analysis suggested survival benefit in patients with concomitant azole treatment (p=0.02) and in patients treated with GO plus azole (p=0.02). This needs to be confirmed in prospective studies.

The AMLSG 12-09 (280) and German SAL AML-AZA trials (281) studied azacitidine (AZA) use. AZA replacing AraC and given prior to or concurrent with etoposide + IDA resulted in worse CR, while giving after etoposide + IDA did not improve CR. Addition of AZA prior to standard induction and maintenance (AraC + DNR) did not improve CR, OS, or EFS overall; authors suggested trends in DNMT3A subgroup should be explored further. The AZA-AML-01 trial compared AZA (75 mg/m^2/day subcutaneously [sc], 7 consecutive days per 28-day treatment cycle, at least 6 cycles) to standard intensive therapy (AraC + either DNR or IDA) in patients age ≥65 years (145,146). The study found no significant difference in response or survival between AZA and standard induction. Red blood cell transfusion independence rates with AZA versus intensive chemotherapy were 57% versus 35%, while grade 3-4 treatment-emergent adverse event rates were similar (anemia 12% versus 14%; neutropenia 30% versus 33%; febrile neutropenia 33% versus 31%; thrombocytopenia 23% versus 21%; and any infections 49% versus 50%). This small study (n=87 in relevant subgroups) suggests AZA alone may be an option in elderly patients who are fit for intensive chemotherapy but choose not to receive it.

Two trials with sorafenib were conducted by the German Study Alliance Leukemia (SAL). In patients age 18 to 60 years (290), sorafenib significantly improved 3-year EFS (40% versus 22%, p=0.013) and RFS (56% versus 38%, p=0.017); OS was 63% versus 56% (p=0.38). Risk of fever, bleeding events, and hand-foot syndrome were higher in the sorafenib arm[5]. In the second trial, conducted in patients age >60 years (292), CR, OS, and EFS were lower with sorafenib (not statistically different) and there were more adverse events including grade 3 infections and early deaths (17% versus 7%, p=0.052).

[3] Note the LAMSA 2007 results were released (subsequent to this review) as an abstract at the ASH conference in December 2015 (305); the reported information has been added to Table 4-13 (ongoing trials). The trial was conducted in elderly patients (age > 60 years) without unfavourable cytogenetics and found the lomustine group had lower primary resistance and relapse, higher rate of CR + Cri, and better EFS; OS appeared improved though the difference was not statistically significant.

[4] Subsequent to external review of this document, results were reported at the December 2015 ASH conference (303). The abstract indicates that midostaurin significantly improved five-year EFS (26.7% vs 19.1%, p=0.0044) and OS (50.8% versuss 43.1%, p=0.007) and the effect was consistent across all FLT3 subgroups. Results have been added to Table 4-13 (ongoing trials).

[5] At the time of this review results were published only as an abstract. Full results were published subsequent to external review (305). Results reported in the previous abstract have not changed though additional information was reported and has been added to Table 4-12.

While cyclosporine A was found to have benefit in the Hellenic trial (74) and SWOG 9126 trial (75), these trials were small and included narrow subgroups of patients. Later studies with next-generation agents such as PCS-833 (valspodar) (76-80) and zosuzuidar (81) did not confirm these results. PSC-833 (76-80) use resulted in more serious adverse effects and either no difference or worse CR and survival outcomes. Vincristine (297) resulted in significantly worse CR and EFS. Amonafide (282) and bevacizumab (283) resulted in increased adverse effects without improvement in CR or survival. No benefit was found for interleukin (IL)-11 (73), lisofylline (287), quinine (288,289), topotecan (296), thalidomide (296), valproic acid (247,298), or zosuquidar (81).

2. What is the most effective systemic post-remission treatment (consolidation and/or maintenance, excluding stem cell transplant) for adults with previously untreated AML?

For this question it is assumed that patients have received induction treatment and remain in remission. Question 3 deals with AML that is refractory to induction or experience relapse. While there is overlap in terminology, consolidation is generally used soon after completion of induction therapy for a limited number of cycles (often two to four cycles), while maintenance therapy is given following consolidation and/or for an extended duration. Where possible, trials have been classified according to the terminology in the original publications. Trials with randomization to consolidation treatment are summarized in Table 4-14, trials randomized to both consolidation and maintenance or those comparing consolidation to maintenance are summarized in Table 4-15, and trials comparing maintenance regimens are summarized in Table 4-16. Some ongoing studies are indicated in Table 4-17.

Induction treatment and CR rates help to define the population being studied and are reported in the tables for this purpose; CR rates are not an outcome of post-remission treatment. Trials in which randomization is to both induction and post-induction treatment at the start, with post-induction treatment determined by the induction randomization group are considered to be primarily studies of induction, although more specifically are evaluation of a treatment pathway. These trials are included only in the induction tables (Tables 4-1 to 4-13).

Consolidation

Table 4-14 includes 25 trials of consolidation. Most consolidation regimens are similar to those used for induction, including use of AraC with anthracyclines, and in some trials the regimens used for induction are extended for additional cycles in patients with CR. It should be noted that HDAC was often given q12h while standard doses were given as continuous infusion. In the NCRI AML16 trial patients (generally age >60 years) were randomized to one course of DNR (50 mg/m^2/day) + AraC (100 mg/m^2 q12h) versus none. No differences in OS or RFS were found (67).

Three trials used AraC alone and compared various doses. A small study by Ahmad et al (307) in patients with known K-RAS status found AraC at 400 mg/m^2/day resulted in better DFS compared with 100 mg/m^2/day; the higher dose resulted in better OS for patients with mutant but not wild-type RAS. The CALGB 8525 trial (34) compared AraC at 100 mg/m^2/day versus 400 mg/m^2/day versus 3 g/m^2 q12h and found better OS and DFS with the highest dose. The benefit was found for patients age <60 years but not patients age >60 y; in the latter group only 29% could tolerate the high dose and 32% experienced serious central nervous system abnormalities at the high dose compared with none at lower doses. The MRC AML15 trial compared AraC at 1.5 g/m^2 q12h versus 3 g/m^2 a12h (6,7,172) and found no difference in

OS or RFS, although there were modest differences in hematologic toxicity; more supportive care and hospitalization occurred at the higher dose.

Studies also evaluated AraC dose when used together with DNR, MTZ, or IDA in patients age <65 years or age <60 years. The SAKK study (85) found 3 g/m^2 q12h AraC superior to 100 mg/m^2/day regarding OS, DFS, and EFS, although there were also more grade 3 adverse events (58% versus 21%). SWOG 8600 (161) did not find benefit for HDAC (2 g/m^2 or 3 g/m^2 q12h) compared with standard-dose AraC (200 mg/m^2/day), although they did reduce AraC dose (from 3 to 2 g/m^2) part way through the trial due to toxicity. The German SAL AML96 trial (88) found no benefit for AraC at 3 g/m^2 q12h compared with 1 g/m^2 q12h. When both AraC and IDA dose were varied (with MTZ in both arms), no significant differences were found for AraC 100 mg/m^2 q12h + IDA 12 mg/m^2/day compared with AraC 1 g/m^2 q12h + IDA 8 mg/m^2/day (308). The Australasian LLG AML7 study compared AraC 3 g/m^2 q12h with AraC 100 mg/m^2/day together with etoposide and IDA and found HDAC to be more toxic and without survival benefit (87).

The CALGB 8923 trial compared AraC alone at 100 mg/m^2/day with AraC at 500 mg/m^2 q12h + MTZ at 6 mg/m^2 q12h in patients age ≥60 years. It found the AraC/MTZ regimen to be more toxic but not more effective. The German SAL AML2003 compared HDAC alone (3 g/m^2 q12h) with AMSA + MTZ + AraC (1 g/m^2 q12h) and found the multi-agent treatment to be more toxic without improvement in survival (and with worse OS on a per protocol basis) (89). The CALGB 9222 trial compared HDAC with HDAC → etoposide + cyclophosphamide → diaziquone + MTZ + GCSF and found similar outcomes but more toxicity with the multi-agent regimen (90). The JALSG AML201 trial compared three courses of HDAC at 2 g/m^2 q12h to standard-dose combination chemotherapy with AraC at 100 mg/m^2/day (four courses: MTZ + AraC, DNR + AraC, ACR + AraC, etoposide + vindesine + AraC) (86). They found both were tolerated with no difference in OS, although HDAC resulted in better DFS in the subgroup with favourable cytogenetics.

In the JALSG GML2000 trial ubenimex added to combination chemotherapy improved DFS (p=0.014); OS was 32.3% versus 18.7% (p=0.111) (185). Macrophage-colony stimulating factor was found in the JALSG AML92 study to improve DFS and relapse rate in the age 15 to 29 years subgroup (66% versus 10%, p=0.013 and 34% versus 90%, p=0.013, respectively), although the differences were not statistically significant in the full population aged 15 to 70 years (41% versus 31%; 54% versus 71%) (310,311). Neutrophil and platelet recovery was significantly faster and time to finish consolidation therapy was shorter.

The EORTC/GIMEMA AML-13 compared ICE (IDA + AraC + etoposide) administered iv with ICE administered with IDA and etoposide orally and AraC sc and found no significant difference in antileukemic effect (313). The non-infusional arm resulted in more vomiting and diarrhea but shorter platelet recovery and less hospitalization.

A common regimen of consolidation supplemented by additional cycles of IDA + AraC + etoposide (MRC AML14) (76,77), AraC + IDA (GOELAM BGMT-95) (82,83), or ACR + vincristine then DNR + AraC then AMSA + AraC (84), or six to eight cycles in which AraC was intensified (HDAC) in two courses (306) did not improve outcomes. The MRC AML12 trial gave three cycles consolidation with AMSA + AraC + etoposide (MACE) then randomized to MTZ + AraC (MidAC) versus IDA + AraC + etoposide (ICE) then MidAC and found no differences in survival (153). The MRC AML15 trial compared MACE→MidAC versus AraC (1.5 g/m^2 q12h) versus AraC (3 g/m^2 q12h) (6,7,172). There were no significant differences in OS or RFS between MACE/MidAC and AraC (1.5 or 3.0 g combined), but MACE/MidAC was associated with more toxicity and myelosuppression, and slower neutrophil and platelet recovery. MACE/MidAC resulted in superior OS in patients with adverse-risk cytogenetics (OS 39% versus 0%, p=0.0004; deaths OR=3.17 favouring MACE/MidAC), although this was based on only 54 patients.

The New Zealand AML-1 trial compared DNR + AraC with etoposide + AMSA and found no difference in survival or relapse, although there was more frequent vomiting and longer duration of severe neutropenia with etoposide + AMSA (312).

The MRC AML15 trial compared MACE→MidAC versus AraC (1.5 g/m^2 q12h) versus AraC (3 g/m^2 q12h), all with or without GO (6,7,172). GO added during consolidation was of no benefit. The HOVON 43 trial (46) found no significant benefit to using GO alone for consolidation.

The ongoing ALFA-0702/Clara trial (347) compared consolidation with three cycles HDAC (3 g/m^2/12 h AraC) to clofarabine (30 mg/m^2/day) + AraC (1 g/m^2/12 h) (see Table 4-17); results were presented at the December 2015 ASH conference.

Consolidation and Maintenance

Trials summarized in Table 4-15 randomized patients to consolidation versus maintenance, or to a combination of consolidation and maintenance versus maintenance or consolidation alone. Interpretation of several of these trials is unclear because consolidation was not the same in all arms.

The EGOG EST 3483 trial studied one cycle consolidation versus two years maintenance (AraC + thioguanine) versus observation alone (321,322). Observation was inferior to maintenance (OS 23% versus 45%, remission at two years 0% versus 16%) and was discontinued. Consolidation resulted in improved OS and EFS compared with maintenance, although this was statistically significant only for EFS in patients age <60 years (EFS 27% versus 16% overall, p=0.068; EFS 28% versus 15%, p=0.047 age <60 years).

The MRC AML9 trial compared two courses DAT alternating with either two courses MAZE (AMSA, AZA, etoposide) or two courses COAP (cyclophosphamide, vincristine, AraC, prednisone); patients still in CR were again randomized to one year maintenance (AraC + thioguanine then COAP) or none (156). They concluded MAZE gives better control (lower relapse rate) but is more toxic, while maintenance conferred no advantage.

The AMLSG AML HD98B trial (245,246) compared IDA + etoposide administered iv for one cycle (intensive; IDA 12 mg/m^2/day for two days; etoposide 100 mg/m^2/day for five days) to oral maintenance for one year (IDA 5 mg/m^2/day for five days; etoposide 100 mg/m^2/day for two days for 12 courses) and found OS and cumulative incidence of relapse were better for intensive consolidation (p<0.001 and p=0.002).

In the Southeast Cancer Study Group trial (314) and JALSG AML97 trial (315), adding maintenance did not significantly improve outcomes. MRC AML11 compared one to four courses consolidation, as well as interferon-alfa maintenance, and found no significant differences (69).

In the ALFA-9802 trial (276,277,316,317), four cycles HDAC followed by four cycles maintenance resulted in similar survival compared with consolidation with one cycle AMSA then one cycle etoposide + MTZ + AraC, although HDAC was significantly better for EFS in patients with intermediate or normal cytogenetics, as well as OS for intermediate-risk cytogenetics. Severe adverse events were less in the HDAC arm. In the same trial, GCSF was also found to improve EFS in patients with intermediate-risk cytogenetics.

In ALFA-9803 study consolidation (one cycle AraC + DNR) was compared with outpatient maintenance (DNR or IDA + AraC over six months) (53,318) in patients age ≥65 years. Outpatient maintenance resulted in better OS and DFS as well as shorter hospitalization and fewer transfusions. No effect was seen in the subset age 65 to 70 years, but this may be due to the small number of patients.

The EORTC/GIMEMA AML8B trial (319) found that standard consolidation and maintenance (AraC 200 mg/m^2/day + DNR), compared with intensive consolidation (AraC 500 mg/m^2 q12h + AMSA then AraC 2 g/m^2 q12h + DNR), resulted in no difference in OS or RFS but less treatment related mortality and toxicity; the intensive arm had lower four-year relapse

(55% versus 75%, p=0.0003). The trial was stopped early due to the adverse effects in the intensive arm.

The German AMLCG 1992 study gave one cycle consolidation with AraC + DNR + thioguanine (TAD) to all patients, then randomized to monthly maintenance (AraC all courses; plus DNR course 1, thioguanine (TG) course 2, cyclophosphamide course 3, TG course 4) versus one course of intensive consolidation (AraC + MTZ [S-HAM]) (320). They found maintenance resulted in better six-year RFS overall (31.4% versus 24.7%, p=0.0118) and for subgroups age 16 to 60 years or poor risk; for age ≥60 years RFS was 18% versus 7% (p=0.1001). Differences in OS were not statistically significant (six-year OS 25% versus 22%, p=0.159). Freedom from relapse at five years was 39% versus 50% (p=0.664) in good-risk patients and 29% versus 17% (p=0.0092) in poor-risk patients.

Maintenance

Table 4-16 includes 29 trials of maintenance, of which 18 compare maintenance with no maintenance. Four trials compared AraC with none. The Memorial Sloan Kettering L-19 trial suggested OS benefit, but included only 12 patients (192,194). HOVON AML-9 (198) and AML-11 (199) trials in patients age >60 years found no difference in OS, while the AML-9 trial found improved three-year and five-year DFS with AraC, and combined analysis of the two trials found improved DFS as well.

IL-2 as maintenance therapy was evaluated in the ALFA-9801 (181), CALGB 9720 (332), CALGB 19808 (331), and EORTC/GIMEMA AML-12 (EORTC 06991) (40,165) trials; overall they found small and inconsistent effects. An individual patient meta-analysis (139) included these trials along with a small trial of IL-2 after transplant (375) and the CCG-2961 trial in children (376). It concluded that IL-2 alone is not an effective remission maintenance therapy. It had access to unpublished data (except EORTC/GIMEMA AML-12 as it had only been published as an abstract) and therefore could also look at various possible subgroups or factors and found no benefit by age group (<21 years, 21 to 60 years, >60 years), sex, ECOG performance status, karyotype, or AML subtype. While five-year data are now available for EORTC/GIMEMA AML-12 and CALGB 19808 (instead of three-year data used in the meta-analysis), this is not expected to change the conclusions. The MP-MA-0201 trial (91-94) was not included in the meta-analysis as it used IL-2 and histamine dihydrochloride together compared with none and, therefore, the effect of either agent alone could not be determined. This trial found three-year and six-year leukemia-free survival (LFS) improved with IL-2 + histamine both overall and in the subgroup of patients in first CR, but not those in subsequent CR. Differences in OS were not statistically significant. The study was not powered to detect OS benefit. A Bayesian meta-analysis (138) concluded that there is a 99% probability of benefit of IL-2 + histamine dihydrochloride and there is 96% probability that this combination is superior to IL-2 alone. The German AMLSG/SAL trial (333) found no difference between IL-2 doses of either 9×10^6 IU/m^2 or 0.9×10^6 IU/m^2.

In JALSG [Japan Adult Leukemia Study Group] trials ubenimex was found to improve OS when given after induction (overall and in patients age >50 years but not <50 years) (328), but did not improve DFS when given after other consolidation and maintenance (168).

Maintenance with GO in the SWOG S0106 trial found GO did not improve DFS (63).

Thioguanine improved OS (median 28 months versus 16 months) in a trial by Lofgren et al (275) but there were only 30 patients and the publication indicates no conclusions can be made.

In the SECSG trial with patients age ≥51 years (207), DNR + AraC had negative effect on OS and RFS. In the GIMEMA GSI 103 AMLE trial with patients age >60 years (208) ATRA + AraC did not significantly impact OS (HR=0.73, p=0.17). In the German AMLCG 1981 study (323-326) with patients age ≥16 years, AraC combined with DNR, TG, or cyclophosphamide in

alternating cycles improved OS and remission duration. The Russian AML-06.06 trial (176,177,327) found AraC + mercaptopurine decreased probability of relapse (50% versus 83%, p=0.07).

SWOG S8124 (334) treated patients with consolidation and late intensification then randomized to maintenance (or not) with the combination vincristine + prednisone + TG + AraC. Maintenance reduced the risk of death or relapse, although the effects on seven-year OS and seven-year EFS were not statistically significant (37% versus 31%, p=0.14 and 29% versus 26%, p=0.18, respectively).

Two trials evaluated duration of maintenance therapy. The JALSG AML87 trial found 12 courses maintenance resulted in better DFS than four courses (297). Jacobs et al found 15 months maintenance resulted in longer remission duration (35 weeks versus 24 weeks) compared with 6 months of maintenance (233), although the regimens were not the same.

The GOELAM SA-2002 study (335) found addition of the androgen norethandrolone added to maintenance (IDA + AraC+ methotrexate + 6-mercaptopurine) improved OS in the subgroup in CR and alive at one year. Differences in OS, EFS, and LFS were not statistically significant.

Addition of bestatin to maintenance (vincristine, cyclophosphamide, 6-mercaptopurine, prednisolone alternating with BHAC-DMP) improved OS and remission duration (p=0.021 and p=0.16, respectively) (336).

SWOG 7823 (213) compared continued maintenance (vincristine, AraC, and prednisone extended from 9 to 12 months) or three courses late intensification (mercaptopurine, vincristine, methotrexate, prednisone) and found better OS and DFS with late intensification but also more severe or life-threatening toxicities (60% versus 21%, p<0.0001). Late maintenance with levamisole had no significant effect on OS or DFS.

EORTC AML-6 (337) randomized patients to six courses at six week intervals of either continued treatment with DNR + vincristine + AraC (same as induction/consolidation) or with AMSA + alternating HDAC or AZA and found adverse effects in the AMSA arm and no difference in DFS.

GIMEMA LANL 8201 (338) found no difference in DFS or OS between no further treatment, 18 courses maintenance (AraC + TG) or intensive post-consolidation treatment (two courses each etoposide, TG, DNR, with AraC in all courses) in patients with sufficiently intensive induction + consolidation.

Small trials (<50 patients) found higher relapse with decitabine compared with low-dose AraC (339); no difference in OS or DFS with DNR + vincristine + AraC compared with HDAC + AMSA + alternating AZA or AMSA (340); and no significant differences in OS, remission duration, or RFS with interferon compared with AraC + TG (341). Improved DFS and probability of remaining in remission was found with AraC + ACR alternating with 6-mercaptopurine and methotrexate (daily stanazol throughout) compared with etoposide + AMSA then ACR + AraC then vincristine + 6-mercaptopurine then methylprednisolone + methotrexate (342).

3. What is the most effective systemic treatment (reinduction, consolidation, maintenance; not including stem cell transplant) for adults with relapsed or refractory AML?

Results for 38 trials conducted in patients with relapsed or refractory AML are summarized in Table 4-18. Most of these are trials involving randomization to reinduction therapy. Two trials randomized patients to maintenance therapy if they had CR to second (non-randomized) induction, five trials randomized patients to reinduction + consolidation,

and one trial randomized patients to reinduction + maintenance. Most of the agents evaluated for reinduction are the same as used in the induction trials (see Question 1). The most common design is adding additional agents to AraC (with or without an anthracycline).

The VALOR trial (369,370) evaluated use of vosaroxin (with AraC in both arms) and found improved CR (30.1% versus 16.3%, p=0.00001) and OS (median 7.5 months versus 6.1 months, p=0.06, adjusted p=0.02; censored for ASCT 6.7 months versus 5.3 months, p=0.03; age ≥60 years, 7.1 months versus 5.0 months, p=0.003; but not for age <60 years, 9.1 months versus 7.9 months, p=0.6). Mortality at 30 days was slightly higher (7.9% versus 6.6%) while 60-day mortality was 19.7% versus 19.4%. The study has only been published as abstracts.

A German AMLCG trial compared AraC at 3 g/m^2 q12h (days 1, 2, 8, 9) versus 1 g/m^2 (age <60 years) or 1 g/m^2 versus 0.5 g/m^2 (age >60 years), using MTZ in all arms (98). With the patients age <60 years, the higher dose resulted in better CR (52% versus 45%, p=0.01) but also more early deaths primarily due to infections. It was suggested outcome could be improved with better supportive care. HDAC benefit was greater in patients age <60 years with refractory AML or with early relapse (CR 46% versus 26%, p=0.05). In patients age >60 years there was no difference in CR; however, there was less difference in doses of AraC used. The ELP1001 trial (348) also found higher rate of CR with higher dose AraC together with cenersen + IDA (CR 21% versus 14% versus 8% for 1 g compared with 100 mg or none, significance not indicated) but also more adverse events.

In the Classic I trial (102), clofarabine compared with placebo (both followed by AraC) improved CR rate and EFS but not OS, with higher rates of serious adverse events (60% versus 49%, primarily infections and deaths). In another German AMLCG trial (104), fludarabine when added to AraC + IDA resulted in higher CR, OS, and RFS, although the differences were not statistically significant. Non-response was 26% versus 37% (p=0.054), and this was significant in younger patients (age <60 years, 24.2% versus 39.5%, p<0.05). Fludarabine was associated with more adverse events (bleeding, nausea/vomiting, pulmonary effects). Comparison of clofarabine versus fludarabine (IDA and AraC in both arms) at the MD Anderson Center (105,106) found CR rates of 43% versus 30% (ns) and 32% versus 25% in two studies. Clofarabine resulted in worse four week mortality (16% versus 4%), more infections (47% versus 35%, ns), and fewer grade 3 and 4 toxicities. Accrual of the second study is continuing. In the UK MRC AML-HR trial (101), fludarabine + HDAC versus DNR + AraC + etoposide resulted in no difference in CR, DFS, or relapse rate; however, four-year OS was 16% fludarabine/HDAC versus 27% DNR/AraC (p=0.05). Authors suggested the fludarabine regimen may be inferior but sufficient enrolment as indicated in powered calculations was not reached. Elacytarabine compared with investigator choice from seven common salvage regimens was found to have no clinically meaningful advantage (361).

Several trials compared anthracycline use. A Leukemia Intergroup trial (349) found AMSA following HDAC resulted in much better CR (60% versus 19%, p=0.01) than HDAC alone but also more severe toxicities. Median OS was six months versus two months (p=0.08). Comparison of AMSA versus IDA (decitabine in both arms) found higher CR rate with IDA (45.5% versus 26.7%) but more grade 3 and 4 toxicity; the authors indicated the study was too small (n=63) to allow conclusions (350). A comparison of AMSA versus MTZ (AraC in both arms) found no statistically significant difference in CR (46% versus 58%, p=0.42) or OS (median 8 months versus 12 months, p=0.33), but that MTZ was better tolerated (97). Pirarubicin was found to result in better CR than MTZ (79% versus 56%, p=0.035; etoposide + AraC in both arms) but with no difference in OS, RFS, and with less requirement for transfusions (351). Comparison of IDA versus MTZ (carboplatin in both arms) found no differences in CR, OS, or DFS (352). All these studies are relatively small (36 to 63 patients) and therefore apparent benefits need confirmation. The SWOG 8326 trial (353) evaluated HDAC ± MTZ and HDAC ± AMSA. The AMSA arm was closed early due to excessive toxicity (induction toxicity 29% AMSA

versus 11% MTZ versus 7% HDAC alone). MTZ resulted in better CR than HDAC alone (44% versus 32%, p=0.15, adjusted p=0.013) although no significant differences in OS or RFS. The study was powered to detect a difference in CR and the authors suggested survival conclusions were limited by the small number of patients (n=162).

Comparison of lomustine with placebo (with HDAC in both arms) found better progression-free survival (PFS) with lomustine (median 54 days versus 34 days, p=0.002) but higher 30-day mortality (11% versus 2%, p=0.016) and other serious adverse events (74% versus 51%, p<0.001) such that OS was lower (median 128 days versus 176 days, p=0.087) (364). CR + CRp was better with lomustine (35% versus 19%, p=0.005); CR was similar overall, although better with lomustine in patients age ≥60 years and worse in patients age <60 years. The study was stopped early due to treatment-related mortality and the authors suggested alternative doses or schedules should be explored to reduce toxicity.

CPX-351 compared with investigator choice (generally AraC + anthracycline) (358) resulted in better but not significant improvement in CR (37% versus 32%), OS (p=0.19; p=0.02 for poor-risk subgroup), and EFS (median 4 months versus 1.4 months, p=0.08). CPX-351 patients had better 60-day and 90-day mortality; the data overall suggest possible benefit but a need for further study.

Three trials evaluated cyclosporine A (CsA) use. CsA added to AraC + DNR + etoposide in the UK MRC AML-R trial (100) or to MTZ + etoposide in the HOVON trial (359) had no benefit (and worse outcome for patients age >60 years in the MRC trial). In contrast, the SWOG 9126 trial (75) found adding CsA to AraC + DNR improved OS, RFS, and rate of resistant disease; CR was better after one course (38% versus 26%, p=0.032) but not significant after all courses (39% versus 33%, p=0.14). Effect was greatest in subgroups P-glycoprotein positive (CR 46% versus 26%; median RFS 17 months versus 7 months). It was suggested CsA reduces resistance to DNR.

Etoposide added to low-dose AraC (10 mg/m^2 q12h sc) + ACR + GCSF (95) resulted in improved CR overall (p=0.0002) and age <60 years (p=0.004) but the results did not reach statistical significance for those age >60 years (50% versus 31%, p=0.16). CR was better with etoposide for unfavourable-risk patients (60% versus 37%, p=0.009), while benefit was not statistically significant for standard-risk patients (81% versus 65%, p=0.12) and favourable-risk patients (93% versus 85%, p=0.50). There was no difference in five-year OS or grade 3 and 4 adverse events. A SECSG study (96) found etoposide added to HDAC improved OS for patients age <50 years (p=0.036), while there was no effect on DFS. CR rates were 38% versus 31% (ns).

In two JALSG trials, GCSF made no difference in EFS or DFS, while CR appeared improved (54% versus 42% and 57% versus 39%) but statistical significance was not reported (362,363). GCSF did not improve CR, OS, DFS, or relapse rate in the UK MRC AML-HR trial (101). In the EMA91 trial, GM-CSF (in combination with MTZ + etoposide + AraC) resulted in PFS of 33% versus 19% (p=0.08); differences in CR, OS, and DFS were not statistically significant (99).

AEG35156 (with HDAC + IDA) did not improve remission; AS1411 (with HDAC) was suggested to improve CR (21% versus 5%) (355) but a planned subsequent trial was terminated (356); and ATRA (with IDA + AraC) was found to have no advantage (357). ATRA did not improve CR, OS, DFS, or relapse rate in the UK MRC AML-HR trial (101). Lestaurtinib (with chemotherapy, either MTZ + etoposide + AraC or AraC alone) was found to have no benefit in CR or OS in the Cephalon 204 trial (365). Quinine (together with MTZ + AraC) had no benefit for CR in a GOELAM trial (366). Lintuzumab (with MTZ + etoposide + AraC) resulted in no difference in CR or OS (17). PCS-833 was evaluated in the ECOG E2995 trial and no difference was found for OS or DFS, while CR was worse with PSC-833 (although not statistically significant); the trial was closed early because of lack of superiority (18). An ECOG study

(367) did not find a difference in CR, OS, or adverse effects between AraC + GO versus AraC + liposomal DNR versus cyclophosphamide + topotecan + mesna, but none of the regimens was effective enough to study further (CR 8%, 7%, 4%). The ECOG E1906 trial (368) did not find a significant difference in CR (CR 6% versus 17% versus 10%; CR + CRi 14% versus 28% versus 15%) between carboplatin + topotecan versus FLAM (flavopiridol + AraC + MTZ) versus sirolimus + MTZ + etoposide + AraC. The sirolimus arm was discontinued early due to lower response rate. The authors suggested FLAM was excessively toxic in elderly but may be suitable in some younger patients. This was a phase II trial of 91 patients and did not report survival results.

The ECOG E5483 trial (372) and a GIMEMA trial (373) evaluated low-dose AraC maintenance and IL-2 maintenance, respectively, in patients with relapsed or refractory AML with subsequent CR. AraC (10 mg/m^2 sc q12h) resulted in non-significant increases in OS (10.9 months versus 7.0 months, p=0.615), DFS (7.4 months versus 3.3 months, p=0.084), and LFS (7.9 months versus 3.7 months, p=0.084), although on an as-treated basis LFS was significantly improved (7.7 months versus 3.1 months, p=0.027). The GIMEMA trial found improvement with IL-2 (RFS 17% versus 0%, one-year DFS 42% versus 15%), but did not reach its accrual goal and results are based on 32 patients such that statistically meaningful comparison could not be made.

4. Which patient characteristics are most important when making treatment decisions?

During the planning stages of the systematic review it was decided to focus on RCTs, while acknowledging that RCTs might not provide the best source of evidence on patient characteristics. RCTs are usually conducted in a well-defined and often narrow patient population and as such are not designed to investigate treatment according to patient characteristics, other than in subgroup analysis (often retrospectively).

For AML, age is often used as a determinant of treatment, and several studies dealt specifically with a patient subset determined by age (young, elderly). Because of the inclusion criteria, trials that accepted patients of a specific age range can provide only limited information regarding whether age is a factor in response. For this review, all studies in adult patients were included, and the inclusion criteria regarding age, as well as median age (when stated) are included in the data tables. When differences in outcome were found according to age ranges, this is also noted in the tables. Specifically excluded were studies of induction therapy in patients (generally elderly) considered unable to tolerate standard (AraC + anthracycline) therapy.

Some treatments were found to be of benefit in only a subset of patients (age, cytogenetic risk or subtype); however, the trials were usually not powered to detect differences in subgroups. The available data are included in the tables and summarized under Questions 1 to 3. In many cases trials were conducted in a subset of patients, it was assumed during study design that certain factors were important, or prognosis was found to be better in certain subsets of patients, but the RCTs were not designed to directly determine which of these factors should guide treatment.

Due to the above limitations, this review, while commenting on some characteristics related to treatment, is not sufficient to address this question. Several guidelines on treatment of AML have included sections on patient factors including age, comorbidities, cytogenetic abnormalities and associated risk category, and response to previous treatment. The most recent are the NCCN guideline (10), the Canadian consensus guideline for older patients (24), and the ESMO guideline for diagnosis, treatment and follow-up (25). Older but comprehensive management guidelines from Britain (26), Italy (27), and the European

LeukemiaNet (2) are also relevant. The reader is referred to these documents for further details.

Ongoing, Unpublished, or Incomplete Studies

As noted earlier, incomplete or ongoing studies found in the literature search are listed in Table 4-13 and Table 4-17. No specific search was done for planned or ongoing trials. Since 2005, the International Committee of Medical Journal Editors (ICMJE) decided trials would not be included for publication unless included on a clinical trials registry (http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/). Therefore, most recent major trials are expected to be listed in one or more registries, such as www.clinicaltrials.gov, www.ISRCTN.org, or other primary registries that participate in the World Health Organization International Clinical Trials Portal (http://www.who.int/ictrp/network/primary/en/). A Canadian-based registry for cancer trials is also available at Canadian Cancer Trials.

For this document, induction trials are not considered incomplete if recruitment is finished and CR data are reported, even if long-term follow-up may result in additional survival data. A note that follow-up is ongoing has been included in the data tables if stated in the publication citied. Due to high rates of recurrence and poor long-term survival rates, follow-up for a period of one to three years was generally considered sufficient and longer-term data are not expected except in some of the largest studies.

DISCUSSION

Induction in de novo AML

Most trials of induction therapy were based on AraC + anthracycline, sometimes with additional chemotherapy agents. A smaller number of trials compared completely different regimens. As AraC + anthracycline has long been the standard therapy, it is noted several studies evaluated different doses of these compounds. HDAC (generally 1-3 g/m^2 q12h) was compared with standard-dose AraC (100 or 200 mg/m^2/day continuous infusion). The relative benefit of HDAC was not consistent. The high-dose AraC was found to be more effective in some studies but with a trade-off of adverse effects including early mortality, especially noted for elderly patients. The largest and most recent trial (EORTC/GIMEMA AML-12) found improved CR with HDAC compared with standard-dose AraC in patients receiving DNR + etoposide (all patients, and subgroups age <46 years or age ≥46 years). OS was also improved overall and in patients age <46 years, with similar trends for EFS and DFS. There was no difference in survival for patients age >46 years. The authors indicated that patients with secondary AML, very-bad-risk cytogenetic abnormalities, and/or FLT3-ITD (internal tandem duplication) mutation benefited with HDAC. There was no difference in induction deaths or non-hematologic toxicities (except conjunctivitis). While the German SAL 60plus trial (patients age >60 years) compared AraC (2 g) + MTZ (10 mg) with AraC (100 mg) + DNR (45 mg), and therefore the relative effect of AraC compared with choice of anthracycline is unclear, both regimens were found to be of equal efficacy and toxicity (159)[6]. Data are not clear as to whether there is an optimal dose in the range 100-400 mg/day. The review by

[6] Final results were presented at the December 2015 ASH conference; the abstract (160) indicates RFS curves were the same until one year, after which they separate such that three-year RFS rates were 14% AraC + MTZ versus 29% DA. As the two arms received different consolidation treatments, differences may be due to consolidation.

Braess et al (124) suggested AraC efficacy is dose and schedule dependent, and that a weighted plasma concentration and exposure times characterize the cytotoxic effect.

Addition of cladribine or fludarabine to induction with AraC + anthracycline (DNR or IDA) has been evaluated. Addition of cladribine improved CR and survival, although when subdivided by age the OS benefit was significant for patients age 50 to 60 years (65) and EFS benefit significant for patients age >40 years (170); differences for younger patients were not statistically significant. Addition of fludarabine did not result in significant differences. Other regimens containing fludarabine (FLAG + IDA; FLAI) were found to be effective, although direct comparison to the same regimen without fludarabine were not made. The NCRI trial (67) and EORTC/GIMEMA AML-14A (68) found clofarabine and AraC resulted in similar adverse effects, CR, and survival outcomes. A recent non-randomized trial by Becker et al (377) evaluated clofarabine + HDAC (2 g/m^2/day) after GCSF priming in 39 patients with AML and 11 patients with MDS or myeloproliferative neoplasm and found a CR rate of 76% (85% for patients without an antecedent hematologic disorder) and median OS of 24 months.

Trials compared doses of DNR in the range 30-90 mg/m^2/day together with AraC. ECOG E1900 (41,42), HOVON 43 AML(45,46), and Lee et al (44) compared 90 mg/m^2/day versus 45 mg/m^2/day and all found higher response rate and better survival with the higher dose. In the HOVON trial, the CR, OS, and EFS benefit was found in patients age 60 to 65 years but there was no statistically significant difference for patients age >65 years. Higher dose was also beneficial in patients with CBF abnormalities. In the ECOG trial, benefit existed for all risk subgroups and was greater in patients age <50 years compared with age 50 to 60 years. In the trial by Lee et al, the survival benefit when analyzed by risk subgroups was only significant in the intermediate-risk subgroup. AML17 (47) found no difference in CR or two-year OS or two-year RFS between 90 and 60 mg/m^2/day but more adverse effects (death within 60 days, primarily due to infection or resistant disease; gastrointestinal toxicity) in the 90 mg arm. While the authors did not account for the increased numbers of deaths due to resistant disease and unknown cause of death in the 90 mg arm, this seems suspicious and may be due to the unique study design whereby randomization to 90 versus 60 mg/m^2 was for only one course, followed by second or third randomization according to risk classification.

Several trials compared IDA with DNR, or MTZ with DNR. IDA was found to result in better CR and OS. The CR benefit also held when IDA was compared with high-dose DNR, in contrast to results in a recent mixed-treatment comparison meta-analysis (48). MTZ also resulted in better CR than standard-dose DNR; studies comparing MTZ with high-dose DNR were not found. Several other anthracyclines have been studied; however, at present, none have sufficient data to indicate their use outside of clinical trials.

Etoposide has been evaluated together with AraC and anthracyclines (primarily DNR). Meta-analysis of all studies found no difference in CR with or without etoposide; however, it was noted that only the MRC AML11 trial was conducted in primarily older patients. Excluding this study, etoposide was found to result in improved CR, although with only small (non-significant) differences in survival. Some trials suggest etoposide may cause faster remission. The benefit of improved CR must be weighed against higher rates of gastrointestinal adverse effects found in some trials.

When added to AraC + DNR, cladribine had significant CR and OS benefit, whereas fludarabine effect was smaller and not significant (65). This suggests that adding fludarabine to a standard AraC + anthracycline may not be beneficial. However, fludarabine-containing regimens were found to be effective in indirect comparisons. The MRC AML15 trial (6,7) found FLAG-IDA (fludarabine + AraC + GCSF + IDA) to be an effective induction regimen with slightly better outcome than with DNR + AraC (CR 84% versus 78%; RFS 45% versus 35%; significance not given). The improvement may be attributed to IDA, fludarabine, or both. FLAG-IDA compared with ADE (AraC + DNR + etoposide) had slightly better (not significant) CR

(84% versus 81%, p=0.2), OS (44% versus 37%, p=0.2) and better RFS (45% versus 34%, p=0.01) but increased death in remission (17% versus 11%, p=0.02). Russo et al (8,9) found FLAI (fludarabine + AraC + IDA) resulted in better CR than ICE (IDA + AraC + etoposide), with CR 74% versus 51% (p=0.01) and fewer adverse effects, although differences in survival were not significant.

Results for induction with ATRA are mixed. There appears to be benefit for specific molecular subgroups (mutant NPM1, ELN-favourable subtypes), but full publication and possibly additional trials are required.

Meta-analyses found GO did not influence CR. GO at 6 mg/m^2 resulted in worse 30-day mortality, although caused no difference at 3 mg/m^2. GO improved RFS, and improved OS when used at 3 mg/m^2. GO at 6 mg/m^2 resulted in worse OS in patients age ≥70 years in the EORTC/GIMEMA AML-17 trial (64). Hills (57) found GO improved OS in subgroups with favourable or intermediate cytogenetics, but not adverse cytogenetics. FLT3 and NPM1 mutation status had no effect.

Meta-analysis by Sung et al (71) and Heuser et al (72) found routine CSF use did not improve response or long-term outcomes. CSF may have a role in supportive care (outside the scope of this review) but should not be given routinely as part of induction chemotherapy.

CsA was evaluated in two small groups of patients with s-AML or therapy-related AML (t-AML). The Hellenic trial (74) included patients age >60 years with s-AML, and found CsA improved CR, OS, and DFS. The SWOG 9126 trial (75) included patients age 18 to 70 years with poor-risk AML; most were refractory or relapsed, but 17% had s-AML or t-AML. In these previously untreated patients, CsA improved OS and RFS. Both trials are small but suggestive of CsA benefit in s-AML. They do not address use of CsA in the broader AML population.

Several other agents were evaluated in RCTs. Flavopiridol (378), homoharringtonine 108), ACR (54,55), and lomustine (82,83) appear to be of benefit. A phase III trial of flavopiridol is planned, while the LAMSA 2007 trial of lomustine is completed but not yet published[7]. ACR is effective but the optimal dose was not determined and relative efficacy compared with DNR is unclear. In the trial of homoharringtonine (56), homoharringtonine + AraC + ACR resulted in better CR, EFS, and RFS compared with DNR + AraC (DA). The relative benefit of homoharringtonine and ACR is uncertain. Sorafenib improved EFS and RFS in patients age 18 to 60 years but resulted in more adverse effects[8]. It resulted in lower (but not statistically different) CR, OS, and EFS in patients age >60 years. PSC-833, AZA, vincristine, amonafide, bevacizumab, IL-11, lisofylline, quinine, topotecan, thalidomide, valproic acid, and zosuquidar were found to be of no benefit.

[7] The LAMSA 2007 results were released (subsequent to this review) as an abstract at the ASH conference in December 2015 (see ongoing trials, Table 4-13).

[8] Note full results of the SORAML trial (305) were published subsequent to this review and additional details have been added to Table 4-12. The publication confirms the results in the abstract that it improved EFS (the primary outcome) and RFS. OS (a secondary outcome) was 63% versus 56% at three years (not significantly different); it was noted that median OS was not reached and longer follow-up was required. This was a phase II trial and the authors indicate a confirmatory trial is needed. Exploratory analysis in patients with FLT3 duplication mutations did not find statistically significant differences, although did indicate the benefit in the overall study was not due to this subgroup. We have also become aware of a non-randomized trial in older patients (age ≥ 60 years) with FLT3-ITD AML reported at ASH 2015(379); it found sorafenib added to chemotherapy doubled one-year OS (62% versus 30%, p<0.001). The various studies together suggest benefit of sorafenib but are inconclusive as to whether there are differences due to age or FLT3 mutation status.

Post-Remission Therapy

Almost all patients in CR will relapse without further treatment. Options include hematopoietic stem cell transplantation (with or without consolidation treatment), or consolidation/maintenance treatment. While several RCTs have compared allogenic or autologous transplant to chemotherapy, issues related to transplantation and when it should be considered are outside the scope of the current review, and other guidelines or reviews should be consulted (10,12,24,28,29).

Consolidation

In contrast to induction treatment, there does not appear to be an accepted standard for post-remission chemotherapy regimens, and many are considered equivalent. Trials including the ECOG EST 3483 trial (321,322) found consolidation or maintenance were better than observation (0% of observation patients still in remission at two years). In other trials with a no treatment arm, survival was low in HOVON 43 AML/SAKK 30/01 (five-year DFS of 16% (45,46)) and NCRI AML16 (three-year RFS of 21% (67)). In contrast, CALGB 8525 found four-year OS of 46% with HDAC consolidation (34) and JALSG AML201 found five-year OS of 58% with HDAC (86), suggesting that post-remission therapy has potential for long-term survival.

The CALGB 8525 trial (34,35) is cited by the NCCN (10) as well as other guidelines as the basis of recommendations to use HDAC in younger patients (age <60 years). Four cycles of AraC at 100 mg/m^2/day, 400 mg/m^2/day, and 3 g/m^2 q12h were compared as consolidation therapy. The HDAC resulted in better OS and DFS for patients age <60 years, while there was no difference between doses for patients age >60 years. The majority of older patients (age >60 years) could not tolerate the high dose and 32% had serious central nervous system abnormalities. The benefit of HDAC regarding continuous CR at five years was significant for CBF-AML and normal karyotype AML; it was less clear for other subtypes (21% HDAC versus 13% low-dose AraC).

Limited studies were found that allowed assessment of anthracycline or other agents added to HDAC. Indirect evidence comparing results from the SAKK trial (85) and CALGB 8525 suggests anthracycline may not be necessary. Both trials had similar survival rates despite the fact that anthracycline (DNR) was used in the SAKK trial and not the CALGB trial. It is noted, however, that the SAKK trials only gave one course of consolidation treatment compared with four courses in the CALGB trial. Other trials (89,90) evaluating addition of various other agents found no improvement compared with HDAC alone.

HDAC results in more adverse effects than AraC at lower doses, and therefore may not be suitable for some patients. In these cases, use of standard-dose AraC together with anthracyclines as for induction may be preferred. The JALSG AML201 trial compared three courses of HDAC at 2 g/m^2 q12h to standard-dose combination chemotherapy with AraC at 100 mg/m^2/day (four courses: MTZ + AraC, DNR + AraC, ACR + AraC, etoposide + vindesine + AraC) (86). They found both were tolerated with difference in OS, although HDAC resulted in better DFS in the subgroup with favourable cytogenetics.

Several of the British MRC trials have used MACE (AMSA [100 mg/m^2/day, days 1 to 5] + AraC [200 mg/m^2/day CI, days 1 to 5] + etoposide [100 mg/m^2/day, days 1 to 5]) followed by MidAC (MTZ [10 mg/m^2/day slow iv days 1 to 5] + AraC [1 g/m^2 by 2h iv infusion q12h, days 1 to 3]) for consolidation. The MRC AML15 trial (7) found MACE→MidAC resulted in better survival than HDAC for patients with adverse-risk (unfavourable) cytogenetics (OS 39% versus 0%, p=0.0004; deaths OR=3.17, confidence interval 1.68 to 5.97). Patients with more than 15% residual blasts in a marrow sample taken at least 18 to 21 days from the end of course

one were defined as high risk irrespective of cytogenetics. No survival differences were found for favourable or intermediate subgroups, but MACE→MidAC resulted in more adverse effects.

Duration of consolidation was studied in four trials. The MRC AML14 trial found that there was no difference between one and two courses of consolidation after two courses DNR + AraC induction (76,77). The GOELAM BGMT-95 trial found no difference between one or two courses of consolidation followed by maintenance (82,83). Elonen et al found no difference between one and six cycles of consolidation (84). The MRC AML11 trial found no difference between one and four courses of consolidation (69). These trials all suggest that simply adding additional cycles of consolidation is not generally beneficial. The CALGB 8525 trial (see earlier in this section) found HDAC consolidation superior to lower doses when given for four cycles. As the studies comparing duration used combination treatment (including AraC + anthracycline), the optimal number of cycles using HDAC alone was not addressed.

The effects of consolidation and induction may be interdependent, as suggested in an abstract of the NCRI AML16 trial (67). This trial administered two cycles of induction with AraC (100 mg/m^2 q12h) + DNR (50 mg/m^2/day) and then either an additional cycle as consolidation (of shorter duration than for induction) or no further treatment and found no difference in OS or RFS. When induction dosage is low (administered for only one cycle or using low-/standard-dose AraC) consolidation may play a larger role in overall patient outcome.

Maintenance

Studies evaluating the use of maintenance therapy found conflicting results. Overall, they suggest that maintenance treatment will benefit some patients, but studies are insufficient to determine selection of patients who will benefit most, or to decide on the most appropriate treatment. GIMEMA LANL 8201 (338) found no difference in DFS or OS between no further treatment, 18 courses maintenance (AraC + TG) or intensive post-consolidation treatment (2 courses each etoposide, TG, DNR, with AraC in all courses) in patients with sufficiently intensive induction + consolidation. In contrast, the HOVON AML-9 trial alone or combined with the HOVON AML-11 trial found low-dose AraC maintenance (10 mg/m^2 sc q12h for 12 days every 6 weeks) after consolidation improved DFS but not OS (198). In the German AMLCG 1981 study (323-326) with patients age ≥16 years, AraC combined with DNR, TG, or cyclophosphamide in alternating cycles improved OS and remission duration. The Russian AML-06.06 trial (176,177,327) found AraC + mercaptopurine decreased probability of relapse (50% versus 83%, p=0.07). IL-2 plus histamine in the MP-MA-0201 trial (91-94), ubenimex (168) in JALSG trials, and bestatin added to maintenance (336) were found to be of benefit.

SWOG S8124 (334) treated patients with consolidation and late intensification then randomized to maintenance (or not) with the combination vincristine + prednisone + TG + AraC. Maintenance reduced the risk of death or relapse, although the effects on seven-year OS and seven-year DFS were not statistically significant (37% versus 31%, p=0.14 and 29% versus 26%, p=0.18, respectively).

Two trials evaluated duration of maintenance therapy. The JALSG AML87 trial found 12 courses of maintenance resulted in better DFS than four courses (297). Jacobs et al found 15 months of maintenance resulted in longer remission duration (35 weeks versus 24 weeks) compared with six months of maintenance (233), although the regimens were not the same.

SWOG 7823 (213) compared continued maintenance (vincristine, AraC, and prednisone extended from 9 months to 12 months) or three courses late intensification (mercaptopurine, vincristine, methotrexate, prednisone) and found better OS and DFS with late intensification but also more severe or life-threatening toxicities (60% versus 21%, p<0.0001).

The ongoing QUAZAR AML-001 trial is studying oral AZA as maintenance therapy in patients age ≥55 years (https://clinicaltrials.gov/ct2/show/NCT01757535).

Relapsed or Refractory AML

A recent review of current treatment strategies by Ramos et al (380), as well as other practice guidelines cited earlier suggests there is no current standard of care for relapsed or refractory AML. The variety of agents used in both comparison arms of the trials in Table 4-18 also suggests there is no standard or consensus on the most appropriate treatment. Many of the trials did not report survival outcomes, or reported only median results. Outcomes were generally poor, with several trials reporting CR rates of <10% to 20% and median survival generally two to six months. However, some trials reported CR rates in the range 40% to 70% and improved longer-term survival. The higher rates were often in both arms of the study, suggesting relative effectiveness of the comparison arm compared with regimens used in other trials but not necessarily improvement due an additional agent. As such, evidence for benefit of some regimens is considered indirect. Some of the most effective regimens are as follows:

- AraC + MTZ: CR of 58% and median survival of 12 months in a trial by Martiat et al (97)
- AraC + MTZ + etoposide ±GM-CSF: CR 65% versus 59% (51% versus 46% refractory, 89% versus 81% relapsed); median OS 303 days versus 254 days (ns); median DFS 251 days versus 240 days (ns) in the EMA91 trial (99)
- AraC + DNR + etoposide (ADE): 54% CR, three-year OS 12%, three-year DFS 22% in the UK MRC AML-R trial (100)
- AraC + DNR + etoposide (ADE): 63% CR, four-year OS 27%, four-year DFS 29% in the UK MRC AML-HR trial (101)
- AraC + pirarubicin + etoposide 79% CR; MTZ + AraC + etoposide CR 56%; median OS approximately 20 months with no difference between arms (351)
- Low-dose CAG (AraC + ACR + GCSF) ± etoposide: CR 71% versus 51%, five-year OS 27% versus 24% (95)
- MTZ + etoposide: CR 43%, five-year OS 11% and five-year DFS 20% in the HOVON trial (359)

Based on the above summary of trials, anthracycline + AraC + etoposide appears to be the strategy with the most evidence. The relative importance of etoposide is unclear; however, it was used in most of the studies listed above and therefore should be considered. Regarding anthracyclines, MTZ and DNR are considered standard. Low-dose CAG + etoposide appears to be an effective alternative, although it was not compared directly with the other regimens. While pirarubicin results are promising, the trial (351) included only 56 patients; it was published in Chinese with an English abstract and could not be fully evaluated.

Etoposide added to low-dose AraC (10 mg/m^2 q12h sc) + ACR + GCSF (95) resulted in improved CR overall (p=0.0002), age <60 years (p=0.004), and for unfavourable-risk patients (p=0.009). There was no difference in five-year OS or grade 3 and 4 adverse events. A SECSG study (96) found etoposide added to HDAC improved OS for patients age <50 years (p=0.036), while there was no effect on DFS. CR rates were 38% versus 31% (ns).

Clofarabine and fludarabine are other agents with evidence of efficacy. In the Classic I trial (102), clofarabine (40 mg/m^2/day for five days) + AraC (1 g/m^2/day) compared with AraC alone improved CR rate (35.2% versus 17.8%, p<0.01) and EFS but not OS, with higher rates of serious adverse events (60% versus 49%, primarily infections and deaths). A recent non-randomized trial by Becker et al (103) evaluated clofarabine + HDAC (2 g/m^2/day) after GCSF priming in 46 patients with relapsed or refractory AML and found a CR rate of 46% and median OS of nine months. Treatment-related mortality was 12%, with all cases due to infections. Studies so far suggest small improvements adding fludarabine to AraC + IDA (104).

Two studies using IDA + AraC in both arms compared addition of clofarabine versus fludarabine (105,106) and found CR rates of 43% versus 30% (ns) and 32% versus 25%. Clofarabine resulted in worse four-week mortality (16% versus 4%), more infections (47% versus 35%, ns), and less grade 3 and 4 toxicities. A further trial is ongoing. Based on the above trials, the NCCN suggested clofarabine ± AraC + GCSF ± IDA as an appropriate regimen, while it suggests fludarabine + AraC + GCSF ± IDA based on a non-randomized trial (13).

Cladribine used in the regimen cladribine + AraC + GCSF ± MTZ or IDA has also been recommended by the NCCN (10) based primarily on non-randomized trials (107,108). Cladribine use is supported by the review by Robak and Wierzbowska (109), as well as trials in de novo AML patients (65,66).

Patient Characteristics

Several guidelines on treatment of AML have included sections on patient factors including age, comorbidities, cytogenetic abnormalities and associated risk category, and response to previous treatment. Appelbaum et al (381) retrospectively studied patients from five SWOG trials and found the cytogenetic profile of AML patients differed with age. In patients age <56 years, 17% had favourable cytogenetics (e.g., t(8:21) or inv(16)), while this decreased to 4% in patients age >75 years. Similarly, unfavourable cytogenetics increased from 35% for patients age <56 years to 51% for age >75 years. While this partially accounted for differences in treatment response, within each subgroup treatment still deteriorated with age. Older patients had poorer performance status, lower white blood cell counts, and higher multidrug resistance. In the subgroup of patients with excellent performance status age had a small effect on early death (2% age <56 years versus 14% age >75 years). In patients with performance status of 3, age was a very important factor: no patients age <56 years died, while 47% age 66 to 75 years and 82% age >75 years died within 30 days of initiation of induction. Elderly patients tend to have more comorbidities that may exclude them from intensive treatment and, thus, RCTs of these patients are rare. Further investigation by this group suggested that variants in DNA repair pathways in older adults may have an impact on both outcome and treatment-related toxicities (382).

Analysis of three JALSG trials found worse survival for patients age >50 years, and this was due to higher relapse rates (383). There were no significant differences among patients age 50 to 54 years, 55 to 69 years, or 60 to 64 years, and the authors concluded that intensive chemotherapy without dose attenuation could be used in fit elderly patients at least up to age 64 years.

In the current review, several studies found elderly patients did worse than younger patients but generally were not able to comment on whether a given treatment was still effective in elderly patients. Molecular analysis/cytogenetics is a relatively new field, and these would not have been considered in older studies or would have been measured differently, so that that useful data are limited. While some studies reported results according to cytogenetic risk group, and chemotherapy effects may have been greater in certain groups, individual trials were generally not designed to determine effectiveness for different cytogenetic groups and were underpowered to find significant differences due to treatment. As such, results are suggestive of areas for further research but not sufficient to make recommendations.

The European LeukemiaNet proposed a standardized reporting system for correlation of cytogenetic and molecular genetic data with clinical data with genetic group categories of favourable, intermediate-I, intermediate-II, and adverse (2). Rollig et al (384) assessed this classification in a cohort of 1557 patients from the AML96 trial and concluded it was the best available framework for younger patients (<60 years) but that alternative prognostic factors were required for the intermediate categories for older patients. An evaluation by

Alpermann et al (385) in 954 patients found no differences in outcomes for intermediate-I versus intermediate-II subgroups and proposed a revised classification: favourable (CBF leukemias, or intermediate cytogenetics with NPM1mutation [mut] or biallelic CEBPAmut), intermediate I (intermediate cytogenetics), intermediate II (intermediate cytogenetics and at least one of the following: MLL-PTD, RUNX1mut, FLT3-ITD/wt ratio ≥0.5), and adverse (adverse cytogenetics).

An international group from USA, Germany, and the Netherlands proposed a 24-gene prognostic signature improving on the European LeukemiaNet classification (386). They used four training sets and two validation sets to develop the signature that divides patients into three risk groups with significantly different OS and EFS ($p<0.001$). The authors proposed this gene signature be used along with a limited number of cytogenetic and molecular abnormalities recommended by the European LeukemiaNet. A large prospective validation trial is still required to confirm the findings.

TABLES

Table 4-1. Induction, cytarabine dose or comparison

Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[9]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
CALGB 8321; 1982-1986 Dillman, 1991 (116)	326 AML; stratified by age 60 y; after June 24, 1984 assigned pts age ≥60 y only to AraC 100 arm	Induction + maintenance AraC dose: 200 mg vs 100 mg	AraC 200 mg/m^2 vs AraC 100 mg/m^2 for induction and maintenance Cycle 1 included AraC (200 or 100 mg/m^2/d CI, d 1-7), DNR (45 mg/m^2/d iv, d 1-3; 30 mg/m^2 age 60), Cycle 2 if needed at same dose: AraC (d 1-5) + DNR (d 1-2) If CR then received monthly sc AraC at same dose as previously + 6-thioguanine (m 1 and 5), VCR and prednisone (m 2, 4, 6, 8), DNR (m 3, 7)	64% (A200) vs 58%, p=0.29 Age <60: 75% vs 64%, p=0.08 Age ≥60: 38% vs 44%, p=0.68	OS: Median 38 w vs 46 w, p=0.64 5-y OS 10% vs 8% Age <60: 65.0 w vs 53.7 w, p=0.159 Age ≥60: 9.6 w vs 11.0 w, p=0.227 Median DFS: 41 w vs 44 w, p=0.86	Median time to remission 6.7 w vs 8.1 w. Early therapy-related deaths 21% vs 13%, p=0.05	NR	Does not support superiority of A200 over A100; pts with performance status of 0 and <60 y had better survival better on A200
MRC AML12; ISRCTN17833622; 1994-2002 Burnett, 2010 (153,154)	2934 Age <60 y, median 41 y, de novo or s-AML/t-AML, (n=239) and high-risk MDS	Induction; consolidation AraC dose: 400 mg vs 200 mg (ATRA)	B. After Amendment (n=1193) DNR + AraC + TG: high (double) vs standard AraC dose Both groups randomized to ATRA (45 mg/m^2, d 1-60) vs none H-DAT 3+10 → H-DAT 3+8: DNR (50 mg/m^2, d 1, 3, 5) + AraC (200 mg/m^2, q12h, d 1-10) + TG (100 mg/m^2 q12h, d 1-10); then same but AraC and TG, d 1-8 S-DAT 3+10 → S-DAT 3+8: DNR (50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2, q12h, d 1-10) + TG (100 mg/m^2 q12h, d 1-10); then same but AraC and TG, d 1-8 Both Phases A & B Randomized consolidation if CR (n=992): MACE then randomized to 1 (MidAC) or 2 further courses (ICE then MidAC)	68% H-DAT vs 69% S-DAT, p=0.8	OS: 31% H-DAT vs 32% S-DAT, p=0.8 RFS: 31% H-DAT vs 30% S-DAT, p=0.7	Induction deaths 8% H-DAT vs 7% S-DAT, p=0.7 Significantly longer hematologic recovery time and more antibiotic use with H-DAT (compared with S-DAT). H-DAT induced significantly greater gastrointestinal toxicity	NR	No benefit for increased AraC dose or for ATRA

[9] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[9]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
China; 2007-2013 Huang, 2014 (147)	297 Age 65-82 y, de novo or s-AML, Karnovsky performance status score ≥60	Induction + consolidation AraC dose + DNR dose: AraC 100 mg vs 75 mg	Standard vs attenuated AraC + DNR Standard: 2 cycles DNR (45 mg/m^2, 3 d) + AraC (100 mg/m^2 CI, 7 d) induction then 2 cycles DNR (45 mg/m^2, 3 d) + AraC (100 mg/m^2, 7 d) then 4 cycles HDAC (1.5 g/m^2, 4 d) Attenuated: 2 cycles DNR (30 mg/m^2, 3 d) + AraC (75 mg/m^2 CI, 7 d) induction then 2 cycles DNR (30 mg/m^2, 3 d) + AraC (75 mg/m^2, 7 d) then 4 cycles HDAC (1 g/m^2, 4 d)	CR+CRi 58.2% vs 55.1%, p=0.60	5-y OS 24 m vs 39 m, p<0.001 PFS 23 m vs 35 m, p<0.001	Early mortality 7.1% vs 0.64%, p<0.01 No overall response: 2.1% vs 13.5% Longer time to neutrophil recover (>1.5×10^9/L; p<0.001) and more grade3+ infections (p<0.001) with standard dose	NR	
Russian; 1989-1991 Parovichnikova, 1992 (155)	16 Age >60 y, median 65 y, AML	Induction DNR dose + AraC dose: 200 mg vs 100 mg AraC	AraC + DNR (std dose) vs AraC + DNR (low dose) Std dose: AraC (100 mg/m^2, q12h iv, 7 d), DNR 45 mg/m^2 iv, 3 d) [DNR reduced to 30 mg/m^2 in 3rd year] Low dose: AraC (50 mg/m^2, q12h iv, 7 d), DNR (30 mg/m^2, 3 d) Maintenance: 5 d rotating AraC with DNR or cyclophosphamide or 6-meractopurine	50% vs 37%	2-y OS 25 ± 6.9 w vs 41.9 ± 15.6 w, p=0.34	Profound neutropenia duration 20 d vs 13 d course 1 and 9 d vs 7 d (course 2). Similar frequency and severity of complications.	NR	Std dose may be used in elderly pts
MRC AML9; 1984-1990 Rees, 1996 (156)	951 Age 1-79 y, median 53 y, age >55 y starting May 1988; de novo or secondary AML; randomization by minimization for age (6 groups), sex, previous randomization	Induction; consolidation; maintenance DNR dose + AraC dose: 100 mg AraC, 5 d vs 10 d	DAT 1+5 vs DAT 3+10 DAT 1+5: DNR (50 mg/m^2 iv, d 1), AraC (100 mg/m^2 iv q12h, d 1-5) and TG (100 mg/m^2 po 12-hourly, d 1-5) DAT 3+10: DNR (50 mg/m^2 iv, d 1, 3, 5), AraC (100 mg/m^2 iv q12h, d 1-10) and TG (100 mg/m^2 po 12-hourly, d 1-10) If substantial blast population remained after 1st induction course, administered a 2nd induction course; for the 1+5 group administered 3rd and 4th induction courses with 2+8 (DNR, d 1, 6; AraC, d 1-8) if needed for CR Pts with CR were randomized (n=441) to 2 courses DAT 2+7 alternating with 2 courses either MAZE (m-AMSA, AZA, etoposide) or COAP (cyclophosphamide, VCR, AraC, prednisone) Those still in CR randomized (n=212) to either 1-y maintenance with 8 courses AraC + TG → 4 courses COAP or no further cytotoxic therapy	66% DAT 3+10 vs 61% DAT 1+5, p=0.15 Subgroups: age 0-49, 83% vs 76%; age 50-59, 63% vs 59%, age 60-69, 48% vs 46%; age ≥70, 45% vs 43%; all ns	5-y OS 23% DAT 3+10 vs 18%, p<0.05; age <60, 25% vs 20%; age ≥60, 12% vs 5% 5-y RFS 28% DAT 3+10 vs 23%, p=0.05	Time to CR shorter with DAT 3+10 (median 34 vs 46 d, p<0.0001) and correspondingly lower total supportive care required. Induction deaths 21% DAT 3+10 vs 16%, p=0.06	Aimed to recruit 1000 pts to be able to assess 10% difference in 5-y OS between induction treatments.	DAT 3+10 more effective than DAT 1+5

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[9]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MRC AML14; LRF AML14; ISRCTN62207270; 1998-2005 Burnett, 2009 (76); Burnett, 2005 (77) [abstract]	1273 Predominantly ≥60 (younger pts permitted if not fit to enter other trials for younger pts), AML (de novo or secondary) or high-risk MDS	Induction; consolidation AraC dose: 400 mg vs 200 mg (Anthracycline DNR dose) (PSC-833)	DNR (50 vs 35 mg/m^2) + AraC (400 vs 200 mg/m^2) Subgroup receiving DNR 35 mg/m^2 ± PSC-833 DNR (50 or 35 mg/m^2 iv, d 1-3) + AraC (200 or 100 mg/m^2 iv q12h, d 1-10) + TG (100 mg/m^2 po q12h, d 1-10). Course 2 same except AraC + TG, d 1-8 - Subgroup of 601 pts randomized to DNR 50, DNR 35, or DNR 35 + PSC-833 (2 mg/kg iv over 2 h with simultaneous CI 10 mg/kg/24 h for 72 h; in both courses) Pts with CR received MTZ (d 1-3) + AraC (q12h, d 1-3) then randomized to no further treatment or a 4th course consisting of IDA (10 mg/m^2 slow iv, d 1, 3) + AraC (100 mg/m^2 by 2h infusion q12h, d 1-3) + etoposide (100 mg/m^2 by 1h infusion daily, d 1-3)	55% AraC$_{400}$ vs 53% AraC$_{200}$, p=0.7	5-y OS: 13% AraC$_{400}$ vs 11% AraC$_{200}$, p=0.5 <u>5-year relapse</u> 83% AraC$_{400}$ vs 84% AraC$_{200}$, p=0.2	Induction death 18% AraC$_{400}$ vs 17% AraC$_{200}$, p=0.6 No important differences in non-hematological toxicity or hematologic recovery	ITT analysis	No difference between AraC$_{400}$ and AraC$_{200}$
UCLA (California); 1986-1991 Schiller, 1992, 1993 (157,158)	102 Newly diagnosed AML, excluded t-AML; age 18-76, median 48	Induction AraC dose: 500 mg vs 200 mg	DNR + intermediate-dose AraC vs DNR + conventional-dose AraC DNR (60 mg/m^2 iv, 3 d), intermediate AraC (500 mg/m^2 iv over 2 h q12h, 6 d), conventional AraC (200 mg/m^2/d CI, 7 d), 2nd induction course if residual leukemia Pts age ≤40 y with CR and donor were offered transplant Pts with remission received 3 courses consolidation	74% vs 71%, ns Age <60: 82% vs 82% Age >60: 58% vs 47%	Median 1065 d follow-up: OS after CR: 39% ±18% vs 31% ±19%, ns DFS after CR: 26% ±16% vs 22% ±16% ns.	More severe gastrointestinal toxicity in intermediate-dose arm but no other significant differences in toxicity	NR	Intermediate-dose (increased) AraC did not substantially improve results
NCT00428558 French Intergroup CBF-2006 trial; 2007-2010 Jourdan, 2013 (36)	198 Age 18-60 y, newly diagnosed CBF-AML (presence of t(8;21) translocation or inv(16)/t(16;16) rearrangement	Induction AraC dose: 500/2000 mg vs 200 mg	DNR + AraC (reinforced) vs DNR + AraC (standard induction) Arm A: DNR (60 mg/m^2/d by 30 min iv infusion, d 1-3) + AraC (500 mg/m^2/d CI, d 1-3) then DNR (35 mg/m^2/d by 30 min iv infusion d 8-9) + AraC (1000 mg/m^2/12 h by 2 h iv infusion, d 8-10) Arm B: DNR (60 mg/m^2/d by 30 min iv infusion, d 1-3) + AraC (200 mg/m^2/d CI, d 1-7) Salvage therapy if no CR If CR, given 3 cycles consolidation	99%	OS from CR: 87% vs 83%, p=0.95 RFS 64% at 36 m in both arms, p=0.89	Early deaths 3% arm A vs 0% arm B	Primary endpoint RFS. Required 96 pts/arm and 78 events to detect increase in 2-y RFS from 50% to 70% with 80% power	Similar efficacy for both arms

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[9]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
German SAL 60plus; 2005-2009 Rollig, 2010 (159) [abstract] Note: Results presented at ASH, Dec 2015. Rollig, 2015 (160)	485 Age >60 y, median 69	Induction MTZ, DNR; AraC dose: 2g vs 100 mg	IMA (intermediate does AraC + MTZ) vs std 3+7 (DNR + AraC) IMA: AraC (1g/m^2 bid, d 1, 3, 5, 7) + MTZ (10 mg/m^2, d 1-3) Std 3+7 (DA): AraC (100 mg/m^2 CI, d 1-7) + DNR (45 mg/m^2, d 3-5) Pts in CR after DA received intermediate-dose AraC + AMSA; pts in CR after IMA received standard-dose AraC + MTZ (2+5)	55% IMA vs 39% DA, p=0.001 Including CR after trial discontinuation 64% vs 55%, p=0.043	Median DFS at 25.7 m: 10.2 m vs 11.7 m (p=0.11) RFS superimposable in first year (median 10 m vs 11 m) then separate; 1-y RFS 46% vs 45%; 3-y RFS 14% vs 29%, p=0.042 Median OS 10 m vs 10 m; 1-y OS 44% vs 45%; 3-y OS 19% vs 19%, p=0.513. Differences in RFS may be due to difference in consolidation used in each arm	Early mortality 18.1% vs 18.4%; SAE + grade4 non-hematological toxicity 19% vs 23%, p=0.1866; median TTR 10.3 m vs 11.1 m, p=0.328 Liver toxicity OR=0.52, p=0.001; gastrointestinal symptoms OR=0.62, p=0.041. Duration of grade 3+ neutropenia and thrombocytopenia longer with IMA (25 d vs 23 d, p=0.032 and 20 d vs 16 d, p<0.001, respectively)	ITT. Primary outcome CR, expected difference of 15% in favour of IMA. Secondary endpoints SAEs, time to relapse, RFS, OS	

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[9]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Australia; ALSGM4; 1987-1991 Bishop, 1996 (163); Matthews 2001 (164)	301 Age 15-60, newly diagnosed AML	Induction AraC dose: 6 g vs 100 mg	HDAC vs std dose AraC All pts received DNR (50 mg/m^2, d 1-3) + etoposide (75 mg/m^2 d 1-7) AraC: 3 g/m^2 q12h on d 1, 3, 5, 7 vs 100 mg/m^2 CI for 7 d; 2nd or 3rd course allowed if CR not achieved; consolidation with AraC (std dose) + DNR + etoposide	1 course: 60% HDAC vs 48%, p=0.04 Overall: 71% HDAC vs 74%, p=0.7.	At median 4.5 y, median survival: 19 m vs 17 m; 5-y survival 31% vs 25% (ns). At 10 y: 26% vs 14%, p=0.22; adjusted p=0.090 Early deaths (during induction) 18% vs 11%; HR=1.9, p=0.079 RFS at 5 y after CR: 49% vs 24%. DFS 22 m vs 12 m, p=0.007 DFS at 10 y after CR: 34% vs 11%, p=0.0039 10 y disease-related failure 48% vs 81%, HR=0.54, p=0.0002; adjusted HR=0.49, p<0.0001	Median remission duration 45 m HDAC vs 12 m, p=0.0005. HDAC was significantly more toxic (p<0.001) for leukopenia, thrombocytopenia, nausea, vomiting; and more patients on HDAC were taken off induction, p=0.003. Overall failure HR=0.75, p=0.039; after adjustment HR=0.72 (0.54-0.95), p=0.020	A target accrual of 300 calculated to provide a power of 0.8 of detecting an increase in the complete response rate from 65% to 80%. ITT analysis	HDAC prolongs remission and DFS but greater early toxicity
Slovakia; 2000-2011 Sabty, 2011 (166) [abstract]	128 Age 15-60 y, newly diagnosed AML	Induction AraC dose: 6 g vs 100 mg (Etoposide)	High-dose AraC + DNR + etoposide (Group C) vs DNR + AraC + etoposide (Group B) Group C (n=44): AraC (3 g/m^2/12 h, d 1, 3, 5, 7) + DNR (50 mg/m^2/d, d 1, 3, 5) + etoposide (50 mg/m^2/d, d 1-5) Group B (n=57): (AraC 100 mg/m^2/d CI, d 1-10) + DNR (50 mg/m^2/d, d 1, 3, 5) + etoposide (50 mg/m^2/d, d 1-5)	81.8% Group C vs 75.4% Group B, p=0.81	5-y OS: 33% vs 41%, p=0.36 DFS: 35% vs 44%, p=0.21	Toxicity similar except conjunctivitis higher in group C	NR	Etoposide can improve CR and outcome
Japan; 1994-1997 Mori, 2000 (167) [Japanese; English abstract and tables]	29 Age 60-75 y, newly diagnosed AML (de novo or s-AML from MDS)	Induction DNR dose + BHAC dose: 150 mg vs 200 mg	BHAC-DM, reduced (S-1) vs conventional dose (S-2) S1: BHAC (150 mg/m^2 d 1-7) + DNR (30 mg/m^2, d 1-3) + 6MP (70 mg/m^2, d 1-7; with allopurinol 300 mg/d) S2: BHAC (200 mg/m^2, d 1-7) + DNR (40 mg/m^2, d 1-3) + 6MP (70 mg/m^2, d 1-7; with allopurinol 300 mg/d) If blasts >15% on d 7 pts received 2 more days therapy	46.2% vs 43.8%	NR	Early deaths: 1pt in each group; no grade 4 adverse effects	NR	Conventional dose is as acceptable as reduced dose in elderly

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[9]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
SWOG 8600; 1986-1991 Weick, 1996 (161); See Appelbaum 1997 (162) for long-term survival	723 Age <65 y, previously untreated AML, de novo or secondary. Stratified by age (<50 y, 50-64 y)	Induction; consolidation. Randomized 2:1 between SDAC and HDAC induction AraC dose: 4 g vs 200 mg	HDAC + DNR vs std-dose AraC (SDAC) + DNR HDAC: DNR (45 mg/m^2/d iv, d 7-9), HDAC (2 g/m^2 iv over 1 h q12h, d 1-6) SDAC: DNR (45 mg/m^2/d iv, d 5-7), std-dose AraC (200 mg/m^2/d CI, d 1-7) Initially pts age <50 y on HDAC received AraC at 3 g/m^2 (HDAC-3) but after 2 years the monitoring committee determined neurotoxicity was too high and HDAC was reduced to 2 g/m^2 for all ages. Near the end of the study they decided HDAC (2 g/m^2) + DNR was also too toxic and induction randomization was stopped early. Those with CR to SDAC were randomized to 2 additional courses SDAC + DNR (d 6-7), or to one course HDAC (d 1-5) + DNR (d 6-7; dose reduced to 30 mg/m^2 for ages 50-64)) Those with CR to HDAC were non-randomly assigned to 1 additional course HDAC as in the 1st course + DNR (dose reduced to 30 mg/m^2 for ages 50-64)	Age <50: 55% HDAC (2 g/m^2) vs 59% (HDAC 3 g/m^2) vs 58%SDAC, p=0.96 Age 50-64: 45% HDAC (2 g/m^2) vs 53% SDAC	At median 51 m follow-up, 4-y OS age <50: 32% HDAC (2 g/m^2) vs 28% HDAC (3 g/m^2) vs 22% SDAC; Age 50-64: 13% HDAC (2 g/m^2) vs 11% SDAC 8-y DFS age <50: 26% HDAC vs 17%; 8-y DFS, age 50-65: 21% vs 8%	HDAC resulted in more fatal ((p=0.0033) and neurologic (p<0.0001) toxicity Induction portion closed slightly early due to toxicity.	600 pts for induction to ensure sufficient pts for consolidation study; increased Dec 1988 when HDAC dose reduced (485 pts SDAC, 188 pts HDAC) to give 80% power to detect 60% increase in odds of CR and to give 220 pts for consolidation randomization in ratio 130:90 to give 86% power to detect HR of 1.5 for DFS.	Induction with HDAC gave no improvement in CR or survival, but more toxicity
JALSG AML89; 1987-1991 Kobayashi, 1996 (168)	326 Age 15+ y (15-82 y, median 48 y), newly diagnosed AML	Induction; maintenance AraC vs BHAC	Chemo + BHAC vs chemo + AraC BHAC (200 mg/m^2 3h infusion daily), AraC (80 mg/m^2 CI daily) All received 6MP (70 mg/m^2 po with 300 mg/d allopurinol) + prednisolone (40 mg/m^2 by 3h infusion, d 1-4) and DNR (40 mg/m^2 iv, d 1-4 plus d 8-12 if necessary) Induction was in response-oriented and individualized manner; continued for 10-12 d until bone marrow became severely hypoplastic with blasts <5% If CR not reached in course 1, then repeated at ≈ 3-4 w intervals After consolidation and maintenance pts with CR were randomized to immunotherapy with ubenimex or no drug	72% BHAC vs 82%, p=0.035	OS at median 47 m was 45% (not reported by group) 55-m EFS 23% vs 35%, p=0.0253. DFS similar, p=0.3387 55-m DFS 53% ubenimex vs 52%, ns	No significant differences in incidence of complications/ toxic effects. Early deaths (30 d)13.8% vs 9.4%, p=0.222	NR	BHAC resulted in worse CR and EFS than AraC; authors suggested this may be due to dose/ duration

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[9]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
EORTC/GIMEMA AML-12; (EORTC 06991); 1999-2008 Willemze, 2014 (40); Willemze, 2011 (165) [abstract, IL-2 results]	1942 AML, age 15-60 y, median 45 y	Induction; maintenance AraC dose: 6 g vs 100 mg	HDAC vs std-dose AraC All received DNR (50 mg/m^2 iv, d 1, 3, 5) + etoposide (50 mg/m^2/d iv, d 1-5) HDAC: 3 g/m^2 q12h in 3-h infusion on d 1, 3, 5, 7 Std-dose AraC: 100 mg/m^2/d CI for 10 d Pts in CR received consolidation with AraC (500 mg/m^2/12h, 6 d) + DNR (50 mg/m^2/d, 3 d). CR pts without suitable stem-cell donor were eligible for 2nd randomization to autologous SCT followed or not by low-dose IL-2 (4-8×10^6 IU/d sc, 5 d/m during 1 y). 528 pts randomized but only 165/263 in IL-2 arm received IL-2 and 197/265 in observation arm were adequately documented	78.7% vs 72.0%, p<0.01; age <46 y: 82.4% vs 75.6%, p=0.01; age 46+: 74.8% vs 68.3%, p=0.03 After 1 course: 75.3% vs 68.2% HDAC significantly better for de novo (age 15-45 only), secondary (15-45, 46+)	6-y OS: 42.5% HDAC vs 38.7% std, p=0.06, (p=0.009 adjusted*) Age <46 y: 51.9% vs 43.3%, p=0.009; age 46-60: 32.9% vs 33.9%, p=0.91 DFS at 6 y: 44.7% vs 41.6%, p=0.27 (p=0.08 adjusted); age <46: 52.8% vs 46.4%, p=0.07 (p=0.02 adjusted); age 46+: 35.5% vs 35.8%, p=0.73 6-y EFS, age <46: 43.6% vs 35.1%, p=0.003; age 46+: 26.6% vs 24.8%, p=0.44 * for some comparisons significance was also reported after adjustment by multivariate analysis	Death during induction 9% vs 7.8%. Similar grade 3-4 non-hematologic toxicities, except conjunctivitis more frequent in HDAC (12.4% vs 0.5%). Analysis at median 6 y and 1091 deaths Analysis at median 6-y follow-up and 308 events	ITT. Powered to detect 8% treatment difference (from 35% to 43%) in 5-y OS, HR=0.80, and treatment age interaction (15-45 vs 46-60 y) with 80% power, based on 2000 pts and 1100 deaths.	HDAC produces higher remission and survival rates, especially in pts age <46

6MP, 6-mercaptopurine (mercaptopurine); AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; ATRA, all-trans retinoic acid; AZA, azacitidine; BHAC, N^4-behenoyl-1-ß-D-arabinosylcytosine; CI, continuous iv infusion; COAP, cyclophosphamide, VCR, AraC, prednisone; CR, complete remission (complete response); DAT, DNR +AraC + 6-thioguanine (TG); DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; GO, gemtuzumab ozogamicin; HAM, high-dose cytarabine + mitoxantrone; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; ICE, idarubicin + cytarabine + etoposide; IL-2, interleukin-2; ITT, intention to treat; iv, intravenously; MACE, amsacrine + AraC + etoposide; MDS, myelodysplastic syndromes; MidAC, MTZ + AraC; MTZ, mitoxantrone; NR, not reported; OS, overall survival; po, oral administration (per os); PR, partial response/remission; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; SAE, severe adverse effect; sc, subcutaneously; SCT, stem cell transplant; std, standard; t-AML, therapy-related AML following treatment of primary malignant disease; TG, 6-thioguanine; VCR, vincristine

Table 4-2. Induction, nucleoside analogues other than cytarabine Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[10]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Polish PALG; 2004-2011 Pluta, 2012 (169) [abstract]	178 Age >60 y, median 66 y, newly diagnosed AML	Induction Cladribine	DNR + AraC + cladribine vs DNR + AraC DNR (45 mg/m^2 iv, d 1-3), AraC (100 mg/m^2 iv, d 1-7), cladribine (5 mg/m^2 iv, d 1-5) Pts with CR after 1 cycle received consolidation	43% vs 33%, p=0.12 Age <65: 47% vs 29%, p=0.09 Age >65: 38% vs 39%, p=0.8	Median OS 9.5 m vs 10 m, p=0.98	Early deaths: 23% vs 15%, p=0.2. No significant differences in toxicity	NR	Higher CR with DAC up to age 65
Polish PALG; 2004-2008 Holowiecki, 2012 (65)	652 Age 16-60 y (median 47 y), untreated AML; stratified by age <40 y, 40+ y	Induction Cladribine (Fludarabine)	DAC (DA + cladribine) vs DAF (DA + fludarabine) vs DA (DNR + AraC) DNR (60 mg/m^2 as 5 min infusion, d 1-3), AraC (200 mg/m^2, d 1-7), cladribine (5 mg/m^2 as 3h infusion, d 1-5), fludarabine (25 mg/m^2 as 30 min infusion, d 1-5) Bone marrow aspirate was performed after the first course of induction as soon as the patient achieved the peripheral blood count required for CR, but not later than d 50 of treatment. Pts with PR received a 2nd course of the same regimen; only 5% of pts received a second course Pts with CR received consolidation followed by maintenance or SCT	DAC vs DA: 62% vs 51% (p=0.02) for 1 course; 67.5% vs 56% (p=0.01) for 2 courses DAF vs DA: 59% vs 56% (p=0.47) for 2 courses	3-y OS: 45% DAC vs 33% DA (median 24 vs 14 m), p=0.02, adjusted HR=0.69 (0.5-0.96), p=0.01 35% DAF vs 33% DA (median 16 m vs 14 m), p=0.98, HR=0.97 Subgroup age >50: 40% DAC vs 18% DA, p=0.005; other subgroups ns 3-y RFS: 45% DAC vs 37% DA (p=0.54); 42% DAF vs 37% DA (p=0.78)	All pts experienced grade 4 neutropenia and thrombocytopenia, no difference among arms. Alopecia, infections, mucositis, vomiting, diarrhea were most frequent grade 3+ non-hematologic adverse effects, no significant differences between arms	OS primary endpoint. 223 pts/arm to detect increase in OS from 40% to 55% with 0.8 power. Not powered for differences in subgroups. ITT for OS	Addition of cladribine is associated with better CR and survival
Sweden; 2000-2001 Juliusson, 2003 (66)	63 Age >60 y, median 71 y, AML, excluded prior MDL, other secondary AML permitted. 2:1 randomization	Induction Cladribine	AraC + IDA ± cladribine AraC (1 g/m^2/2 h bid for 4 d), IDA (10 mg/m^2/1h for 2 d), cladribine (5 mg/m^2/1h starting 2h before AraC twice daily for 4 d) 2nd induction for pts with CR: AraC (1 g/m^2/2 h, d 1-4) + IDA (10 mg/m^2/1h, d 1-2) ± cladribine (5 mg/m^2/1h, d 1-4) 2nd induction cycle for pts with PR (5-20% blasts): AraC (1 g/m^2/2 h, d 1-5) + IDA (10 mg/m^2/1h, d 1-2) ± cladribine (5 mg/m^2/1h, d 1-5) All pts with CR received 3rd course AraC (200 mg/m^2/12 h × 2, d 1-5) + IDA (10 mg/m^2/1 h, d 1) pts with CR received an optional 4th course: AraC (100 mg/m^2, d 1-5) + IDA (10 mg/m^2/1h, d 1) ± cladribine (5 mg/m^2, d 1-5)	51% vs 35% after 1 course, p=0.014. 63% vs 60% after 2 courses	No difference between arms	No difference in toxicity between arms. No difference in recovery from cytopenia.	Primary outcome: time to recovery from cytopenia, need for supportive care. OS by ITT	NR

[10] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[10]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Polish PALG; 1999-2002 Holowiecki, 2004 (170)	400 Age 16-60 y, median 45, newly diagnosed AML, including preceding MDS (n=63). Stratified age <40 y and 40+ y	Induction + consolidation Cladribine	DAC-7 (DNR + AraC + cladribine) vs DA-7 (DNR + AraC) DNR (60 mg/m^2/d, d 1-3), AraC (200 mg/m^2/d, d 1-7), cladribine (5 mg/m^2/d, d 1-5) Bone marrow aspirate was performed after the first course of induction therapy as soon as the patient achieved peripheral blood morphology values required for CR, but not later than on d 50 since the start of the treatment Pts with PR received a 2nd course of the same regimen Pts with non-remission after 1 cycles or partial/non-remission after 2 cycles received CLAG (cladribine, AraC, GCSF) Pts with CR (n=280) entered consolidation treatment: AraC + MTZ then pts in original DAC-7 group received AraC (2 g/m^2 iv q12h, d 1, 3, 5) + cladribine (5 mg/m^2 iv, d 1, 3, 5), DA-7 group received AraC	72% DAC-7 vs 69%, ns After 1st course: 63.5% vs 47%, p=0.0009; age >40 61% vs 43%, p=0.005; age ≤40 71% vs 55%	OS at 3 y: 34% vs 31%, ns 3-y EFS 43% vs 34%, ns; age >40 44% vs 28%, p=0.05; age ≤40 43% vs 46%, ns	Median hospitalization 33 d vs 40 d, p=0.002 Toxicity similar Early deaths 15.5% vs 14%	CR after 1 cycle was primary endpoint. Power of 0.85 to detect 15% difference in CR after 1 cycle with 400 pts	Cladribine improves 1 cycle response rate, may improve survival in pts age >40
EORTC/GIMEMA AML-14A (EORTC 06061) Selleslag, 2014 (68)	62 Age 18-60 y (median 50 y), untreated intermediate/ bad-risk AML or high-risk MDS (n=5)	Induction Clofarabine	1 –hr infusion vs push injection of clofarabine All received AraC and IDA Clofarabine: 10 mg/m^2, d 2, 4, 6, 8, 10 AraC: 500 mg/m^2 q12h, d 1-6 IDA: 10 mg/m^2/d 1, 3, 5 Induction was for 1 or 2 cycles; consolidation if CR	CR+CRi: 84% both arms	OS at 1 y: 74% each arm In pts with CR: DFS at 1 y: 58% vs 65% (ns)	Similar adverse effects	NR	Impressive CR, similar adverse effect profiles
NCRI AML16; 2006-2010 Burnett, 2012 (58) [GO vs none]; Burnett, 2012 (67) abstract]; Russell, 2015 (150) [abstract]	1115 Older pts suitable for intensive chemotherapy. Generally age >60 y, median 67 y; some younger pts if not suitable for trial for younger pts. De novo AML (72%), s-AML (17%), or high-risk MDS (10%)	Induction; consolidation; maintenance Clofarabine (GO)	DNR + AraC (DA arm) ± GO vs DNR + clofarabine (DClo arm) ± GO; GO given only in 1st of 2 induction cycles; GO vs no GO (n=1115) After 800 pts enrolled, subsequent pts received DNR/AraC ± GO DNR + AraC (3+10) ± GO → DNR + AraC (3+8): DNR (50 mg/m^2/d, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-10) ± GO (3 mg/m^2, d 1), then 2nd cycle DNR (50 mg/m^2/d, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-8) DNR + clofarabine ± GO → DNR + clofarabine: DNR (50 mg/m^2/d, d 1, 3, 5) + clofarabine (20 mg/m^2/d, d 1-5) ± GO; then 2nd cycle same without GO Post-induction, pts with CR were randomized to DNR (50 mg/m^2, d 1, 3) + AraC (100 mg/m^2 q12h, d 1-5) vs none; Maintenance: Pts not planned for allograft were then randomized to AZA (75 mg/m^2/d for 5 d; repeat q6w x9) vs none	63% DA vs 57% DClo; CR+CRi 71% DA vs 66% DClo, p=0.12 After 1 course: 54% vs 47%, OR=1.33, p=0.04	3-y OS 23% DA vs 22% DClo, p=0.3 3-y RFS 18% DA vs 21% DClo, p=1.0 5-y OS 15% vs 14%, p=0.6 5-y RFS 14% vs 15%, p=0.9	60-d mortality 15% DA vs 14% DClo. DA and DClo were equitoxic although DA arm had quicker neutrophil and platelet recovery and DClo had less transfusion support, antibiotics, and hospitalization	ITT. Primary outcome OS. Powered to detect difference of 10% in 2-y OS from 25% to 35% (equivalent to HR=0.76) with 90% power. 800 pts and 552 deaths required.	DA and DClo resulted in similar outcomes

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[10]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
China; 2005-2011 Yang, 2012 (11) [Chinese]	55 Newly diagnosed AML	Induction Fludarabine	FLAG vs IDA + AraC Fludarabine (30 mg/m^2/d, d 1-5), AraC (1 g/m^2/d, d1-5), GCSF (300 µg/d, d0-5) IDA (10-12 mg/m^2/d, d 1-3), AraC (100-150 mg/m^2/d, d 1-7)	92.0% vs 86.7%	NR	NR	NR	
Polish PALG; 2004-2008 Holowiecki, 2012 (65)	652 Age 16-60 y (median 47 y), untreated AML; stratified by age <40 y, 40+ y	Induction Fludarabine (Cladribine)	DAC (DA + cladribine) vs DAF (DA + fludarabine) vs DA (DNR + AraC) DNR (60 mg/m^2 as 5 min infusion, d 1-3), AraC (200 mg/m^2, d 1-7), cladribine (5 mg/m^2 as 3h infusion, d 1-5), fludarabine (25 mg/m^2 as 30 min infusion, d 1-5) Bone marrow aspirate was performed after the first course of induction as soon as the patient achieved the peripheral blood count required for CR, but not later than d 50 of treatment. Pts with PR received a 2nd course of the same regimen; only 5% of pts received a second course Pts with CR received consolidation followed by maintenance or SCT	DAC vs DA: 62% vs 51% (p=0.02) for 1 course; 67.5% vs 56% (p=0.01) for 2 courses DAF vs DA: 59% vs 56% (p=0.47) for 2 courses	3-y OS: 45% DAC vs 33% DA (median 24 vs 14 m), p=0.02, adjusted HR=0.69 (0.5-0.96), p=0.01 35% DAF vs 33% DA (median 16 m vs 14 m), p=0.98, HR=0.97 Subgroup age >50: 40% DAC vs 18% DA, p=0.005; other subgroups ns 3-y RFS: 45% DAC vs 37% DA (p=0.54); 42% DAF vs 37% DA (p=0.78)	All pts experienced grade 4 neutropenia and thrombocytopenia, no difference among arms. Alopecia, infections, mucositis, vomiting, diarrhea were most frequent grade 3+ non-hematologic adverse effects, no significant differences between arms	OS primary endpoint. 223 pts/arm to detect increase in OS from 40% to 55% with 0.8 power. Not powered for differences in subgroups. ITT for OS	Addition of cladribine is associated with better CR and survival
GOELAM SA4; NCT00925873; 1996-2000 Witz, 2004 (171) [Symposium presentation]; Pigneux, 2010 (83)	289 Age 60-75 y	Induction + consolidation Fludarabine	IDA + AraC + fludarabine vs IDA + AraC GCSF in both arms (5 µg/kg, d 1 to neutrophil recovery) IDA (8 mg/m^2/d, d 1-5), AraC (100 mg/m^2/d CI, d 1-7), fludarabine (20 mg/m^2/d iv for 30 min, d 2-7) Consolidation: intermediate-dose AraC (500 mg/m^2 q12h for 4 d) ± fludarabine according to initial randomization	65% vs 62%	2-y OS 37% vs 32% 2-y DFS 47.2% vs 33.6%, p=0.15	Extrahematological toxicities similar	NR	
Italian; 1999-2002 Russo, 2005 (8,9)	112 Age <60 y, newly diagnosed AML	Induction Fludarabine vs etoposide (Etoposide vs fludarabine)	FLAI vs ICE (one cycle) FLAI: fludarabine (25 mg/m^2/d, d 1-5) + AraC (2 g/m^2/d, d 1-5) + IDA (10 mg/m^2/d, d 1, 3, 5) ICE: IDA (10 mg/m^2/d, d 1, 3, 5) + AraC (100 mg/m^2/d CI, d 1-10) + etoposide (100 mg/m^2/d, d 1-5) Post-induction with HDAC (3 g/m^2/12 h/d, d 1-6) for all pts; if CR then received 2nd consolidation with MTZ + etoposide + AraC and/or stem cell transplant	74% FLAI vs 51%, p=0.01 After HDAC: 81% vs 69%, p=0.1	4-y OS: 32% vs 32%, p=0.7 4-y RFS 31.5% vs 44%, p=0.7	Death during induction 2% vs 9% (p=0.08); FLAI resulted in less hematological toxicities (p=0.002) and non-hematological toxicities (especially gastrointestinal (p=0.0001)	Primary endpoint CR rate. Required 55 pts/arm to detect 20% increment in CR rate with 70% power	FLAI more effective and less toxic for induction

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[10]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MRC AML15; ISRCTN17161961; 2002-2007 induction; 2002-2009 consolidation Burnett, 2011 (6); Burnett, 2013 (7); Pallis, 2011 (172) [p-glycoprotein]	3106. Induction, n=3106; consolidation, n=1440. Effect of GO induction, n=1113. Effect of GO consolidation, n=948. ADE vs FLAG-IDA, n=1268. ADE vs DA, n=1983 Age >15 y, Predominantly <60 y, untreated AML (de novo or secondary), APL excluded. Children age 0-14 (n=87) allowed in some arms	Induction; consolidation Fludarabine + IDA vs DNR (Etoposide) (GO)	<u>Induction</u> DA (DNR + AraC) ± GO vs FLAG-IDA (fludarabine + AraC + GCSF + IDA) ± GO vs ADE (AraC + DNR + etoposide) [± GO starting 2005] DA 3+10 ± GO → DA 3+8: DNR (50 mg/m^2 d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-10) ± GO (3 mg/m^2 d 1) then 2nd cycle with DNR (50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-8) FLAG-IDA ± GO → FLAG-IDA: fludarabine (30 mg/m^2 iv, d 2-6) + AraC (2 g/m^2 over 4 h starting after fludarabine, d 2-6) + GCSF (lenograstin 263 µg sc daily, d 1-7) + IDA (8 mg/m^2 iv daily, d 4-6) ± GO (3 mg/m^2 d 1); then 2nd cycle same without GO ADE 10+3+5 → ADE 8+3+5: DNR (50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-10) + etoposide (100 mg/m^2 d 1-5) then 2nd cycle same except AraC d 1-8 Consolidation See Table 4-14	<u>DA vs FLAG-IDA vs ADE</u> 78% DA vs 82% ADE, p=0.06 (OR/HR =1.24, 0.99-1.54) 84% FLAG-IDA vs 81% ADE, p=0.2 CR+CRi after 1 cycle: 63% DA vs 70% ADE, p=0.002; 77% FLAG-IDA vs 67% ADE, p<0.001 Subgroup Pgp-positive: 86% FLAG-IDA vs 78% DA/ADE; Subgroup Pgp-negative 86% FLAG-IDA vs 90% DA/ADE	<u>DA vs FLAG-IDA vs ADE</u> OS: ADE vs DA no difference (HR=1.00); 44% FLAG-IDA vs 37% ADE, HR=0.92 (0.79-1.06), p=0.2 RFS, relapse risk, death in remission similar for ADE vs DA (RFS 35% DA vs 32% ADE, p=0.8). FLAG-IDA (compared with ADE) reduced relapse (38% vs 55%, p<0.001), improved RFS (45% vs 34%, p=0.01), but increased death in remission (17% vs 11%, p=0.02)	<u>DA vs FLAG-IDA vs ADE</u> Induction deaths 6% DA vs 5% ADE, p=0.7; 7% FLAG-IDA vs 7% ADE, p=0.7. Grade 3-4 gastrointestinal toxicity greater with ADE compared with DA; other toxicities of modest clinical significance. FLAG-IDA compared with ADE had delay in recovery of neutrophils and platelets (p<0.001) resulting in more transfusions and antibiotics.	ITT Non-GO questions: At least 1000 pts per induction question to give 90% power to detect 10% survival difference at p<0.05 and 800 pts in consolidation to give 80% power to detect a 10% difference in OS	<u>DA vs FLAG-IDA vs ADE</u> FLAG-IDA is effective for induction
MD Anderson; 2001 Giles, 2003 (173)	34 Age ≥50 y, median 66 y, untreated, adverse karyotype AML (other than inv(16), t(8;21), -y, -X)	Induction + consolidation Troxacitabine	Bayesian adaptive randomized allocation IDA + AraC [IA] vs troxacitabine + AraC [TA] vs troxacitabine + IDA [TI] IDA + AraC: IDA (12 mg/m^2/d iv for 3 d), AraC (1.5 g/m^2/d iv over 2 h for 3 d) Troxacitabine + AraC: troxacitabine (6 mg/m^2/d iv for 5 d), AraC (1 g/m^2/d iv over 2 h for 5 d) Troxacitabine + IDA: troxacitabine (4 mg/m^2/d iv for 5 d) + IDA (9 mg/m^2/d iv for 3 d) Pts with CR received 1st consolidation course as per induction therapy, then subsequent cycles of same regimen at reduced doses TI arm stopped after 5 pts; TA arm stopped after 11 pts (and trial ended)	Within 49 d: 55% IA vs 27% TA vs 0% TI Overall: 55% IA, 45% IA, 20% TA 70% probability TA inferior to IA	OS equivalent	Recurrence rates 70% IA, 80% TA, 100% TI	CR was primary endpoint. Max 75 pts	Troxacitabine regimens not superior to IDA + AraC

ADE, AraC + DNR + etoposide; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; AZA, azacitidine; CI, continuous iv infusion; CR, complete remission (complete response); CRi, complete remission with incomplete recovery; DA, DNR + AraC; DFS, disease-free survival; DClo, DNR + clofarabine; DNR, daunorubicin; EFS, event-free survival; FLAG, fludarabine + high-dose AraC + GCSF; FLAI, Fludarabine + AraC + IDA; GCSF, granulocyte-colony stimulating factor; GO, gemtuzumab ozogamicin; HAM, high-dose cytarabine + mitoxantrone; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; ICE, idarubicin + cytarabine + etoposide; IDA, idarubicin; ITT, intention to treat; iv, intravenously; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OS, overall survival; PR, partial response/remission; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; SAE, severe adverse effect; sc, subcutaneously; SCT, stem cell transplant; std, standard

Table 4-3. Induction, anthracycline dose or schedule Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[11]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MRC AML14; LRF AML14; ISRCTN62207270; 1998-2005 Burnett, 2009 (76); Burnett, 2005 (77) [abstract]	1273 Predominantly ≥60 y (younger pts permitted if not fit to enter other trials for younger pts), AML (de novo or secondary) or high-risk MDS	Induction; consolidation DNR dose: 50 vs 35 mg (AraC dose) (PSC-833)	DNR (50 vs 35 mg/m^2) + AraC (200 vs 400 mg/m^2) Subgroup receiving DNR 35 mg/m^2 ± PSC-833 DNR (50 or 35 mg/m^2 iv, d 1-3) + AraC (100 or 200 mg/m^2 iv q12h, d 1-10) + TG (100 mg/m^2 po q12h, d 1-10). Course 2 same except AraC + TG, d 1-8 - Subgroup of 601 pts randomized to DNR 50, DNR 35, or DNR 35 + PSC-833 (2 mg/kg iv over 2 h with simultaneous CI 10 mg/kg/24 h for 72 h; in both courses) Pts with CR received MTZ (d 1-3) + AraC (q12h, d 1-3) then randomized to no further treatment or a 4th course consisting of IDA (10 mg/m^2 slow iv, d 1, 3) + AraC (100 mg/m^2 by 2h infusion q12h, d 1-3) + etoposide (100 mg/m^2 by 1h infusion daily, d 1-3)	55% DNR_{50} vs 57% DNR_{35}, p=0.6 52% DNR_{50} vs 57% DNR_{35} vs 47% DNR_{35} + PSC, p=0.06 (PSC vs not) 53% $AraC_{200}$ vs 55% $AraC_{400}$, p=0.7	5-y OS: 13% DNR_{50} vs 13% DNR_{35}, p=0.3 13% DNR_{50} vs 15% DNR_{35} vs 9% DNR_{35} + PSC, p=0.02 (PSC vs not) 11% $AraC_{200}$ vs 13% $AraC_{400}$, p=0.5 4th course vs only 3 courses: 22% vs 20%, p=0.7 5-year relapse 85% vs 84%, p=0.3 85% DNR_{50} vs 82% DNR_{35} vs 84% DNR_{35} + PSC, p=0.9 (PSC vs not) 84% $AraC_{200}$ vs 83% $AraC_{400}$, p=0.2 4th course vs only 3 courses: 80% vs 84%, p=0.3	Induction death 16% DNR_{50} vs 15% DNR_{35}, p=0.6 16% DNR_{50} vs 14% DNR_{35} vs 27% DNR_{35} + PSC, p=0.0003 (PSC vs not) 17% $AraC_{200}$ vs 18% $AraC_{400}$, p=0.6 No important differences in non-hematological toxicity or hematologic recovery	ITT analysis	No difference between DNR_{50} and DNR_{35} Pts did worse with PSC-833 No difference between $AraC_{200}$ and $AraC_{400}$ No difference between 3 and 4 courses
China; 2007-2013 Huang, 2014 (147)	297 Age 65-82 y, de novo or s-AML, Karnovsky performance status score ≥60	Induction + consolidation AraC dose + DNR dose: AraC 100 mg vs 75 mg	Standard vs attenuated AraC + DNR Standard: 2 cycles DNR (45 mg/m^2, 3 d) + AraC (100 mg/m^2 CI, 7 d) induction then 2 cycles DNR (45 mg/m^2, 3 d) + AraC (100 mg/m^2, 7 d) then 4 cycles HDAC (1.5 g/m^2, 4 d) Attenuated: 2 cycles DNR (30 mg/m^2, 3 d) + AraC (75 mg/m^2 CI, 7 d) induction then 2 cycles DNR (30 mg/m^2, 3 d) + AraC (75 mg/m^2, 7 d) then 4 cycles HDAC (1 g/m^2, 4 d)	CR+CRi 58.2% vs 55.1%, p=0.60	5-y OS 24 m vs 39 m, p<0.001 PFS 23 m vs 35 m, p<0.001	Early mortality 7.1% vs 0.64%, p<0.01 No overall response: 2.1% vs 13.5% Longer time to neutrophil recover (>1.5×10^9/L; p<0.001) and more grade3+ infections (p<0.001) with standard dose	NR	

[11] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[11]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
German AMLCG Buchner, 1997 (174) [abstract]; Buchner, 2001 (175) [review]	343 Age ≥60 y (60-83 y, median 66 y), primary AML	Induction DNR dose: 60 vs 30 mg	TAD with (60 vs 30 mg/m^2 DNR, 3 d) 60 mg/m^2 DNR, n=240 30 mg/m^2 DNR, n=103 Unequal numbers in arms because the 30 mg arm was closed when significantly superior response rate to the higher dose became obvious Pts in CR received TAD consolidation followed by monthly maintenance for 3 y	52% vs 45%, p=0.026 [54% vs 43%, p=0.038 in (175)] 1 course: 38% vs 20%, p=0.002 Age ≥65: 52% vs 32%, p=0.006	5-y OS 16% vs 10% Subgroup age ≥65: 14% vs 5%, p=0.002 5-y RFS 22% vs 17%; DFS 22% vs 17%, ns	Early and hypoplastic death 20% vs 31%, p=0.031	NR	60 mg/m^2 DNR is superior to 30 mg/m^2 in producing higher response rate and longer survival in pts age ≥60
Russian AML-95; 1995-1999 Parovichnikova, 2010 (176) [abstract and poster], (177) [Russian]; Savchenko, 1999 (178) [Russian, English abstract]; Parovitchnikova, 2003 (179) [abstract]	251 median age 39 y	Induction + maintenance DNR dose: 60 vs 45 mg	AraC + DNR (7+3 (45)) then 3 y maintenance vs AraC + DNR (7+3 (45)) then 1 y maintenance vs AraC + DNR (7+3 (60)) then 1 y maintenance AraC (100 mg/m^2 bid iv, d 1-7), DNR (45 or 60 mg/m^2, d 1-3) Maintenance with 7+3 (6-MP) for 3 or 1 y: AraC + 6MP (60 mg/m^2 bid 1-3 d) Total DNR dose 540-720 mg/m^2 # induction courses not stated, but 4 used in subsequent studies	75.5% vs 60% vs 63% 64.6% (45 mg/m^2) vs 64.6% (60 mg/m^2)	OS NR 6-y DFS: 28% (45 mg/m^2) vs 29% (60 mg/m^2) DFS 28% with 1 y maintenance vs 15% with 3-y maintenance, ns	Early lethality 8.1%, 22.4%, 16%. 3.5-y RFS 16%, 46%, 50%, ns	NR	More intense induction (60 vs 45 mg/m^2) can be used.
NCT00474006, Korea; 2001-2008 Lee, 2011 (44)	383 Age 15-60 y, median 43 y, previously untreated AML	Induction DNR dose: 90 vs 45 mg	High-dose DNR + AraC vs std DNR + AraC High-dose: DNR (90 mg/m^2/d, 3 d) + AraC (200 mg/m^2/d, 7 d) Std dose: DNR (45 mg/m^2/d, 3 d) + AraC (200 mg/m^2/d, 7 d) Pts with persistent leukemia were given a 2nd course: AraC (200 mg/m^2 CI over 24 h for 5 d) + DNR (45 mg/m^2 CI over 24 h for 2 d) Pts with CR received consolidation	82.5% HD vs 72.0% std dose, p=0.014 Adjusted HR=0.555, p=0.024	OS: At median 52.6 m, 5-y OS 46.8% vs 34.6%, p=0.030 Adjusted HR=0.739, p=0.032 At median 52.6 m, EFS 40.8% vs 28.4%, p=0.030; adjusted HR=0.774, p=0.048 RFS 49.4% vs 39.6%, p=0.432	Survival benefit was greatest in intermediate-risk subgroup (OS 51.0% vs 33.5%, p=0.016); differences were not significant for good and poor-risk groups	Endpoints CR, OS<RFS, EFS. 300 pts to give power of 0.8 to detect EFS HR=1.75/1.0 (0.57)	High-dose DNR improves CR and survival in pts age <60

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[11]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ECOG E1900, NCT00049517; 2002-2008 Fernandez, 2009 (41); Luskin, 2014 (42) [abstract]; Patel, 2012 (molecular subgroups) (43)	657 Age 17-60 y (median 48 y), untreated AML	Induction + consolidation DNR dose: 90 vs 45 mg	DNR high-dose (90 mg/m^2/d for 3 d + AraC; vs DNR std dose (45 mg/m^2/d for 3 d) + AraC AraC in all pts (100 mg/m^2/d CI, 7 d) 2nd induction cycle if residual leukemic blasts using AraC as above + DNR (45 mg/m^2/d for 3 d)	70.6% vs 57.3%, p<0.001 1 cycle: 52% vs 37% Age <50: 74.3% vs 59.4%	OS: At median 80 m follow-up, HR=0.74 (0.61-0.89), p=0.001 [median 23.7 m vs 15.7 m] Age <50: HR=0.66 (0.50-0.85), p=0.002 [median 34.3 m vs 19.0 m] Age ≥50: HR=0.81 (0.62-1.06), p=0.12 [median 16.9 m vs 12.2 m] Patel (43) reported benefit in specific mutations or risk groups; later abstract (42) reported benefit in all subgroups	No significant differences in SAEs. Induction deaths 5.5% vs 4.5%, p=0.60	ITT. 85% power to detect 23% decrease in HR for death, 2-y follow-up, n=830 with 563 deaths. Interim at 282 and 423 deaths. Secondary outcome CR, n=747 to detect 10% improvement with 85% power	Terminated early by data and safety monitoring committee at 3rd interim analysis when significant survival differences became apparent. High-dose better survival in all subgroups
HOVON 43 AML; SAKK 30/01; ISRCTN77039377; NTR212; 2000-2006 Lowenberg, 2009, 2010 (45,46)	813 Age 60-83 y, median 67 y; AML (including 169 with s-AML) or high-risk refractory anemia (n=39, 5%)	Induction; consolidation (post-remission) DNR dose: 90 vs 45 mg	AraC + DNR (escalated) vs AraC + DNR (conventional dose) AraC (200 mg/m^2 CI, 7 d), escalated dose DNR (90 mg/m^2, d 1-3), conventional dose DNR (45 mg/m^2, d 1-3) 2nd induction cycle with AraC (1000 mg/m^2 q12h, d 1-6) If CR, then either transplant or 2nd randomization to GO (6 mg/m^2; 25% of pts) or none (60% of pts) [113 pts GO, 119 control]. GO for up to 3 cycles, only 58% received all 3 cycles	64% escalated vs 54%, p=0.002 1 course: 52% vs 35%, p<0.001 Age 60-65: 73% vs 51% (OR=2.64, 1.63-4.29); age 66-70: 59% vs 58% (OR=1.04, ns); age ≥70 60% vs 52% (OR=1.38, ns)	2-yr OS 31% vs 26%, p=0.16; age 60-65: 38% vs 23%, p<0.001; age >65: p=0.43; CBF abnormalities, p=0.09 favouring escalated 2-y EFS 20% vs 17%, p=0.12; age 60-65: 29% vs 14%, p=0.002; age >65: p=0.64; CBF abnormalities: p=0.09 favoring escalated 2-yr DFS 30% vs 29%, p=0.77	No difference in rate of hematologic toxic effects, 30-d mortality (11% vs 12%), SAE after cycle 2. More grade 2-4 infections, platelet transfusions in escalated-dose group; overall grade 2-4 side effects 80% vs 74%, p=0.08	ITT. EFS primary endpoint. With 800 pts estimated 765 EFS events and 87% power to show improvement with HR=0.80 (1-y EFS from 22% to 30%).	Dose escalation gives more rapid and higher response rate without increased toxicity; survival benefit in pts age 60-65

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[11]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
NCRI AML17; ISRCTN55675535; 2011-2013 Burnett, 2015 (47,152)	1206 (3215) Median 53 y (range 16-72 y), AML or high-risk MDS. 84% de novo AML, 10% s-AML (including t-AML), 6% high-risk MDS High risk after induction: Group A, 393 pts (311 adverse features, median age 55 y; Group B/C, 82 relapse/ refractory, median age 47 y)	Induction; consolidation DNR dose: 90 vs 60 mg (GO, etoposide)	90 mg/m^2 DNR + AraC vs 60 mg/m^2 DNR + AraC [± GO ± etoposide] 90 or 60 mg/m^2 DNR: (90 or 60 mg/m^2/d, d 1, 3, 5; Course 2: 50 mg/m^2/d, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-10) After course 1, pts were defined by risk of relapse; pts designated favourable or intermediate risk received 2nd course with DNR (50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-8) along with treatment depending on molecular group • FLT3 mutation (n=130) randomized to Lestaurtinib (CEP-701: 40-80 mg bd from 2 d post chemo to 2 d before next course, up to max 28 d) vs placebo • CBF received GO (3 mg/m^2 on d 1 of course 2) • Non CBF, non-FLT3, and not poor risk (n=118) randomized to everolimus (5-10 mg/d, from 2 d post chemo to 2 d before next course, max 28 d) or not Of the pts eligible for lestaurtinib or everolimus, 371 randomized to addition 1 or 2 course of the treatment plus AraC (3 g/m^2 q12h, d 1, 3, 5) High (poor) risk (Group A: CR but adverse features; Group B: no CR; Group C: relapse): 393 pts were randomized (2:1) to DNR + clofarabine or FLAG + IDA DNR (50 mg/m^2, d 1, 3, 5) + clofarabine (20 mg/m^2, d 1-5) FLAG-IDA: fludarabine (30 mg/m^2, d 2-6) + AraC (2 g/m^2, 4 h post fludarabine, d 2-6) + GCSF (263 µg sc, d 1-7) + IDA (8 mg/m^2, d 4-6)	73% vs 75%, p=0.6 CR + CRi: 81% vs 84%, p=0.2; 68% vs 66%, p=0.4 after course 1	2-y OS 59% vs 60%, HR=1.16 (0.95-1.43), p=0.15; 2-y OS from CR 70% vs 69%, p=0.8 2-y RFS 51% vs 48%, HR=1.05, p=0.7 Relapse rate at 2 y: 39% vs 43%, p=1.0 High risk after induction Group A, median 25.8 m follow-up, 4-y OS 30% DNR-Clo vs 48%FLAG-IDA, p=0.10; 4-y RFS 34% DNR-Clo vs 46% FLAG-IDA, p=0.2 Group B/C median 12.7 m follow-up: 3-y OS 11% vs 35%, p=0.4 (18 m OS censored for transplant 30% vs 38%) Group A/B/C: HR=1.29 favouring FLAG-IDA, p=0.07	30-d mortality 6% vs 4%, p=0.09. 60-d mortality 10% vs 5%, p=0.001 DNR-90 group had higher rates death due to infection (n=25 vs n=11) or resistant disease (n=14 vs n=2) DNR -90 group had more grade 3-4 gastrointestinal toxicity Poor Risk: FLAG-IDA resulted in slower count recovery and more supportive care;	ITT. 1700 pts to give 90% powered to detect HR=0.80 in 5-y DFS improved from 45% to 53%; closed by monitoring committee after 1206 pts due to early mortality with DNR 90 mg/m^2	No survival benefit of 90 mg/m^2 vs 60 mg/m^2 DNR overall or in subgroups Results of 2nd or 3rd randomizations will be reported separately but did not impact DNR dose comparison
ECOG; 1981-1982 Kahn, 1984 (180)	40 Age ≥70 y by protocol (69+ y accepted), AML	Induction DNR dose + AraC dose: 60 mg × 3 vs 50 mg × 1	DAT full-dose vs attenuated schedule Full dose: DNR (60 mg/m^2/d iv, d 1-3), AraC (25 mg/m^2 iv push d 1 then 200 mg/m^2/d CI, d 1-5), TG (100 mg/m^2 po q12h, d 1-5) Attenuated DAT: DNR (50 mg/m^2 iv, d 1), AraC (100 mg/m^2 sc q12h, d 1-5), TG (100 mg/m^2 po q12h, d 1-5) Second course of same therapy allowed if PR or no response Pts with CR or PR received maintenance therapy with TG + AraC	25% full vs 30%, ns	OS median 29 d full vs 150 d, p<0.02	Early deaths (60 d): 60% full dose vs 25%, p=0.05 More than 100 d out of hospital: 12% full vs 59% Study terminated early due to high death rate of full-dose arm	NR	Attenuated chemotherapy is preferred for elderly patients

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[11]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MRC AML9; 1984-1990 Rees, 1996 (156)	951 Age 1-79 y, median 53 y, age >55 y starting May 1988; de novo or secondary AML; randomization by minimization for age (6 groups), sex, previous randomization	Induction; consolidation; maintenance DNR dose + AraC dose: 50 mg, 1 vs 3 d	DAT 1+5 vs DAT 3+10 DAT1+5: DNR (50 mg/m^2 iv, d 1), AraC (100 mg/m^2 iv q12h, d 1-5) and TG (100 mg/m^2 po 12-hourly, d 1-5) DAT 3+10: DNR (50 mg/m^2 iv, d 1, 3, 5), AraC (100 mg/m^2 iv q12h, d 1-10) and TG (100 mg/m^2 po 12-hourly, d 1-10) If substantial blast population remained after 1st induction course, administered a 2nd induction course; for the 1+5 group administered 3rd and 4th induction courses with DAT 2+8 (DNR, d 1, 6; AraC, d 1-8) if needed for CR Pts with CR were randomized (n=441) to 2 courses DAT 2+7 alternating with 2 courses either MAZE (m-AMSA, AZA, etoposide) or COAP (cyclophosphamide, VCR, AraC, prednisone) Those still in CR randomized (n=212) to either 1 y maintenance with 8 courses AraC + TG → 4 courses COAP or no further cytotoxic therapy	66% DAT 3+10 vs 61% DAT 1+5, p=0.15 Subgroups: age 0-49, 83% vs 76%; age 50-59, 63% vs 59%, age 60-69, 48% vs 46%; age ≥70, 45% vs 43%; all ns	5-y OS 23% DAT 3+10 vs 18%, p<0.05; age <60, 25% vs 20%; age ≥60, 12% vs 5% 5-y RFS 28% DAT 3+10 vs 23%, p=0.05	Time to CR shorter with DAT 3+10 (median 34 vs 46 d, p<0.0001) and correspondingly lower total supportive care required. Induction deaths 21% DAT 3+10 vs 16%, p=0.06	Aimed to recruit 1000 pts to be able to assess 10% difference in 5-y OS between induction treatments.	DAT 3+10 more effective than DAT 1+5
Russian; 1989-1991 Parovichnikova, 1992 (155)	16 Age >60 y, median 65 y, AML	Induction DNR dose + AraC dose: 45 vs 30 mg	AraC + DNR (std dose) vs AraC + DNR (low dose) Std dose: AraC (100 mg/m^2, q12h iv, 7 d), DNR 45 mg/m^2 iv, 3 d) [DNR reduced to 30 mg/m^2 in 3rd year] Low dose: AraC (50 mg/m^2, q12h iv, 7 d), DNR (30 mg/m^2, 3 d) Maintenance: 5 d rotating AraC with DNR or cyclophosphamide or 6-mercaptopurine	50% vs 37%	2-y OS 25 ± 6.9 w vs 41.9 ± 15.6 w, p=0.34	Profound neutropenia duration 20 d vs 13 d course 1 and 9 d vs 7 d (course 2). Similar frequency and severity of complications.	NR	Std dose may be used in elderly pts
ALFA-9801; NCT00931138; 1999-2006 Pautas, 2010 (181)	468 Age 50-70 y; median 60 y, de novo AML	Induction + consolidation; maintenance IDA dose, DNR: IDA 12 mg × 4 vs 12 mg × 3	High dose DNR vs IDA × 4 vs IDA × 3 (std IDA) AraC at 200 mg/m^2/d CI, d 1-7 for all pts High dose DNR (80 mg/m^2/d × 3 d) vs IDA (12 mg/m^2/d ×4) vs std dose IDA (12 mg/m^2/d × 3) Pts with resistant disease after 1 course could receive 2nd course with reduced HAM 2 courses consolidation if CR: AraC 1 g/m^2 1h infusion, q12h, 4 d) + either DNR (80 mg/m^2/d, d 1 for course 1 or d 1-2 for course 2) or IDA (12 mg/m^2/d, d 1 for course 1 or d 1-2 for course 2) according to initial randomization Maintenance (n=161): 2nd randomization for pts in CR to recombinant-IL-2 (rIL-2; 5×10^6 U/m^2 × 5 d each month) for 12 months vs none	No difference after 1 course. After all induction: 70% vs 78% vs 83%, p=0.04	ns, p=0.19 ns at 4 y (p=0.19); trend to shorter with DNR vs IDA3 (p=0.10)	NR	ITT, powered to show 15% difference between arms in second randomization	High dose-DNR or high-dose IDA had no clinically relevant superiority over std-dose IDA

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[11]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Japan; 1994-1997 Mori, 2000 (167) [Japanese; English abstract and tables]	29 Age 60-75 y, newly diagnosed AML (de novo or s-AML from MDS)	Induction DNR dose + BHAC dose: DNR 30 vs 40 mg	BHAC-DM, reduced (S-1) vs conventional dose (S-2) S1: BHAC (150 mg/m^2 d 1-7) + DNR (30 mg/m^2, d 1-3) + 6MP (70 mg/m^2, d 1-7; with allopurinol 300 mg/d) S2: BHAC (200 mg/m^2, d 1-7) + DNR (40 mg/m^2, d 1-3) + 6MP (70 mg/m^2, d 1-7; with allopurinol 300 mg/d) If blasts >15% on d 7 pts received 2 more days therapy	46.2% vs 43.8%	NR	Early deaths 1pt in each group; no grade 4 adverse effects	NR	Conventional dose is as acceptable as reduced dose in elderly
Turkey; 1987-1994 Koc, 2004 (182)	40 Age 18+ y (median 30 y), newly diagnosed AML	Induction + consolidation MTZ admin: 30 min or 24 h	AraC + bolus MTZ vs AraC + CI MTZ AraC (100 mg/m^2/d for 7 d), MTZ (10 mg/m^2/d, 3 d; either 30 min infusion or 24h infusion) 2nd course in pts without CR Pts with CR had 2 cycles consolidation with bolus or CI MTZ (10 mg/m^2/d, 2 d) + AraC (100 mg/m^2/d, 5 d) Maintenance: MTZ (bolus or CI, d 1, 5) and AraC at same doses for total of 12 cycles chemotherapy; max cumulative dose of MTZ 160 mg/m^2	75% vs 80%, p=0.99	OS median 9.8 m vs 14 m; 10-y OS 10.7% vs 21.3%, p=0.26 Age <40: 8.8 m vs 15.2 m, p=0.03 Median DFS 19.6 m vs 29.2 m; 10-y DFS 16.7% vs 28.6%, p=0.36 Age <40: DFS 11.2 m vs 29.3 m, p=0.02	Grade III-IV alopecia (p<0.05) and grade I-II hepatotoxicity (p=0.01) more frequent in CI arm. More grade III-IV nausea was observed in the bolus arm (9% vs 3%, p=0.10).	NR	Both bolus and iv MTZ effective but long-term survival low for both.
USA; 1991-1994 Feldman, 1997 (183)	54 Age >60 y (median 70 y), newly diagnosed AML, pre-existing MDS or other hematologic disorder included (n=20)	Induction MTZ dose: 80 × 1 vs 12 mg × 3	MTZ (80 mg/m^2 d 2) + AraC vs MTZ (12 mg/m^2, d 1-3) + AraC AraC (3 g/m^2 iv over 3 h, d 1-5); MTZ (iv infusion over 15 min; 80 mg/m^2/d, d 2; or 12 mg/m^2/d, d 1-3) No consolidation chemotherapy if CR, but observed for relapse	57% high-dose vs 42%, ns	OS median 9 m vs 6 m, ns Median RFS 5 m vs 3 m, ns; Median time to relapse 7 m vs 5 m	Significant toxicity included mucositis, diarrhea, transient hyperbilirubinemia, cardiac events but no difference between regimens. Induction death 3 pts high-dose vs 8 pts low-dose	An 80% power was required to accept an absence of significant difference	Toxicity of high-dose not worse. For survival, study designed to detect or exclude a very large difference and under-powered to confirm or reject smaller differences

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[11]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
JALSG AML95; 1995-1997 Ohtake, 2010 (184)	437 Age 15-64 y with previously untreated AML, excluding FAB-M3; excluded prediagnosed MDS	Induction IDA (# cycles)	Response-oriented individual induction (duration determined by response) vs std fixed-schedule induction using IDA + AraC IDA (12 mg/m^2 iv, d 1-3 d) + AraC (100 mg/m^2 CI, d 1-7) In the individualized group, bone marrow aspiration was performed on d 8, and if the marrow was not severely hypoplastic and had more than 15% blasts, additional IDA was given on d 8 and AraC on d 8 to 10, or if the marrow was severely hypoplastic and had more than 15% blasts, additional IDA was given on d 8 and AraC on d 8 and 9. Pts in both groups without CR received a 2nd course after 3-4 weeks Pts with CR received consolidation and maintenance	79.4% vs 81.9%, p=0.598	7-y OS: 37% vs 39%, p=0.496 7-y EFS: 22% vs 23%, p=0.546; RFS of CR pts 27% vs 29%, p=0.712 Subgroup age ≥50: RFS 17% vs 34%, p=0.026 Subgroup age <50: RFS 34% vs 25%, p=0.194	Early death 4.8% vs 1.8%, p=0.105; no significant differences in complications	ITT	No advantage of response-oriented induction compared with fixed schedule Difference in RFS by age subgroup cannot be explained, may be bias or confounding
JALSG GML200; UMIN-CTR (Japan): CM000000220, CM000000224; 2000-2005 Wakita, 2012 (185)	245 Age 65-80 y, median 71 y, newly diagnosed AML, excluding FAB-M3 or pre-diagnosed MDS	Induction; consolidation DNR (# cycles)	Fixed-schedule or response-oriented induction with DNR + BHAC DNR (40 mg/m^2/d by 30 min infusion, d 1-3; for pts age ≥70 used 30 mg/m^2/d) + BHAC (200 mg/m^2/d by 3h infusion, d 1-8) In the individualized group, bone marrow aspiration was performed on d 8, and if the marrow was not severely hypoplastic and had more than 20% blasts, additional BHAC was given on d 9 and 10. If 20–50% of blasts remained, DNR was added on d 8, and if more than 50% of blasts remained, DNR was added on d 8 and 9. Another bone marrow aspiration was performed on d 10, and if the marrow was not severely hypoplastic and had more than 20% blasts, additional BHAC was given on d 11 and 12. If 20–50% of blasts remained, DNR was added on d 11, and if more than 50%of blasts remained, DNR was added on d 11 and 12 Pts in both groups without CR received a 2nd course after 3-4 weeks All patients who had achieved CR were randomized (n=123) to consolidation therapy with or without ubenimex (see Table 4-14)	60.1% fixed group vs 63.6% individualized, p=0.6913 1 course: 46.3% vs 43.8%	4-y OS 18.2% vs 17.1%, p=0.807 (median 448 d vs 496 d) Multivariate analysis found no difference by induction treatment group, p=0.8264 4-y RFS 8.8% fixed vs 17.9%, p=0.467 (median 301 d vs 399 d)	Early death (30 d) 4.1% vs 3.3%	ITT. Primary endpoint of 1st randomization was CR. 98 pts/group to have 70% power to demonstrate 10% non-inferiority in CR (60% vs 55%).	Could not demonstrate that response-oriented individualized therapy was not inferior

6MP, 6-mercaptopurine (mercaptopurine); AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; AZA, azacitidine; BHAC, N^4-behenoyl-1-β-D-arabinosylcytosine (widely used in Japan instead of AraC since 1979); CI, continuous iv infusion; COAP, cyclophosphamide, VCR, AraC, prednisone; CR, complete remission (complete response); CRi, complete remission with incomplete recovery; DAT, DNR +AraC + 6-thioguanine (TG); DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; FLAG, fludarabine + high-dose AraC + GCSF; GCSF, granulocyte-colony stimulating factor; HAM, high-dose cytarabine + mitoxantrone; GO, gemtuzumab ozogamicin; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; IDA, idarubicin; IL2, interleukin-2; ITT, intention to treat; iv, intravenously; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OS, overall survival; po, oral administration (per os); PR, partial response/remission; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; SAE, severe adverse effect; sc, subcutaneously; std, standard; t-AML, therapy-related AML following treatment of primary malignant disease; TAD, thioguanine + cytarabine + daunorubicin; TG, 6-thioguanine; VCR, vincristine

Table 4-4. Induction, anthracycline comparison: IDA versus DNR Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[12]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
China; 2009-2011 Jia, 2011 (186) [Chinese, English abstract]	68 AML (n=45) or ALL (n=23), age <65 y	Induction IDA vs DNR	AML pts: IDA (domestic) + AraC vs DNR (imported) + AraC IDA (8 mg/m^2, 3 d), DNR (25 mg/m^2, 3 d), AraC (150 mg/m^2, 7 d) ALL: [VCR, domestic IDA, cyclophosphamide, l-asparaginase, prednisone] vs [VCR, imported DNR, cyclophosphamide, l-asparaginase, prednisone]	AML + ALL: 60% IDA vs 48% DNR, (p=0.50 for CR + PR) AML: 54.2% vs 47.6%	NR	Duration of remission >1 y: 17 pts IDA vs 6 pts DNR, p=0.02.	NR	IDA more effective than DNR
South Africa; 1985-1987 Bezwoda, 1990 (187)	104 Age <70 y, ANLL, no prior therapy for leukemia	Induction IDA vs DNR	IDA + AraC vs DNR + AraC IDA (20 mg/m^2/d po, 3 d), AraC (25 mg/m^2 iv loading dose then 100 mg/m^2/d CI, 7 d), DNR (30 mg/m^2/d iv, 3 d) 2 cycles planned; pts in remission received 1 cycle consolidation with same regimen	67% IDA vs 58%, ns; 1 cycle 48% vs 29%, p=0.01	OS NR Median duration remission 14 m vs 10 m	IDA resulted in less nausea (35% vs 73%), vomiting (25% vs 60%), stomatitis (8% vs 31%), shorter duration of neutropenia, less need for platelet support. Median duration CR 62 w vs 48 w, ns. Clinical cardiotoxicity in 4 pts (8%) with DNR vs 0 with IDA	NR	IDA is safe and effective
Japan Masaoka, 1996 (188)	64 Age 15-70 y, previously untreated ANLL (no previous treatment with IDA, DNR or AraC; no influence of any other previous therapy)	Induction IDA vs DNR	IDA + AraC vs DNR + AraC IDA (12 mg/m^2/d iv bolus, d 1-3), DNR (40 mg/m^2/d iv bolus, d 1-3), AraC (80 mg/m^2 2h iv infusion q12h, 7 d) After the first course bone marrow and peripheral blood were tested. If insufficient response, additional IDA/DNR or a second treatment course were administered	59.4% vs 40.6%, p=0.211, adjusted p=0.004; p=0.010 for IDA to be equivalent or superior Age 15-39: 60% vs 55.6% Age 40-49: 75% vs 27.3% Age 50-59: 55.6% vs 44.4% Age 60-69: 40.0% vs 33.3%	NR	Duration to attain <5% leukemic cells in bone marrow was shorter in IDA group (p=0.072). IDA group had more diarrhea (43.8% vs 28.1%; no difference in grade 3+); DNR had more changes on ECG parameters; other adverse reactions were similar	Assuming response rate of 80% IDA and 60% DNR, using α=0.06 and ß=0.20, target of 30 pts per group	IDA + AraC is treatment of choice

[12] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[12]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
France; 1987-1991 Reiffers, 1996 (189)	220 Age 55-75 y, untreated de novo AML	Induction + consolidation + maintenance IDA vs DNR	IDA + AraC vs DNR + AraC IDA (8 mg/m^2/d, iv bolus, 5 d), DNR (50 mg/m^2/d, iv bolus, 3 d), AraC (100 mg/m^2/d CI, 7 d) Pts with CR received consolidation (n=131): AraC (50 mg/m^2 q12h sc, 5 d) + either DNR (30 mg/m^2 iv bolus d 1-3) or IDA (8 mg/m^2 iv bolus d 1-3) according to the initial randomization arm Maintenance in pts with persistent CR (n=112): [AraC (50 mg/m^2 sc q12h, 5 d) + DNR (30 mg/m^2 d 1) or IDA (8 mg/m^2 d 1) according to initial randomization for 5 courses] and a continuous regime of methotrexate (15 mg/m^2 im, 3 times every 15 d) and 6MP (100 g/m^2 po for 15 d) as alternating 15 d courses for 2 years	67.9% IDA vs 61.1% DNR, p=0.30 Age 55-64: 83% vs 58%, p=0.007 Age 65-75: p=0.44	3-y OS: median 328 d IDA vs 273 d DNR, p=0.3 3-y DFS similar overall (p=0.22) but better with IDA in age >65 (median 21.6 m vs 9.4 m, p=0.016) EFS longer in IDA (p=0.07; median p=0.03)	Hematologic and non-hematologic toxicities similar in both arms	NR	IDA probably more efficient for pts age 55-75
ECOG E3993; 1993-1997 Rowe, 2004 (190)	348 Age >55 y, previously untreated AML	Induction DNR vs IDA vs MTZ (GM-CSF)	DNR vs IDA vs MTZ; all received AraC (100 mg/m^2/d CI for 7 d) DNR (45 mg/m^2/d iv, d 1, 2, 3); IDA (12 mg/m^2/d, d 1, 2, 3); MTZ 12 mg/m^2/d, d 1, 2, 3) 2nd induction cycle if residual leukemia Starting 1994 was also randomization to GM-CSF (250 µg/m^2/d sc) vs placebo starting 2 d before induction Also see GM-CSF section	41% DNR, 43% IDA, 46% MTZ, ns Age <70: 46% DNR, 55% IDA, 51% MTZ, p=0.04 DNR vs IDA Age≥70: 30% DNR, 24% IDA, 33% MTZ, p=0.37 IDA vs MTZ	OS median 7.7 m, 7.5 m, 7.2 m Median DFS: 5.7 m, 9.4 m, 7.1 m; p=0.68 for DNR vs IDA	NR	84% power to detect CR from 55% DNR to 75% either IDA or MTZ.	No conclusion regarding best anthracycline
GIMEMA; 1984-1987 Mandelli, 1991 (50)	255 Age 55-80 y, median 62 y; previously untreated ANLL; included those with previous myelodysplastic disorders	Induction + consolidation IDA vs DNR	IDA + AraC vs DNR + AraC IDA: 12 mg/m^2/d for 3 d; DNR 45 mg/m^2/d for 3 d; AraC 100 mg/m^2/d CI, d 1-7 2nd course if not CR: IDA 2 d or DNR 2 d; AraC 5 d CI Consolidation: 4 courses IDA (12 mg/m^2, d 1) + AraC (50 mg/m^2 sc) + TG (50 mg/m^2 po q8h, d 1-5) or DNR 45 mg/m^2 d 1) + AraC + TG	40% IDA vs 39% One cycle: 29.8% vs 20%, p=0.02	OS median survival 87 d vs 169 d, p=0.23 Median RFS 299 d vs 284 d Median response duration 274 d vs 239 d	Early or hypoplastic death 37.9% vs 21.6%; early death included deaths prior to treatment (n=15) Resistant disease 14% vs 31% Clinical complications similar except more infections in IDA group, p=0.06	ITT	IDA acts more rapidly but no overall advantage; lower dose of IDA may reduce toxicity

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[12]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Mexico Rubio Borja, 1993 (52) [abstract]	89 Age >16 y, mean 35 y, de novo AML	Induction IDA vs DNR	IDA + AraC vs DNR + AraC [2 cycles] IDA (10 mg/m^2, 3 d), DNR (45 mg/m^2, 3 d), AraC (100 mg/m^2, 7 d), 2nd cycle as above except AraC (5 d), IDA (2 d), DNR (2 d)	55% IDA vs 45% DNR, ns	NR	Early deaths 30% vs 20%. Similar toxicity, no significant difference	NR	
SECSG AML 305; 1985-1989 Vogler, 1992 (191); see Berman 1997 for long-term data (192)	230 Age >14 y (median 60 y) previously untreated AML (M1-M6; 7% IDA and 13% DNR were M3)	Induction + consolidation IDA vs DNR	IDA + AraC vs DNR + AraC IDA (12 mg/m^2 slow iv, d 1-3), DNR (45 mg/m^2 slow iv, d 1-3), AraC (100 mg/m^2/d CI, 7 d), 2nd induction course if blasts persisted Pts with CR received 3 courses consolidation: AraC (100 mg/m^2 q12h, 5 d) + TG (100 mg/m^2 po q12h, 5 d) + either DNR or IDA according to initial randomization (DNR, 50 mg/m^2 d 1; IDA, 15 mg/m^2 d 1) Late intensification (maintenance) at 13-week intervals, but abandoned after 47 pts due to 6 deaths secondary to aplasia [AraC 100 mg/m^2 CI, d 1-5; DNR 45 mg/m^2 or IDA 12 mg/m^2, d 1-2]	71% IDA vs 58% DNR, p=0.032 After 1 course: 55% vs 45%	OS median 297 d vs 277 d [in text], ns; 11 m IDR vs 9 m DNR [in figure], p=0.0913 Age 15-50: 34% vs 25%, median 511 d vs 585 d, p=0.68; age 51-60: 21% vs 5%, median 364 d vs 179 d, p=0.16; age >60, 10% vs 7%, median 235 d vs 209 d, p=0.66 After longer follow-up (about 9 y): IDA better, p=0.087 Median remission duration 433 d vs 328 d, p=0.11. Relapses as of Jan 1, 1992: 53% IDA vs 74%, p<0.01	Non-hematologic toxicities during induction similar. 5 pts deaths from IDA vs 1 DNR during late intensification Those who received late intensification had longer survival than without (DNR group: median 17 m vs 11 m, p=0.025; IDA group 42 m vs 13 m, p=0.008); more infections in IDA arm (95% vs 83%, p=0.026)	NR	IDA more effective for induction
US Multicenter Study Group; 1985-1989 Wiernik, 1992 (193); see Berman, 1997 for long-term data (192)	214 Adults, median 55 y; previously untreated AML; excluded treatment-related AML; stratified by age (18-50 y, 51-60 y, >60 y)	Induction IDA vs DNR	IDA + AraC vs DNR + AraC IDA (13 mg/m^2/d, d 1-3), DNR (45 mg/m^2/d bolus iv, d 1-3), AraC (100 mg/m^2/d CI, 7 d), 2nd course in pts without CR Post-remission therapy consisted of 2 courses same as induction therapy but for 2 d DNR/IDA and 5 d AraC	70% vs 59%, p=0.08; with 1 course: 55% vs 38%, p=0.015 Age 18-50: 88% vs 70%, p=0.035 Age 51-60: 71% vs 65%, ns Age >60: 50% vs 44%, ns	IDA better, median 12.9 m vs 8.7 m, p=0.038 Age >60: 3.4 m vs 3.2 m Age 18-60: 16.5 m vs 10.7 m, p=0.03 For OS after CR, median 549 d vs 478 d; 2-y OS 18% vs 8% After longer follow-up (10 y), IDA vs DNR, p=0.10	CR duration longer in IDA arm (9.4 m vs 8.4 m, p=0.021); toxicity similar although IDA pts had more prolonged myelosuppression during consolidation	ITT for primary analyses.	IDA is superior to DNR at doses used

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[12]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
EORTC/GIMEMA AML-10; 1993-1999 Mandelli, 2009 (49)	2157 Age 15-60 y, median 44 y, previously untreated AML (primary or secondary)	Induction + consolidation DNR vs MTZ vs IDA	DNR vs MTZ vs IDA [+ AraC + etoposide in all] DNR (50 mg/m^2, 5 min infusion, d 1, 3, 5), MTZ (12 mg/m^2, 30 min infusion, d 1, 3, 5), IDA (10 mg/m^2, 5 min infusion, d 1, 3, 5) All patients received AraC + etoposide in induction and + AraC in consolidation; 2nd induction course with same drugs if PR AraC (25 mg/m^2 iv bolus then 100 mg/m^2 CI daily for 10 d); etoposide (100 mg/m^2 iv over 1 h, d 1-5) If CR: consolidation with AraC (500 mg/m^2 as 2h infusion q12h, d 1-6) plus DNR/MTZ/IDA as previously (d 1-6) Younger pts with sibling donor assigned to allogenic SCT; rest were to receive autologous SCT	68.7% DNR, 69.8% MTZ, 66.9% IDA; MTZ vs DNR p=0.63; IDA vs DNR p=0.49	median 1.4 y (all groups), ns 5-y OS: 31.4% DNR, 33.7% MTZ, 34.3% IDA; MTZ vs DNR HR=0.95, p=0.43; IDA vs DNR HR=0.94, p=0.35	Similar hematopoietic recovery after induction; shorter recover after DNR consolidation (p<0.001). Similar grade 3-4 adverse effects after induction; DNR consolidation resulted in less frequency of severe infections (p=0.001) and other toxicities (p=0.01 vs IDA: p=0.20 vs MTZ)	ITT. 1353 pts (744 deaths) to detect increase in 5-y OS from 40% to 50% for IDA vs DNR and MTZ vs DNR. Would allow detection of 10% difference in CR (70% vs 80%).	MTZ or IDA results in better efficacy for pts who do not receive allogeneic SCT (no HLA-compatible sibling donor)
EORTC/GIMEMA AML-10; 1993-1999 Mandelli, 2009 (49)	1007	Induction + consolidation DNR vs MTZ vs IDA	Pts without HLA sibling donor Autologous SCT in 478 pts See other entry for data for all pts		5-y OS 35.7% DNR vs 43.2% MTZ vs 44.7% IDA: MTZ vs DNR HR=0.81 (0.63-1.05), p=0.03; IDA vs DNR HR=0.77 (0.59-1.00), p=0.01 5-y DFS 29.1% DHR vs 37.1% MTZ vs 37.0% IDA; MTZ vs DNR HR=0.80 (0.63-1.03), p=0.02; IDA vs DNR HR=0.83 (0.65-1.07), p=0.06	Of pts in CR without HLA-identical sibling, autologous SCT performed in 37% DNR vs 29% MTZ vs 31% IDA; lower rates in MTZ and IDA (p<0.001) due to toxicity and/or lower success rate of stem-cell collection	NR	IDA and MTZ better if no sibling donor
EORTC/GIMEMA AML-10; 1993-1999 Mandelli, 2009 (49)	465	Induction + consolidation DNR vs MTZ vs IDA	Pts with sibling donor available (potentially suitable for allogenic SCT); 322 (69.2%) had allogeneic SCT See other entry for data for all pts		5-y OS: 54.3% DNR vs 48.0% MTZ vs 52.8% IDA; MTZ vs DNR HR=1.19 (0.78-1.83), p=0.28, IDA vs DNR HR=1.03 (0.67-1.59), p=0.87 5-y DFS 47.9% DNR vs 44.1% MTZ vs 45.6% IDA; MTZ vs DNR HR=1.09 (0.73-1.63), p=0.58, IDA vs DNR HR=0.99 (0.66-1.47), p=0.93	NR	NR	No difference in long-term outcome

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[12]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Memorial Sloan Kettering L-19; 1984-1989 Berman, 1991 (194); see Berman, 1997 for long-term data (192)	130 Age 16-60 y (median 38 y), newly diagnosed AML; exclude pre-existing MDS, secondary leukemia or CML	Induction + consolidation; maintenance IDA vs DNR	IDA + AraC vs DNR + AraC IDA (12 mg/m^2/d for 3 d), AraC (25 mg/m^2 iv bolus then 200 mg/m^2 CI for 5 d) DNR (50 mg/m^2/d for 3 d) If CR after 1 or 2 induction cycles then received 2 courses of consolidation therapy using same drugs as induction but lower dose (IDA 12 mg/m^2/d for 2 d or DNR 50 mg/m^2/d for 2 d, AraC 25 mg/m^2 iv bolus then 200 mg/m^2/d CI for 4 d) Pts remaining in remission were randomized (n=12) to 1 y maintenance with low-dose AraC (5 mg/m^2 sc q12h for 14 d each month) or no further therapy	80% IDA vs 58%, p=0.005 1 course: 60% vs 28%, p=0.01. CR higher for IDA for each age group: Age 18-30, 80% vs 55%; age 31-50, 85% vs 62%; age 51-60, 71% vs 58%	OS at 5-y follow-up (median 2.5 y): 19.7 m IDA vs 13.5 m, p=0.025. OS at 10 y follow-up: IDA better, p=0.015 Only 12 pts randomized to maintenance or not; median OS 54 m maintenance vs 23 m, p=0.37	Median time to remission (for pts with CR) was 33 d IDA vs 41 d DNR. No significant difference in non-hematologic toxicity.	Primary outcome CR. O'Brian-Fleming multiple-testing procedure to permit 4 interim analyses (after each group of 20 pts/arm) and stopping if significance reached.	IDA can replace DNR in pts age <60 with newly diagnosed AML.
JALSG AML201; C000000157; 2001-2005 Ohtake, 2011 (51); Miyawaki, 2011 (86)	1057 Age 15-64 y, de novo AML excluding FAB M3 or pre-diagnosed MDS	Induction; consolidation (post-remission) IDA vs DNR	High-dose DNR + AraC vs std dose IDA + AraC Stratified by age (younger or older than 50 y) and FAB classification DNR (50 mg/m^2/d, 5 d); IDA (12 mg/m^2/d, 3 d); AraC (100 mg/m^2/d CI, d 1-7) 2nd course given after 3-4 weeks for pts without CR Patients with CR (n=781) were randomized to 3 courses HDAC (2 g/m^2 q12h for 5 d) vs 4 courses std-dose chemotherapy [course 1: MTZ + AraC; course 2: DNR + AraC; course 3 ACR + AraC; course 4: AraC + etoposide + vindesine]	77.5% DNR vs 78.2% IDA, p=0.79. Concluded non-inferior 1st course: 61.1% DNR vs 64.1% IDA, p=0.39 FAB M6: 38% DNR vs 78% IDA, p=0.037; no differences in other subgroups	5-y OS 48% DNR vs 48% IDA, p=0.54 5-y RFS 41% vs 41%, p=0.97	Early deaths (60 d) 2.1% DNR vs 4.7% IDA, p=0.03; sepsis (grade 3-5) 4.9% vs 8.7%, p=0.02; recover y from neutropenia and thrombocytopenia (27 d vs 28 d, p=0.0011; 24 vs 25 d, p=0.0034)	ITT. Powered to demonstrate non-inferiority of DNR compared with IDA. 840 pts to give 90% power at 1% level to demonstrate non-inferiority assuming 80% CR rate.	High-dose DNR and std dose IDA equally effective for adults age <65.
GOELAMS LAM-2001 NCT01015196; 2001-2005 Chevallier, 2010 (195)	823 Age 17-60 y, median 48 y, previously untreated non-M3-AML; t-AML allowed	Induction IDA vs DNR	IDA + AraC vs DNR + AraC IDA (8 mg/m^2/d iv, d 1-5), DNR (60 mg/m^2/d iv, d 1-3), AraC (200 mg/m^2/d iv, d 1-7) 2nd induction if d 15 bone marrow >5% blasts and/or Auer rods using same agents as cycle 1 but different dose/schedule: AraC (1 g/m^2/12 h iv, d 17-20), IDA (8 mg/m^2/d iv, d 17-18), DNR (35 mg/m^2/d iv, d 17-18) Pts without HLA-identical sibling donor received auto-HSCT (one or 2 times)	83% vs 81%	OS: Subgroup with auto-HSCT: 4-y OS 57% vs 50%, p=0.16 Subgroup with auto-HSCT: 4-y LFS 46% vs 34%, p=0.02	NR	Main objective was comparison of auto-HSCT strategies	

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[12]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
German AML Intergroup Study B: 2002-2008 OSHO 061; NCT01414231 (AML 2002 #061) Buchner, 2012 (196); https://clinicaltrials.gov/ct2/show/NCT01414231	373 Age 18-60 y, median 47 y	Induction + consolidation IDA + HDAC vs DNR	Study B (n=373): HDAC and IDA vs common control arm IDA (12 mg/m^2 over 20-30 min iv, d 1-3) + AraC (2 g/m^2, d 1, 3, 5, 7) [AraC either in 2 fractions/d over 3 h iv or by CI] Patients achieving remission received induction-type consolidation and autologous, family donor, or unrelated donor SCT Common control arm. Induction: AraC (100 mg/m^2/d CI, d 1-7) + DNR (60 mg/m^2/d iv over 2 h, d 3-5); 2nd course starting on d 22. Consolidation: 3 cycles at monthly intervals of HDAC (3 g/m^2 over 3 h q12h, d 1, 3, 5)	CR+CRi: 74%vs 70%, ns	5-y OS 46.6% vs 44.3%, p=0.933 5-y RFS 46.7% vs 44.8%, ns 5-y EFS 34.5% vs 31.5%, p=0.432	NR	Primary endpoint EFS, secondary OS and RFS. Power to discover a 15% difference in 5-y survival probabilities was >90%	No significant differences of the 5 treatment arms compared with the common (std) arm
ALFA-9803; NCT00363025; 1999-2006 Gardin, 2007 (53)	429 Age ≥65 y, median 72 y, previously untreated AML (s-AML); 20% or more myeloid marrow blasts	Induction; consolidation IDA vs DNR	IDA + AraC vs DNR + AraC IDA (9 mg/m^2 d 1-4) vs DNR (45 mg/m^2 d 1-4) AraC 200 mg/m^2 iv, d 1-7 in both arms Consolidation if CR (2nd randomization; n=164): intensive (single course as for induction) vs outpatient (ambulatory; 6 monthly cycles 45 mg/m^2 DNR or 9 mg/m^2 IDA, d 1 plus 60 mg/m^2/12 h AraC iv, d 1-5)	59% IDA vs 54% DNR, p=0.28 CR in 1 cycle: 59% IDA vs 48% DNR, vs p-0.03	2-y OS 27% (all pts), similar in both induction arms, p=0.37	Induction death rate 9% vs 10%, p=0.87	ITT. Primary endpoint 2-y OS	No noticeable difference between DNR and IDA
ALFA-9801; NCT00931138; 1999-2006 Pautas, 2010 (181)	468 Age 50-70 y; median 60 y, de novo AML	Induction + consolidation; maintenance IDA × 4 vs IDA×3 vs DNR	High dose DNR vs IDA × 4 vs IDA × 3 (std IDA) AraC at 200 mg/m^2/d CI, d 1-7 for all pts High dose DNR (80 mg/m^2/d × 3 d) vs IDA (12 mg/m^2/d × 4) vs std dose IDA (12 mg/m^2/d × 3) Pts with resistant disease after 1 course could receive 2nd course with reduced HAM 2 courses consolidation if CR: AraC 1 g/m^2 1h infusion, q12h, 4 d) + either DNR (80 mg/m^2/d, d 1 for course 1 or d 1-2 for course 2) or IDA (12 mg/m^2/d, d 1 for course 1 or d 1-2 for course 2) according to initial randomization Maintenance (n=161): recombinant-IL-2 vs none	No difference after 1 course. After all induction: 70% vs 78% vs 83%, p=0.04	4-y OS 23% vs 34% vs 32%, p=0.19 4-y EFS 12% vs 22% vs 21%, p=0.19; trend to shorter with DNR vs IDA3 (p=0.10)	NR	ITT, powered to show 15% difference between arms in second randomization	High dose-DNR or high-dose IDA had no clinically relevant superiority over std-dose IDA

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[12]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ALFA-9801 and ALFA-9803; 1999-2006 Gardin, 2013 (197)	727 Joint analysis, age ≥50 y, median 67 y; excluded high-dose IDA arm	Induction IDA vs DNR (Anthracycline DNR dose)	DNR (total 240 mg/m^2) vs DNR (total 180 mg/m^2) vs IDA (total 36 mg/m^2) AraC at 200 mg/m^2/d CI, d 1-7 for all pts High dose IDA arm not included	IDA vs DNR: 69% vs 61%, p=0.029	IDA vs DNR: median 14.2 m, p=0.13	Cure rate, IDA vs DNR 16.6% vs 9.8%, p=0.018 overall; 27.4% vs 15.9% p=0.049 age <65 y	NR	IDA predicts better long-term outcome

6MP, 6-mercaptopurine (mercaptopurine); ACR, aclarubicin; ANLL, acute non-lymphoid leukemia; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; CI, continuous iv infusion; CR, complete remission (complete response); DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; GM-CSF, granulocyte-macrophage colony-stimulating factor; HAM, high-dose cytarabine + mitoxantrone; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; IDA, idarubicin; IL-2, interleukin-2; ITT, intention to treat; iv, intravenously; LFS, leukemia-free survival; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OS, overall survival; po, oral administration (per os); PR, partial response/remission; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; sc, subcutaneously; SCT, stem cell transplant; std, standard; TG, 6-thioguanine; VCR, vincristine

Table 4-5. Induction, anthracycline comparison: MTZ versus DNR Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[13]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
HOVON AML-9; 1986-1993 Lowenberg, 1998 (198), Lowenberg, 1997 (199)	489 Age >60 y, median 68 y, AML	Induction + consolidation; maintenance MTZ vs DNR	MTZ + AraC vs DNR + AraC MTZ (8 mg/m^2 iv bolus, d 1-3), AraC (100 mg/m^2 CI, d 1-7), DNR (30 mg/m^2 iv bolus, d 1-3) 2nd induction course if PR Consolidation if CR using same agents but 1 d of DNR or MTZ 2nd randomization (n=147) after consolidation for patients in CR: no further therapy (arm A) vs low-dose AraC (10 mg/m^2 sc q12h, d 1-12 at 42-d intervals for 8 cycles or until relapse) Insufficient pts in consolidation arms (228 planned vs 147 actual) so additional pts were randomized in the HOVON AML-11 trial (199) and a meta-analysis of the results of the two studies was performed. The AML-11 trial used higher AraC during induction (200 mg/m^2) but both trials used 10 mg/m^2 during maintenance. [note that the AML-11 is a trial of GCSF for induction]	46.6% MTZ vs 38.0% DNR, p=0.067	5-y OS 6% vs 9%, ns. OS median 39 w vs 36 w, p=0.23. Survival from CR median 74 w vs 55 w; 5-y survival 12% vs 16%, RR=0.85 (0.633-1.149) 5-y DFS 8% in each arm; median DFS 39 w vs 39 w. DFS from CR similar, p=0.73	Death (early or post-induction) 21.1% MTZ vs 14.9% DNR, p=0.079 Neutropenia duration median 22 d MTZ vs 19 d DNR. More severe infections with MTZ (25.1% vs 18.6%, p=0.036)	488 pts to detect difference in CR rate from 40% to 55%. Final analysis after 425 deaths. 208 pts to detect 15% difference (10% vs 25%) in DFS at 3 y between maintenance groups with final analysis after 171 events	MTZ provided better response rates, but overall survival and DFS did not improve. Low-dose AraC maintenance improved DFS but effect unclear in AML-11 trial with higher AraC during induction; no significant difference in OS
Argentina; 1985-1987 Pavlovsky, 1994 (200)	143 Previously untreated AML, adult	Induction MTZ vs DNR	MTZ (12 mg/m^2 iv) + AraC vs DNR (45 mg/m^2 iv) + AraC Both groups received AraC (100 mg/m^2 CI for 7 d) Those with CR had consolidation with MTZ or DNR	50% MTZ vs 39% DNR after 1 cycle 53% MTZ vs 43% DNR overall, p=0.34	Median survival 103 d vs 160 d, p=0.85	Median duration remission 185 d vs 165 d, p=0.85; more early deaths with MTZ (24 vs 15 in first 21 d)due to myelosuppression and deficiency in supportive care but more failure with DNR	NR	MTZ and DNR similar efficacy and safety overall

[13] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[13]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
German SAL 60plus; 2005-2009 Rollig, 2010 (159) [abstract] Note: Results presented at ASH, Dec 2015. Rollig, 2015 (160)	485 Age >60 y, median 69	Induction MTZ, DNR; AraC dose: 2g vs 100 mg	IMA (intermediate does AraC + MTZ) vs std 3+7 (DNR + AraC) IMA: AraC (1g/m^2 bid, d 1, 3, 5, 7) + MTZ (10 mg/m^2, d 1-3) Std 3+7 (DA): AraC (100 mg/m^2 CI, d 1-7) + DNR (45 mg/m^2, d 3-5) Pts in CR after DA received intermediate-dose AraC + AMSA; pts in CR after IMA received standard-dose AraC + MTZ (2+5)	55% IMA vs 39% DA, p=0.001 Including CR after trial discontinuation 64% vs 55%, p=0.043	Median DFS at 25.7 m: 10.2 m vs 11.7 m (p=0.11) RFS superimposable in first year (median 10 m vs 11 m) then separate; 1-y RFS 46% vs 45%; 3-y RFS 14% vs 29%, p=0.042 Median OS 10 m vs 10 m; 1-y OS 44% vs 45%; 3-y OS 19% vs 19%, p=0.513. Differences in RFS may be due to difference in consolidation used in each arm	Early mortality 18.1% vs 18.4%; SAE + grade4 non-hematological toxicity 19% vs 23%, p=0.1866; median TTR 10.3 m vs 11.1 m, p=0.328 Liver toxicity OR=0.52, p=0.001; gastrointestinal symptoms OR=0.62, p=0.041. Duration of grade 3+ neutropenia and thrombocytopenia longer with IMA (25 d vs 23 d, p=0.032 and 20 d vs 16 d, p<0.001, respectively)	ITT. Primary outcome CR, expected difference of 15% in favour of IMA. Secondary endpoints SAEs, time to relapse, RFS, OS	
Lederle Coop Group; 1984-1987 Arlin, 1990 (201)	200 Age >15 y (median 60 y), previously untreated ANLL, no prior MDS	Induction MTZ vs DNR	MTZ + AraC vs DNR + AraC (7+3) MTZ (12 mg/m^2/d, d 1-3), DNR (45 mg/m^2/d, d 1-3), AraC (100 mg/m^2/d CI, 7 d) 2nd induction course (5 d AraC and 2 d MTZ or DNR) if residual disease 2 courses of consolidation with same drugs and doses used in induction (5 d AraC, 2 d MTZ or DNR)	63% vs 53%, p=0.15 Age <60: 80% vs 69% Age ≥60: 46% vs 37%	Median 328 d vs 247 d, ns. Age <60: 444 vs 379 d; Age >60: 98 d vs 51 d	Median time to CR 35 d vs 43 d; median duration of remission 240 d vs 198 d, p=0.27 [age <60, 232 d vs 191 d; age >60 296 d vs 230 d]. No significant difference in SAEs	NR	MTZ and DNR are of comparable safety and efficacy; differences favoured MTZ but not significant; need larger study to verify

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[13]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MRC AML12; ISRCTN17833622; 1994-2002 Burnett, 2010 (153,154)	2934 Age <60 y, median 41 y, de novo or s-AML/ t-AML (n=239) and high-risk MDS; 16.7% were age 0-14 (children) of which all but 2 pts were in the MAE vs ADE comparison; 2.9% age ≥60. Due to inclusion of children in MAE vs ADE, results cannot be directly compared with H-DAT/ S-DAT results	Induction; consolidation MTZ vs DNR	A. Before Amendment (n=1658) MAE (MTZ + AraC + etoposide) vs ADE (AraC + DNR + etoposide) A subset of both groups randomized to GCSF or not in first cycle (n=480): GCSF 263 µg in course 1, commencing on d 8 after chemotherapy for 10 d or until the neutrophil count exceeded 0.5×10^9/L for two consecutive days, whichever was shorter MAE 10+3+5 → MAE 8+3+5: MTZ (12 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2, q12h, d 1-10) + etoposide (100 mg/m^2, d 1-5) followed by same except AraC, d 1-8 ADE 10+3+5 → ADE 8+3+5: DNR (50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-10) + etoposide (100 mg/m^2, d 1-5) followed by same except AraC, d 1-8 Both Phases A & B Randomized Consolidation if CR (n=992): MACE then randomize to 1 (MidAC) or 2 further courses (ICE then MidAC)	78% MAE vs 78% ADE, p=0.9 74% GCSF vs 74% placebo, p=1.0	8-y OS 42% MAE vs 39% ADE, p=0.5 30% GCSF vs 37% placebo, p=0.09 8-y RFS 43% MAE vs 37% ADE, p=0.09 32% GCSF vs 33% placebo, p=0.5	Induction death 6% MAE vs 6% ADE, p=0.6 9% GCSF vs 5% placebo, p=0.11 Adverse Effects Significantly longer hematologic recovery time and more antibiotic use with MAE (compared with ADE. MAE induced significantly greater gastrointestinal toxicity	ITT. 1200 pts to each induction question to give 95% (75%) power to detect difference of 10% (7.5%) survival. 800 pts in consolidation to give 80% power to detect 10% difference in OS	OS for 2-3 courses MAE vs 4-5 courses ADE ns, but OS 2-3 courses ADE worse than 2-3 courses MAE, p=0.003; OS worse with 2-3 courses ADE than 4-5 courses ADE, p=0.08
ALFA-9000; 1990-1996 Castaigne, 2004 (203)	592 Adults age ≤65 y (15-65; median 46 y, newly diagnosed AML including s-AML, stratified by age (<50 y, ≥50 y)	Induction DNR vs DNR → MTZ	DNR + AraC [control, arm A] vs DNR + AraC → MTZ + AraC (arm B) vs time-sequenced DNR + AraC → MTZ + AraC (arm C) Arm A [3+7, control]: DNR (80 mg/m^2 iv, d 1-3) + AraC (200 mg/m^2 CI, d 1-7) Arm B [double induction]: DNR + AraC + MTZ (12 mg/m^2 iv, d 20-21) + AraC (500 mg/m^2/12 h iv, d 20-22) Arm C [timed-sequence]: DNR + AraC (500 mg/m^2 CI, d 1-3) + MTZ (12 mg/m^2 iv, d 8-9) + AraC (500 mg/m^2/12 h iv, d 8-10) Consolidation if CR: 1 cycle AMSA + AraC, then 1 cycle MTZ + AraC + etoposide	57% vs 70% vs 61% (after salvage 77% vs 77% vs 74%p p=0.99 A-B, p=0.64 A-C) Fewer pts needed salvage to reach CR in arm B (6%) than arm A (20%) or arm C (13%), p<0.001	5-y OS, arms A, B, C: 28% vs 29% vs 32% 5-y EFS, arms A, B, C: 16% vs 17% vs 25%, ns; age <50 also ns	RFI: arm B vs A, p=0.39; arm C vs A, p=0.15 RFI, subgroup age <50: arm C vs A, p=0.038; arm B vs A ns Induction deaths: 12% arm A, 16% arm B, 16% arm C (p=0.3 arm B vs A; p=0.25, arm C vs A)	ITT	

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[13]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Sweden Wahlin, 1991 (202)	44 Age 18-78 y, median 52.5 y, previously untreated AML	Induction + consolidation MTZ vs DNR	MTZ + AraC vs DNR + AraC MTZ (12 mg/m^2 iv over 15-30 min, d 1-3), AraC (100 mg/m^2 iv CI, d 1-7), DNR (45 mg/m^2 iv over 15-30 min, d 1-3) 2nd induction course if PR, on a 2+5 schedule Post-induction, 2 courses, MTZ arm: MTZ (12 mg/m^2, d 1-2) + AraC (100 mg/m^2 CI, d 1-5) Post-induction, 2 courses DNR arm: DNR (45 mg/m^2 iv over 15-30 min, d 1-2) + AraC (100 mg/m^2 CI, d 1-5)	67% vs 70%	Median 365 d vs 401 d, p=0.31	Toxicity similar, no significant difference in number and severity of adverse events	NR	MTZ and DNR similar efficacy and toxicity
ECOG E3993; 1993-1997 Rowe, 2004 (190)	348 Age >55 y, previously untreated AML	Induction DNR vs IDA vs MTZ (GM-CSF)	DNR + AraC vs IDA + AraC vs MTZ + AraC DNR (45 mg/m^2/d iv, d 1, 2, 3); IDA 12 mg/m^2/d, d 1, 2, 3); MTZ 12 mg/m^2/d, d 1, 2, 3); AraC (100 mg/m^2/d CI for 7 d) 2nd induction cycle if residual leukemia Starting 1994 was also randomization to GM-CSF (250 µg/m^2/d sc) vs placebo starting 2 d before induction Also see GM-CSF section	41% DNR, 43% IDA, 46% MTZ, ns Age <70: 46% DNR, 55% IDA, 51% MTZ, p=0.04 DNR vs IDA Age≥70: 30% DNR, 24% IDA, 33% MTZ, p=0.37 IDA vs MTZ	OS median 7.7 m, 7.5 m, 7.2 m Median DFS: 5.7 m, 9.4 m, 7.1 m; p=0.68 for DNR vs IDA	NR	84% power to detect CR from 55% DNR to 75% either IDA or MTZ.	No conclusion regarding best anthracycline

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[13]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MRC AML11; 1990-1998 Goldstone, 2001 (69)	1314 Initially accepted age 56+ y; age ≥60 y starting end of 1994, although younger pts allowed if not suitable for more intensive chemo in AML10/AML12. 2% of pts age <56. Any de novo or secondary AML	Induction; consolidation; maintenance MTZ vs DNR (Etoposide) (GCSF)	2 courses induction: DAT vs ADE vs MAC (1:1:2 ratio) DAT 3+10 → DAT 2+5: DNR (50 mg/m^2 slow iv, d 1, 3, 5) + AraC (100 mg/m^2 12-hourly iv, d 1-10) + TG (100 mg/m^2 12-hourly po, d 1-10) then same but DNR, d 1, 3 and (AraC + TG), d 1-5 ADE 10+3+5 → ADE 5+2+5: DNR (50 mg/m^2 slow iv, d 1, 3, 5) + AraC (100 mg/m^2 12-hourly iv, d 1-10) + etoposide (100 mg/m^2 iv 1-h infusion, d 1-5) then same but DNR, d 1, 3, and AraC, d 1-5 MAC 3+5 → MAC 2+5: MTZ (12 mg/m^2 iv 30-min infusion, d 1-3) + AraC (100 mg/m^2 12-hourly iv, d 1-5) then same but MTZ, d 1, 3 A subset of pts (n=226) were randomized to receive GCSF (293 µg/d sc, d 8 of course 1 until neutrophil recovery or maximum of 10 d) or placebo Pts in remission (n=371) randomized to stop after a third course (DAT 2+7) or after 4 additional courses (DAT 2+7, COAP, DAT 2+5, COAP) Third randomization (n=362): IFN-α maintenance for 1 year vs none	62% DAT vs 55% MAC, p=0.04 Benefit of DAT in pts <70 and >70	5-y OS: 12% DAT vs 10% MAC, p=0.1 8% ADE vs 10% MAC, p=0.2 5-y DFS: 18% DAT vs 15% ADE vs 16% MAC	No important differences in non-hematologic toxicity, or for number of days for neutrophil and platelet recovery	ITT	
EORTC/GIMEMA AML-10; 1993-1999 Mandelli, 2009 (49)	2157 Age 15-60 y, median 44 y, previously untreated AML (primary or secondary)	Induction + consolidation DNR vs MTZ vs IDA	DNR vs MTZ vs IDA [AraC + etoposide in all arms] All patients received AraC + etoposide in induction and + AraC in consolidation AraC (25 mg/m^2 iv bolus then 100 mg/m^2 CI daily for 10 d); etoposide (100 mg/m^2 iv over 1 h, d 1-5) DNR (50 mg/m^2, 5 min infusion, d 1, 3, 5), MTZ (12 mg/m^2, 30 min infusion, d 1, 3, 5), IDA (10 mg/m^2, 5 min infusion, d 1, 3, 5) 2nd course with same drugs if PR If CR: consolidation with AraC (500 mg/m^2 as 2h infusion q12h, d 1-6) plus DNR/MTZ/IDA as previously (d 1-6) Younger pts with sibling donor assigned to allogenic SCT; rest were to receive autologous SCT	68.7% DNR, 69.8% MTZ, 66.9% IDA; MTZ vs DNR p=0.63; IDA vs DNR p=0.49	median 1.4 y (all groups), ns 5-y OS: 31.4% DNR, 33.7% MTZ, 34.3% IDA; MTZ vs DNR HR=0.95, p=0.43; IDA vs DNR HR=0.94, p=0.35	Similar hematopoietic recovery after induction; shorter recover after DNR consolidation (p<0.001). Similar grade 3-4 adverse effects after induction; DNR consolidation resulted in less frequency of severe infections (p=0.001) and other toxicities (p=0.01 vs IDA: p=0.20 vs MTZ)	ITT. 1353 pts (744 deaths) to detect increase in 5-y OS from 40% to 50% for IDA vs DNR and MTZ vs DNR. Would allow detection of 10% difference in CR (70% vs 80%).	MTZ or IDA results in better efficacy for pts who do not receive allogeneic SCT (no HLA-compatible sibling donor)

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[13]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
EORTC/GIMEMA AML-10; 1993-1999 Mandelli, 2009 (49)	1007	Induction + consolidation DNR vs MTZ vs IDA	Pts without HLA sibling donor Autologous SCT in 478 pts See other entry for data for all pts	NR	5-y OS 35.7% DNR vs 43.2% MTZ vs 44.7% IDA: MTZ vs DNR HR=0.81 (0.63-1.05), p=0.03; IDA vs DNR HR=0.77 (0.59-1.00), p=0.01 5-y DFS 29.1% DHR vs 37.1% MTZ vs 37.0% IDA; MTZ vs DNR HR=0.80 (0.63-1.03), p=0.02; IDA vs DNR HR=0.83 (0.65-1.07), p=0.06	Of pts in CR without HLA-identical sibling, autologous SCT performed in 37% DNR vs 29% MTZ vs 31% IDA; lower rates in MTZ and IDA (p<0.001) due to toxicity and/or lower success rate of stem-cell collection	NR	IDA and MTZ better if no sibling donor
EORTC/GIMEMA AML-10; 1993-1999 Mandelli, 2009 (49)	465	Induction + consolidation DNR vs MTZ vs IDA	Pts with sibling donor available (potentially suitable for allogenic SCT); 322 (69.2%) had allogeneic SCT See other entry for data for all pts	NR	5-y OS: 54.3% DNR vs 48.0% MTZ vs 52.8% IDA; MTZ vs DNR HR=1.19 (0.78-1.83), p=0.28, IDA vs DNR HR=1.03 (0.67-1.59), p=0.87 5-y DFS 47.9% DNR vs 44.11 MTZ vs 45.6% IDA; MTZ vs DNR HR=1.09 (0.73-1.63), p=0.58, IDA vs DNR HR=0.99 (0.66-1.47), p=0.93	NR	NR	No difference in long-term outcome

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[13]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Turkey; 1992-1995 Beksac, 1998 (204)	99 Age >14 y, previously untreated ANLL; also included pts with myelodysplastic features of <6 m duration. Median age Groups 1, 2, 3 were 40 y, 31 y, 36 y, p<0.05 (G1 vs G2); G3 had more pts age >60 (n=7 vs n=2 in other groups)	Induction + consolidation IDA vs MTZ vs DNR + etoposide	Group 1: AraC + IDA vs Group 2: AraC + DNR + etoposide vs Group 3: AraC + MTZ Group 1: AraC (100 mg/m^2 CI, d 1-7) + IDA (12 mg/m^2/d iv, d 1-3; 10 mg/m^2 for pts age >50); 2nd course if >5% blasts on d 21; if CR then 2 courses of consolidation: IDA (15 mg/m^2 iv bolus, d 1; 12 mg/m^2 for age >50) + AraC (100 mg/m^2 q12h for 2-h infusion, d 1-6) Group 2: AraC (100 mg/m^2 iv q12h, d 1-10) + DNR (50 mg/m^2/d, d 1, 3, 5) + etoposide (100 mg/m^2/d, d 1-5); consolidation: 1 cycle AraC (100 mg/m^2 q12h, d 1-8) + DNR (50 mg/m^2/d, d 1, 3, 5) + etoposide (100 mg/m^2/d, d 1-5); 2nd cycle: AraC (200 mg/m^2/d CI, d 1-8) + AMSA (100 mg/m^2 1h infusion, d 1-5) + etoposide (100 mg/m^2/d, d 1-5); 3rd cycle: AraC (100 mg/m^2 q12h, d 1-3) + MTZ (10 mg/m^2 30 min infusion, d 1-5) Group 3: MTZ (12 mg/m^2/d iv bolus, d 1-3) + AraC (100 mg/m^2/d CI, d 1-10); consolidation: MTZ (15 mg/m^2 iv, d 1) + AraC (100 mg/m^2 2 h iv infusion q12h, d 1-6)	76.5%, 72.2%, 68.9%, p=0.79, ns 1st course: 35% vs 58% vs 52%	5-y OS: 26.5%, 18.9%, 14.8%, p=0.079 After 45 m follow-up, 3-y RFS 17 m, 9 m, 9 m; better for Group 1, p=0.014 5-y RFS: G1 better only when excluded pts with transplant (p=0.05)	Induction deaths 9.7%, 12.9%, 14.8% Median time to CR: 51 d vs 28 d vs 32 d, p<0.05 [may be due to age distribution]	NR	IDA-containing regimen superior
German AML Intergroup Study E: 2004-2008, NCT00180102; MK1-95; AML2003 Buchner, 2012 (196)	622 Age 16-60 y, median 47 y	Induction + consolidation MTZ + AMSA vs DNR	Study E (n=622): 4 arms Intensified vs std therapy AraC vs AraC + MTZ + m-AMSA Risk-adapted intensified versus a standard-intensity treatment strategy. The intensified strategy included early allogeneic SCT during remission induction for high-risk patients and allogeneic related-donor SCT in first CR as well as autologous SCT as the priority for intermediate-risk patients. Consolidation chemotherapy was randomly assigned among three courses of HDAC alone versus AraC in combination with AMSA and MTZ. Common control arm. Induction: AraC (100 mg/m^2/d CI, d 1-7) + DNR (60 mg/m^2/d iv over 2 h, d 3-5); 2nd course starting on d 22. Consolidation: 3 cycles at monthly intervals of HDAC (3 g/m^2 over 3 h q12h, d 1, 3, 5)	CR+CRi: 74%vs 70% control arm, ns	5-y OS 46.4% vs 44.3% control arm, p=0.735 5-y RFS 47.3% vs 44.8%, ns 5-y EFS 34.8% vs 31.5%, p=0.546	NR	Primary endpoint EFS, secondary OS and RFS. Power to discover a 15% difference in 5-y survival probabilities compared with common arm was >90%	No statistically significant differences with any of the 5 treatment arms compared with the common (std) arm

ADE, AraC + DNR + etoposide; ANLL, acute non-lymphoid leukemia; AMSA, amsacrine; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; CI, continuous iv infusion; COAP, cyclophosphamide, VCR, AraC, prednisone; CR, complete remission (complete response); DAT, DNR +AraC + 6-thioguanine (TG); DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; GCSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HAM, high-dose cytarabine + mitoxantrone; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; ICE, idarubicin + cytarabine + etoposide; IDA, idarubicin; IFN, interferon; ITT, intention to treat; iv, intravenously; MAC, MTZ + AraC; MACE, amsacrine + AraC + etoposide; MAE, MTZ + AraC + etoposide; MDS, myelodysplastic syndromes; MidAC, MTZ AraC; MTZ, mitoxantrone; NR, not reported; OS, overall survival; po, oral administration (per os); PR, partial response/remission; RFI, relapse-free interval (after induction); RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; SAE, severe adverse effect; sc, subcutaneously; SCT, stem cell transplant; std, standard; t-AML, therapy-related AML following treatment of primary malignant disease; TG, 6-thioguanine; VCR, vincristine

Table 4-6. Induction, anthracyclines other than IDA or MTZ compared with DNR Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[14]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Japan; 1983-1985 Nagura, 1994 (205)	433 Age 15-65 y, AML, no prior treatment, reported response by FAB subtype	Induction ACR vs DNR	ACR + BHAC vs DNR + BHAC DNR (25 mg/m^2/d bolus iv, d 1-2 and thereafter as necessary depending on response), ACR (14 mg/m^2/d bolus iv, 10-14 d) All patients received BHAC (170 mg/m^2/d, 2 h iv), 6MP (70 mg/m^2/d po) + prednisolone (20 mg/m^2/d po)	53.9% vs 63.7%, p=0.0587 Excluding M3 cases: 57.0% vs 63.3%, p=0.275	OS median 9.5 m vs 15.8 m; 7-y OS 20.2% vs 19.3%, p=0.0091 Median DFS pts with CR: DFS 14.1 m vs 15.4 m 7-y DFS 27.7% vs 21.1%, p=0.851	DNR group less diarrhea, ileus, pneumonia, renal failure; other adverse effects similar	NR	DNR comparable to ACR
China; 2007-2011 ChiCTR-TRC-06000054 Jin, 2013 (56)	620 Untreated AML, age 14-59 y	Induction ACR vs DNR (Homoharringtonine)	ACR + homoharringtonine vs DNR + homoharringtonine vs DNR; all had AraC (100 mg/m^2, d 1-7) HAA: homoharringtonine (2 mg/m^2/d, d 1-7) + AraC + ACR (20 mg/d, d 1-7) HAD: homoharringtonine (2 mg/m^2/d, d 1-7) + AraC + DNR (40 mg/m^2/d, d 1-3) DA: DNR (40-45 mg/m^2/d, d 1-3) + AraC	73% HAA vs 61% DA, p=0.011 67% HAD (p=0.20 vs DA) 73% HAA vs 67% HAD, p=0.22	3-y OS: 44.5% HAA vs 43.5% HAD vs 42.7% DA; p=0.53 HAA vs DA, p=0.92 HAD vs DA adjusted for prognostic factors: HAA vs DA, HR=0.68 (p=0.213) 3-y EFS: 35.4% HAA vs 32.7% HAD vs 23.1% DA; p=0.0023 HAA vs DA, p=0.08 HAD vs DA 3-y RFS: 48.8% HAA vs 46.3% HAD vs 37.9% DA, p=0.09 HAA vs DA, p=0.19 HAD vs DA RFS adjusted HAA vs DA HR=0.59 (p=0.0080)	Adverse events similar, except more early deaths compared with DA: HAA (5.8%; p=0.0067) and HAD (6.6%, p=0.0030), DA (1%) Benefit of HAA and HAD greatest in subgroup with favourable cytogenetics	ITT; primary endpoint CR + EFS. 200 pts/arm to detect 3-y EFS difference of 12% (23% vs 35%) HR of 0·70. Adequate power for CR	HAA is an option
SECSG; 1982-1985 Stein, 1990 (207)	299 Age 51+, AML, FAB M1-M6; excluded pts with previous myelodysplasia in first 2 years of study	Induction; maintenance AMSA vs DNR	AMSA + AraC vs DNR + AraC AraC (100 mg/m^2/d CI, 7 d), DNR (45 mg/m^2 iv, d 1-3), m-AMSA (200 mg/m^2 iv, d 1-3) Patients with PR received a 2nd cycle of induction Patients with CR received consolidation (not randomized) then if still in remission were randomized (n=76) to maintenance phase: no further treatment vs AraC (100 mg/m^2/d CI, 5 d) + DNR (45 mg/m^2 iv, d 1-2), repeated every 13 weeks for 4 cycles	42% vs 47% DNR, p=0.45; 31% vs 40% including pts not fully evaluable 1 cycle: 36% vs 31%	NR	Induction toxicities similar except severe hepatic toxicity 10% vs 4% DNR, p<0.05. Induction deaths 38% vs 25% DNR, p=0.018	NR	No evidence of benefit for substituting m-AMSA for DNR; m-AMSA more toxic

[14] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[14]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Sweden LGMS; 1984-1988 Oberg, 2002 (206)	90 Age ≥60 y, median 72 y, untreated AML; excluded previous MDS	Induction ACR vs DNR	ACR + AraC + TG vs DNR + AraC + TG AraC (100 mg/m^2 twice daily by 10 min iv infusion, d 1-7), TG (100 mg/m^2 twice daily po, d 1-7), DNR (60 mg/m^2 once daily by 30 min iv infusion, d 5-7), ACR (80 mg/m^2 by 30 min iv infusion, d 5-7) Pts given 1-3 cycles of induction; if no CR then further treatment was optional Pts with CR were to receive consolidation with same agents; however, it was not given according to protocol and therefore no analysis was reported	47% vs 51% TAD, ns Age >70 y: 24% vs 35%, ns	Long-term survival not significantly different Median cause-specific survival 77 d vs 345 d, ns	Median duration of remission 10.7 m vs 11.6 m. Early deaths 36% vs 16% Nausea, mucositis, diarrhea, alopecia similar in both groups.	NR	Similar efficacy in both arms; numerous early deaths and substantial relapse
Sweden LGMS; 1980-1986 POCAL/POCAL-DNA; Paul, 1991 (209)	120 Age 15-60 y, mean 41.4 y, previously untreated ANLL	Induction + consolidation Doxorubicin-DNA vs doxorubicin vs DNR	Group R1: DNR + AraC (n=25) Group R2: Prednisolone + VCR + AraC + TG + doxorubicin (n=49) Group R3: Prednisolone + VCR + AraC + TG + doxorubicin-DNA (n=46) Group R1: (reference; only for first 3 of 6 years of study): DNR (1.5 mg/kg in 45 min infusion, d 1) + AraC (1 mg/kg iv twice daily, d 1-5); repeated on d 11-15 unless CR or severe bone marrow hypoplasia (in the later the drug-free interval was extended); if progression after 2 courses, a second dose of DNR was given on d 2 in the 3rd course; if still no CR, then treated according to R2 or R3 but evaluated with R1 group Group R2: doxorubicin (30 mg/m^2 over 4 h, d 4, 5) + AraC (100 mg/m^2 CI, d 1-7) + TG (50 mg/m^2 × 2 po, d 1-7) + VCR (2 mg iv, d 1, 5) + prednisolone (30 mg/m^2 × 2 po, d 1-7); repeated, d 14 if no CR or severe bone marrow hypoplasia. If no remission after 2 courses, doxorubicin was increased to 45 mg/m^2 on d 4 and 5 and VCR omitted in 3rd course. If no remission, AMSA given at 75 mg/m^2 daily × 7 d Group R3: identical to R2 except doxorubicin-DNA conjugates used instead of doxorubicin. Pts with M4 or M5 leukemias who progressed after 3 courses on R1 or 2 courses on R2/R3 received etoposide (100 mg/m^2, d 1-3) + AraC (1 mg/kg × 2 sc, d 1-5) + DNR (R1, 1.5 mg/kg), doxorubicin (R2, 60 mg/m^2) or doxorubicin-DNA (R3, 60 mg/m^2) on d 1 Pts in group R1 had consolidation/maintenance for 5 y with monthly DNR + AraC alternating with TG + AraC; DNR discontinued when cumulative dose of 700 mg/m^2 reached Pts in group R2 or R3 with CR had consolidation with 16 monthly courses, with doxorubicin or doxorubicin-DNA according to initial randomization in the first 8 courses	56% R1, 65% R2, 75% R3, ns Original therapy (without rescue): 44%, 63%, 72%	OS median 7.6 m R1, 12.1 m R2, 27.3 m R3; R3 vs R1/R2, p<0.01 5-y OS: 8% R1, 4% R2, 22% R3 Pts with CR: median 20.3 m R1, 18.3 m R2, 47.0 m R3; R3 vs R1/R2, p<0.025 Median duration of remission: 7.7 m R1, 13.2 m R2, 23.6 m R3; R3 significantly longer, p<0.025	R3 had less cardiotoxicity (p<0.05 vs R1/R2), severe intestinal toxicity (p<0.02 vs R2), hepatic toxicity (p<0.08 vs R2), renal toxicity (p<0.08 vs R2). Early deaths: 0% R1, 14% R2, 6% R3	NR	Binding doxorubicin to DNA appears to increase efficacy and reduce toxicity

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[14]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Danish; 1984-1987 De Nully Brown, 1997 (54); Hansen, 1991 (55)	174 De novo AML	Induction ACR vs DNR	3+7 ACR + AraC vs DNR + AraC ACR (75 mg/m^2/d, d 1-3), DNR (45 mg/m^2/d, d 1-3), AraC (100 mg/m^2/d CI, d 1-7) Anthracycline dose reduced by 33% for those over age 60 y 2nd course with DNR or ACR (2 d) plus AraC (5 d) if CR not achieved Pts with CR (n=99) eligible for consolidation treatment (n=84); other pts removed from study but included in OS analysis	66% ACR vs 50% DNR, p=0.043 One course: 51% vs 34% age 17-60: 72% ACR vs 51% DNR, p=0.02 age 17-39: 72% vs 60% age 40-60: 71% vs 46%%, p=0.048 age 61-65: 47% vs 45% [note reduced dose given]	4-y OS 29% vs 20%, p=0.26; 5-y OS 27% ACR vs 20% DNR, ns; 10-y OS 24% vs 16%, ns Pts with CR: 5-y OS 37% vs 34%; 10-y OS 37% vs 25%, ns 5-y DFS 23% vs 31%; 10-y DFS 23% vs 22%, ns	Hematological toxicity identical in both groups. Grade 3-4 adverse events: cardiotoxicity 5% vs 2%; stomatitis 18% vs 12%. Deaths during induction 24% vs 22%	NR	ACR at least as good or better than DNR; dose may have been too low in age >65
GIMEMA GSI 103 AMLE; 2001-2004 Latagliata, 2008 (208)	301 Age 61-75 y, median age 68 y	Induction + consolidation; maintenance DNX vs DNR	DNX + AraC vs DNR + AraC Both groups received hydroxycarbamide pretreatment at 2 g/m^2/d, day -5 to 0. DNX: 80 mg/m^2, d 1-3; DNR: 45 mg/m^2, d 1-3; AraC: 100 mg/m^2 CI, d 1-7 2nd induction cycle if PR; if CR after 1st or 2nd cycle then received additional cycle as consolidation After consolidation, pts with CR had 2nd randomization (n=102) to [AraC (20 mg, twice a day, d 1-10) + ATRA (45 mg/m^2, d 1-10)] q28d × 12 vs none	49.3% DNX vs 51.0% DNR, p=0.941	Crossover in survival curves at 8-12 m; DNX worse in early months (HR=1.97, p=0.0975); DNX better later on 2nd randomization: HR=0.73, p=0.1664	Induction deaths 18.9% DNX vs 13.1% DNR; early deaths after CR (6 months) 12.5% vs 2.6%, p=0.053; relapse at 2 y from CR was 59% vs 78%, p=0.064	ITT	DNX could possibly have a role
Japan, KRN8602 Leukemia Study Group; 1993-1997 Takemoto, 1999 (210)	58 Age 15-59 y, newly diagnosed de novo AML	Induction KRN vs DNR	KRN + AraC vs DNR + AraC KRN (15 mg/m^2/d iv push, d 1-5), DNR (40 mg/m^2/d iv push, d 1-3), AraC (100 mg/m^2/d CI, d 1-7) Principally a 2-cycle regimen, with the 2nd course started within 3-4 w or when complete blood counts had recovered	78.6% vs 73.1%; failed to show equivalence (p=0.087)	NR	Similar time to reduce leukemic cells to <5%. KRN arm had higher nausea/ vomiting and anorexia (96.6% and 100% vs 78.6% and 75.0%, p=0.046 and p=0.004); other adverse effects similar	Primary endpoints CR and toxicity.	

6MP, 6-mercaptopurine (mercaptopurine); ACR, aclarubicin; ANLL, acute non-lymphoid leukemia; AMSA, amsacrine; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; ATRA, all-trans retinoic acid; BHAC, N^4-behenoyl-1-β-D-arabinosylcytosine (widely used in Japan instead of AraC since 1979); CI, continuous iv infusion; CR, complete remission (complete response); DA, DNR + AraC; DFS, disease-free survival; DNR, daunorubicin; DNX, DaunoXome, a liposomal formulation of daunorubicin; EFS, event-free survival; HAA, homoharringtonine + AraC + ACR; HAD, homoharringtonine + AraC + DNR; HAM, high-dose cytarabine + mitoxantrone; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; IDA, idarubicin; ITT, intention to treat; KRN, KRN8602 (3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin hydrochloride); iv, intravenously; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OS, overall survival; po, oral administration (per os); PR, partial response/remission; RFS, recurrence-free survival; sc, subcutaneously; std, standard; AD, thioguanine + cytarabine + daunorubicin; TG, 6-thioguanine; VCR, vincristine

Table 4-7. Induction, Other anthracycline comparisons Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[15]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Egypt Abu-Taleb, 2013 (211) [abstract]	90 Age ≥60 y, de novo AML	Induction Doxorubicin vs none	Low dose AraC (LDAC) + doxorubicin vs LDAC LDAC (20 mg/m^2 sc, d 1-14), doxorubicin (25 mg/m^2 iv, d 1-2) Pts in both groups with CR received consolidation with 3 cycles of the induction regimen 2+14 regimen	CR 15.6% doxorubicin vs 4.4%, p=0.027	OS median 9 m vs 6 m (2 y follow-up)	Early death 11% vs 2.2%; neutropenia grade 3: 66.7% vs 46.7%, neutropenia grade 4: 33.3% vs 11.1%; blood transfusion 17.7% vs 60%	NR	
SWOG 7823; 1978-1982 Morrison, 1992 (213); see Appelbaum,1997 (162) for long-term results	642 Age >15 y, newly diagnosed AML. Induction stratified by age (<50 y, ≥50 y). Late intensification stratified by age and induction arm	Induction + consolidation; maintenance. Continued maintenance vs late intensification. Late maintenance vs none Rubidazone vs doxorubicin	ROAP (rubidazone/VCR/AraC/prednisone) vs ADOAP (the same combination using adriamycin [doxorubicin] in place of rubidazone) Rubidazone (200 mg/m^2 iv, d 1), adriamycin (40 mg/m^2, d 1); all pts received VCR (2 mg iv, d 1), AraC (70 mg/m^2/d CI, d 1-7), prednisone (100 mg/d po, d 1-5) Pts with persistent leukemic cells on d 7/8 and 9/10 received AraC for 5 d; up to 3 courses given and if still not CR pts were considered as induction failure Rubidazone withdrawn by manufacturer after 303 pts (147 with rubidazone) and the remaining pts therefore received adriamycin Pts with CR after induction received consolidation with 3 monthly courses similar to remission induction except anthracycline and VCR were reduced by 25% and AraC increased to 100 mg/m^2/d CI for 5 d for the 1st course; if no sepsis and high granulocyte/platelet counts increases AraC to 150 mg/m^2/d for subsequent courses. See Table 4-16 for maintenance details	54% vs 54%, p=0.93 Randomized pts only: 54% vs 55%, p=0.86	OS at median 10.4 y follow-up, no difference between groups, p=0.6 DFS p=0.74	Life-threatening or fatal toxicities significantly lower among rubidazone group (26% vs 49%, p=0.0001)	NR	As rubidazone not available and DNR found superior to doxorubicin in other studies, the induction portion is of limited relevance
Czech; 1998-2000 Indrak, 2001 (216) [Czech, English abstract]	60 AML, Age 55-75 y, median 63 y	Induction IDA vs MTZ	IDA + AraC (3+7) vs MTZ + AraC	41. 9% IDA vs 51.7% MTZ, p=0.44	OS median 22 w vs 35 w, p=0.44 DFS median 44 w vs 40 w, p=0.98	NR	NR	Differences ns likely due to small numbers; suggestion that MTZ more favourable

[15] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[15]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
France; 1984-1987 Tilly, 1990 (212)	87 Age >65 y, de novo ANLL, pts suitable for intensive chemo. Excluded s-AML and t-AML	Induction Rubidazone vs none	Low-dose AraC vs rubidazone + AraC Low-dose AraC: 10 mg/m^2 q12h for 21 d, sc Rubidazone (100 mg/m^2 iv for 4 d) + AraC (200 mg/m^2 CI, 7 d) 2nd induction if no CR: low-dose arm same as 1st course; rubidazone arm: rubidazone for 2 d + AraC for 3 d Maintenance treatment if CR	32% low-dose vs 52%, p<0.001	OS median 8.8 m vs 12.8 m, p>0.12	Low-dose arm: less early deaths (10% vs 31%, p<0.001), infectious complications (p<0.01), transfusions (p<0.02), and shorter hospital stay (p<0.01); more PR and failure (p<0.001)	NR	Need to reduce toxicity of intensive chemo or improve efficacy of low-dose AraC
GOELAM1; 1987-1992 age >50; 1987-1994 age 15-50 Harousseau, 1996 (214)	731 Age 15-65 y, de novo AML	Induction (and consolidation vs transplant) Rubidazone vs IDA	AraC + IDA vs AraC + rubidazone AraC (200 mg/m^2/d CI, d 1-7), IDA (8 mg/m^2/d iv, d 1-5), rubidazone (200 mg/m^2/d iv, d 1-4) If (after 1 course) bone marrow hypoplastic and <50% blasts gave 2nd induction course for 3 d AraC + 2 d same anthracycline as 1st course If bone marrow was normocellular and blastic or >50% blasts, considered a failure and given salvage regimen (HDAC recommended)	71% vs 71% Age ≥50: 75% vs 61%, p=0.03 Age 15-50: 70% vs 76%, p=0.06; after salvage 77.5% vs 82%, ns	OS at median 4 y follow-up: median OS 21 m, OS 39% ± 2% both arms, ns At median 4 y: DFS in pts with CR was 39% ± 3%, in both arms, ns	Early death 9 vs 6 pts	ITT OS; per protocol DFS	IDA and rubidazone similar; IDA better CR in age ≥50 only
Thailand Intragumtornchai, 1999 (215) [abstract]	104 Age 15-60 y, median 35 y, newly diagnosed AML	Induction IDA vs doxorubicin	AraC + IDA vs AraC + doxorubicin [one course] AraC (100 mg/m^2/d, 7 d), IDA (12 mg/m^2/d, 3 d), doxorubicin (30 mg/m^2/d, 3 d)	80.4% vs 56.1%, p=0.014	NR	No significant difference in rates of life-threatening infection or other adverse effects; 6 deaths due to infection in each arm	NR	Higher CR with IDA
GOELAM; 1987-1992 Pignon, 1996 (217)	251 Age 50-65 y, de novo AML	Induction Zorubicin vs IDA	AraC + IDA vs AraC + zorubicin AraC (200 mg/m^2 CI, d 1-7); zorubicin (200 mg/m^2 iv, d 1-4); IDA (8 mg/m^2 iv, d 1-5) 2nd course if minor residual disease (<50% leukemic blasts in hypocellular marrow) with AraC (3 d) + anthracycline (2 d) as in the 1st course Consolidation with HDAC + m-AMSA	73% IDA vs 60%, p=0.033	OS: no difference At median 73 m: no significant difference in DFS or EFS; median DFS was 12 m (17 m if CR)	Early or aplastic death 9% vs 16% pts, p=0.08; less severe mucositis in IDA (p=0.009); no other significant differences in toxicity	NR	IDA more effective for CR but did not affect OS

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[15]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Turkey; 1992-1995 Beksac, 1998 (204)	99 Age >14 y, previously untreated ANLL; also included pts with myelodysplastic features of <6 m duration. Median age Groups 1, 2, 3 were 40 y, 31 y, 36 y, p<0.05 (G1 vs G2); G3 had more pts age >60 (n=7 vs n=2 in other groups)	Induction + consolidation IDA, MTZ, DNR + etoposide	Group 1: AraC + IDA vs Group 2: AraC + DNR + etoposide vs Group 3: AraC + MTZ Group 1: AraC (100 mg/m^2 CI, d 1-7) + IDA (12 mg/m^2/d iv, d 1-3; 10 mg/m^2 for pts age >50); 2nd course if >5% blasts on d 21; if CR then 2 courses of consolidation: IDA (15 mg/m^2 iv bolus, d 1; 12 mg/m^2 for age >50) + AraC (100 mg/m^2 q12h for 2-h infusion, d 1-6) Group 2: see Table 4-5 or Table 4-8 Group 3: MTZ (12 mg/m^2/d iv bolus, d 1-3) + AraC (100 mg/m^2/d CI, d 1-10); consolidation: MTZ (15 mg/m^2 iv, d 1) + AraC (100 mg/m^2 2 h iv infusion q12h, d 1-6)	76.5%, 72.2%, 68.9%, p=0.79, ns 1st course: 34% vs 36% vs 52%	5-y OS: 26.5%, 18.9%, 14.8%, p=0.079 After 45 m follow-up, 3-y RFS 17 m, 9 m, 9 m; better for Group 1, p=0.014 5-y RFS: G1 better only when excluded pts with transplant (p=0.05)	Induction deaths 9.7%, 12.9%, 14.8% Median time to CR: 51 d vs 28 d vs 32 d, p<0.05 [may be due to age distribution]	NR	IDA-containing regimen superior
Sweden LGMS; 1980-1986 POCAL/POCAL-DNA; Paul, 1991 (209)	120 Age 15-60 y, mean 41.4 y, previously untreated ANLL	Induction + consolidation Doxorubicin-DNA vs doxorubicin vs DNR	Group R1: DNR + AraC (n=25) Group R2: Prednisolone + VCR + AraC + TG + doxorubicin (n=49) Group R3: Prednisolone + VCR + AraC + TG + doxorubicin-DNA (n=46) See Table 4-6 for details and DNR results	65% R2, 75% R3, ns Original therapy (without rescue): 61%, 70%	OS median 12.1 m R2, 27.3 m R3; R3 vs R1/R2, p<0.01 5-y OS 4% R2, 22% R3 Pts with CR: median 18.3 m R2, 47.0 m R3; R3 vs R1/R2, p<0.025 Median duration of remission: 13.2 m R2, 23.6 m R3; R3 significantly longer, p<0.025	R3 had less cardiotoxicity (p<0.05 vs R1/R2), severe intestinal toxicity (p<0.02 vs R2), hepatic toxicity (p<0.08 vs R2), renal toxicity (p<0.08 vs R2). Early deaths (within 14 d): 0% R1, 14% R2, 6% R3	NR	Binding doxorubicin to DNA appears to increase efficacy and reduce toxicity
China; 2002-2003 Liu, 2006 (218) [Chinese, English abstract]	155 Newly diagnosed AML (except M3), ALL, CML-blast	Induction IDA source	IDA (domestic) + AraC vs IDA (imported) + AraC AML: IDA (8 mg/m^2, d 1-3), AraC (100 mg/m^2, d 1-7), 1-2 cycles ALL: IDA + VCR + cyclophosphamide + prednisone	Acute leukemia: 78.1% domestic vs 76.9 imported%, p>0.05	NR	Grade 3+ hematological toxicity 74.0 vs 73.1%, p=0.73; other toxicities manageable and difference ns	NR	Both IDA comparable

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[15]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
NCT00788892, USA + Canada; 2008-2009 Lancet, 2014 (219)	126 Age 60-75 y, median 70 y, newly diagnosed untreated AML; pts with antecedent hematologic disorders (usually MDS) also eligible	Induction + consolidation. Randomized 2:1 CPX-351: 7+3 CPX-351	CPX-351 vs AraC + DNR (7+3) CPX-351 (100 U/m^2 by 90 min infusion, d 1, 3, 5; equivalent to 100 mg/m^2 AraC and 44 mg/m^2 DNR with each dose); In 2nd cycle and in consolidation (up to 2 cycles), CPX-351 given on d 1 and 3. Control: AraC (100 mg/m^2/d CI for 7 d), DNR (60 mg/m^2/d, d 1-3). DNR reduced to 45 mg/m^2 at investigator discretion. Consolidation therapy at investigator discretion (recommended AraC 100-200 mg/m^2, 5-7 d ± DNR for 2 d; or AraC 1-1.5 g/m^2/dose) Control arm pts with persistent AML after 1-2 induction courses were permitted to cross over to receive CPX-351 as first salvage.	CR+CRi: 66.7% vs 51.2%, p=0.07 s-AML 57.6% vs 31.6%, p=0.06	OS median 14.7 m vs 12.9 m, HR=0.88, p=0.61 s-AML: median 12.1 m vs 6.1 m, HR=0.46, p=0.01 EFS: median 6.5 m vs 2.0 m, HR=0.83, p=0.36 s-AML: EFS 4.5 m vs 1.3 m, HR=0.59, p=0.08	Recovery from cytopenias slower after CPX-351 and more grade 3-4 infections, but no increase in infection-related deaths (3.5% vs 7.3%). 60-d mortality 4.7% vs 14.6%, p=0.053	Primary endpoint CR+CRi. Patients who crossed over were analyzed according to original group. 120 pts to detect 23% increase in response rate with 85% power at p=0.1	CPX-351 beneficial, especially for s-AML Phase III trial planned
German AMLCG 1985 (also referred to as AMLCG-86); 1985-1992 Buchner, 1999 (220)	725 Age 16-60 y, newly diagnosed primary AML; excluded APL after trial of ATRA trial	Induction Anthracycline TAD/HAM	TAD (cycle 1) → HAM (cycle 2) vs TAD → TAD TAD: std-dose AraC (100 mg/m^2 CI, d 1-2, 30 min infusion q12h, d 3-8) + DNR (60 mg/m^2 iv in 30 min, d 3-5) + TG 100 mg/m^2 po q12h, d 3-9) HAM: HDAC (3 g/m^2 over 3 h q12h, d 1-3) + MTZ (10 mg/m^2 over 30 min iv, d 3-5) Consolidation and maintenance if CR	71% TAD-HAM vs 65%, p=0.072 Poor prognosis subgroup: 65% vs 49%, p=0.004	5-y OS: 32% vs 30%, p=0.338 Poor prognosis group (5-y): 24% vs 18%, p=0.009 EFS: 25% vs 19%, p=0.208 Pts with CR: RFS after 5 y: 35% vs 29%, p=0.897 Poor prognosis group EFS: median 7 vs 3 m, 17% vs 12% at 5 y, p=0.012	Early or hypoplastic death rate 14% vs 18%, p=0.108 Grade 3+ adverse events were similar in both groups	ITT. Power of 0.8 to detect min difference of 3 m in EFS based on n=300 pts	HAM may contribute specific benefit to poor-risk patients, requires confirmation
German AMLCG 1985 Schoch, 2001 (221); see Buchner, 1999 (220) for further details	45 Subgroup of pts with complex karyotype aberrations and poor prognosis	Induction Anthracycline TAD/HAM	Retrospective subgroup analysis: TAD ×2 n=13; TAD-HAM n=32	56% TAD-HAM vs 23%, p=0.04	OS median 7.6 m vs 4.5 m, p=0.13; OS after 3 y 19.6% vs 7.6% Median EFS 2 m vs <1 m, p=0.04; EFS at 3 y 11% vs 0%	NR	NR	HAM may benefit those with complex aberrant karyotype but survival still low

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[15]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
German AML Intergroup Study D: 2002-2008 NCT00266136 Buchner, 2012 (196); see Buchner, 2006 (222) for full results comparing TAD → HAM vs HAM → HAM	808 Age 16-60 y, median 47 y	Induction + consolidation Anthracycline TAD/HAM, DNR	Study D (n=808): TAD → HAM vs HAM → HAM; also combined results vs common control arm [One course std dose and one course HDAC vs 2 courses HDAC] TAD: AraC (100 mg/m^2/d CI, d 1-2, 30 min iv q12h, d 3-8) + DNR (60 mg/m^2, 60-min iv infusion, d 3-5) + thioguanine (100 mg/m^2 po q12h, d 3-9) HAM: AraC (3 g/m^2 age <60 or 1 g/m^2 age ≥60, 3h iv infusion q12h, d 1-3) + MTZ (10 mg/m^2, 60 min iv infusion, d 3-5) In the same step, patients <60 years were upfront randomly assigned to TAD consolidation and prolonged maintenance treatment by monthly courses of standard-dose AraC based chemotherapy versus TAD and autologous SCT Common control arm. Induction: AraC (100 mg/m^2/d CI, d 1-7) + DNR (60 mg/m^2/d iv over 2 h, d 3-5); 2nd course starting on d 22. Consolidation: 3 cycles at monthly intervals of HDAC (3 g/m^2 over 3 h q12h, d 1, 3, 5)	CR + CRi: 76% vs 70%, ns [combined results compared with control arm]	Combined results compared with control arm: 5-y OS 43.6% vs 44.3%, p=0.995 5-y RFS 43.9 vs 44.8%, ns 5-y EFS 33.6% vs 31.5%, p=0.486	NR	Primary endpoint EFS, secondary OS and RFS. Power to discover a 15% difference in 5-y survival probabilities was >90%	No statistically significant differences with any of the 5 treatment arms compared with the common (std) arm
AMLCG 2008 AML-CG 2008 NCT01382147; LN_AMLCG_2010_334; 2010-2012 Braess, 2013 [abstract] (230); http://www.leukemia-net.org/trial/detail_trial_en.html?id=334	396 De novo or s-AML, age 18-86 y, median 58 y	Induction Anthracycline TAD/HAM	age <60: TAD → HAM [std double induction] vs HAM × 2 [S-HAM] [dose –dense regimen] age ≥70: HAM (1 or 2 cycles) vs HAM × 2 [S-HAM] Younger pts (age <60) std arm: one cycle TAD-9 [std dose AraC (100 mg/m^2 CI, d 1+2 and 100 mg/m^2 iv over 30 min q12h, d 3-8) + DNR 60 mg/m^2 iv over 1 h, d 3-5) + TG (100 mg/m^2 po q12h, d 3-9)] then one cycle HAM starting at d 21 [HDAC (3 g/m^2 iv over 3 h q12h, d 1-3; 1 g/m^2 age ≥60) + MTZ (10 mg/m^2 iv over 1h, d 3-5)] Elderly pts (age ≥70) std arm: 1 cycle HAM; additional cycle HAM if residual leukemia in d 16 bone marrow aspirate Experimental arm 2 cycles HAM with a 3 d interval [sequential HAM; S-HAM]: HDAC (3 g/m^2 iv over 3 h q12h, d 1+2, or 1 g/m^2 age ≥60), MTZ (10 mg/m^2 iv over 1 h, d 3+4) Age 60-69 allocated to young or elderly cohort at physician discretion	CR+CRi: 77% S-HAM vs 72%, p=0.202	[follow-up continuing]	Duration of critical neutropenia and thrombocytopenia significantly less with S-HAM (29 d vs 45 d and 33 d vs 46 d). Early deaths identical, except lower for 1 g/m^2 S-HAM subgroup	Powered for 15% difference in CR+CRi	S-HAM feasible with less hematologic toxicity

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[15]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
German AMLCG 1999 [AMLCG 99]; NCT00266136; 1999-2011 Buchner, 2006 (222), full report at n=1770; Buchner, 2004, 2006 (223,224) [GCSF: letter, abstract]; several subsequent abstracts on subgroups by age or other factors (225-229)	3350 3232 evaluable pts to this study, plus 118 to standard arm Age 16-85 y, de novo AML; also s-AML or high-risk MDS (18% age <60 y, 32% age ≥60 y).	Induction. Induction + consolidation + maintenance GCSF Anthracycline TAD/HAM (GCSF)	TAD → HAM vs HAM → HAM [One course std dose and one course HDAC vs 2 courses high-does AraC] TAD: AraC (100 mg/m^2/d CI, d 1-2, 30 min iv q12h, d 3-8) + DNR (60 mg/m^2, 60-min iv infusion, d 3-5) + thioguanine (100 mg/m^2 po q12h, d 3-9) HAM: AraC (3 g/m^2 age <60 or 1 g/m^2 age ≥60, 3h iv infusion q12h, d 1-3) + MTZ (10 mg/m^2, 60 min iv infusion, d 3-5) All pts age <60 received 2nd course; pts ≥60 received 2nd course if >5% residual blasts in bone marrow All pts with CR received consolidation (same as TAD induction) + monthly maintenance for 3 y with AraC (100 mg/m^2 q12h sc, d 1-5) + second agent in rotating sequence: DNR (45 mg/m^2 by 1-h infusion, d 3-4) or TG (100 mg/m^2 po q12h, d 1-5) or cyclophosphamide (1 g/m^2 iv injection, d 3) Pts age <60 also randomized at start of trial to post-remission therapy by prolonged maintenance or autologous SCT At 32/52 centers, ½ patients were randomly assigned to receive GCSF (150 µg/m^2 sc daily) from 48 hours before until the last dose of each chemotherapy course during the first year (n=895 in GCSF sub-study)	At 1770 pts: 61% TAD-HAM vs 60% HAM-HAM, ns Age <60: 71% vs 68% Age ≥60: 53% vs 53%; after only 1 cycle 30% vs 36%, p=0.049	At 1770 pts, OS at 3 y: 44% vs 40%, ns Age ≥60: 18% vs 19% At 2693 pts no significant difference in 5-y OS with TAD-HAM vs HAM-HAM or GCSF vs no GCSF At 1770 pts, no significant difference in RFS or RD (45% vs 49% at 3 y) At 2693 pts, no significant difference in 5-y relapse rate	At 1770 pts: Early or hypoplastic death 16% vs 16%, ns. No significant differences in severe adverse events. Genetic groups and age were only risk factors predicting CR, OS, RD; HAM-HAM induction was associated with slightly superior RD (p=0.0715)	ITT analysis	

ANLL, acute non-lymphoid leukemia; AMSA, amsacrine; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; ATRA, all-trans retinoic acid; CI, continuous iv infusion; CPX-351, a liposomal formulation of cytarabine and daunorubicin (5:1 molar ratio); CR, complete remission (complete response); CRi, complete remission with incomplete recovery; DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; GCSF, granulocyte-colony stimulating factor; HAM, high-dose cytarabine + mitoxantrone; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; IDA, idarubicin; ITT, intention to treat; iv, intravenously; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OS, overall survival; po, oral administration (per os); PR, partial response/remission; RAEB-t, refractory anemia with excess of blasts in transformation; RD, remission duration; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; S-HAM, sequential high-dose cytosine arabinoside and mitoxantrone; sc, subcutaneously; SCT, stem cell transplant; std, standard; t-AML, therapy-related AML following treatment of primary malignant disease; TAD, thioguanine + cytarabine + daunorubicin; TG, 6-thioguanine; VCR, vincristine

Table 4-8. Induction, etoposide Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[16]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Australia; ALSGM2; 1984-1987 Bishop, 1990, (231); Matthews, 2001 (164)	264 Age 15-70 y, de novo AML (ANLL); long-term results (10-y) and age ≤60 y subgroup analysis (164)	Induction + consolidation Etoposide	AraC + DNR ± etoposide AraC 100 mg/m^2 CI, 7 d; DNR 50 mg/m^2 iv, d 1-3; etoposide 75 mg/m^2 iv, d 1-7 2nd or 3rd course if CR not achieved CR pts: consolidation with same agents as for induction but attenuated 5 d AraC + 2 d DNR + 5 d etoposide; or 5 d AraC + 2 d DNR); maintenance same in all pts	59% vs 56%, p=0.7 Age <30: 81% vs 67%, p=0.3 Age <55: 68% vs 57%, p=0.18 Age ≥55: 43% vs 54%, p=0.4	OS median 13 m vs 9 m, p=0.4 (17 m vs 9 m age <55 p=0.03; 5 m vs 8 m age ≥55, p=0.16) Median remission duration 18 m vs 12 m, p=0.01 (27 m vs 12 m age <55, p=0.01; 9 m vs 14 m age ≥55, p=0.9) RFS at 4 y: 36% vs 15%, adjusted p=0.016	Etoposide resulted in more diarrhea (p=0.05); for pts age ≥55 it resulted in more grade 3+ stomatitis (26% vs 7%, p=0.02). During consolidation etoposide resulted in more hematologic toxicity, p=0.003	NR	Addition of etoposide increased duration of remission and RFS; may be greater benefit in younger pts but needs confirmation
Australia; ALSGM2; 1984-1987 Matthews, 2001 (164)	222 Long-term data, excluded pts with APL (M3 AML, n=42) from analysis	Induction + consolidation Etoposide	See Bishop, 1990 (231)	61% vs 57%, p=0.59; adjusted p=0.36 Age ≤60: 68% vs 57%, p=0.16 Induction deaths HR=1.36, p=0.28	OS at 10 y: 15% vs 12%, p=0.62 Age ≤60: 19% vs 13%, p=0.21 DFS at 10 y: 20% vs 14%, p=0.54 DFS age ≤60: 25% vs 16%, p=0.42 10-y overall failure HR=0.90, p=0.45; adjusted HR=0.93, p=0.59	10 y disease related failure: 59% vs 76%, HR=0.72, p=0.045; adjusted HR=0.74, p=0.077	NR	
NCRI AML16; 2010-2012 Burnett, 2013 (249) [abstract]	616 Median age 67 y (53-82 y); 75% de novo AML, 16% secondary AML, 8% high-risk MDS	Induction Etoposide (ATRA)	Once accrued all patients for AraC vs clofarabine comparison, added new 2×2 induction comparison DA (DNR + AraC) ± ATRA vs ADE (DNR + AraC + etoposide) ± ATRA DNR (50 mg/m^2, d 1-3), AraC (100 mg/m^2 bid, d 1-10 course 1 or d 1-8 course 2), ATRA (45 mg/m^2/d for 60 d), etoposide (100 mg/m^2/d, d 1-5)	CR: 53% DA vs 53% ADE CR+CRi: 68% DA vs 70% ADE, OR=0.92 (0.65-1.30), p=0.6	OS at 2 y, 36% DA vs 33% ADE, p=0.6 RFS at 2 y: 36% DA vs 23% ADE, p=0.3	No difference in early mortality between DA and ADE arms	NR	

[16] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[16]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Russian AML-92 1992-1994 Parovichnikova, 2010 (176) [abstract and poster], (177) [Russian]; Savchenko, 1995, 1999 (178,232) [Russian, English abstract]; Parovitchnikova, 2003 (179) [abstract]	185 AML. 243 randomized (including APL), 132 pts analyzed in full publication (232) Age 16-60 y, median age 38 y	Induction + maintenance Etoposide	AraC + DNR (7+3) + etoposide vs AraC + DNR (7+3) AraC (100 mg/m^2 bid iv, d 1-7), DNR (45 mg/m^2, d 1-3), etoposide (120 mg/m^2 iv, d 17-21) Maintenance for 3 y: rotating courses 5+2 vs 7+3 repetition Total DNR dose 855 mg/m^2 # induction courses not stated, but 4 used in subsequent studies	65.6% vs 58.6%	OS NR 5-y RFS 37% vs 32%	Induction death 22.3% vs 20.7%; 10-y CR 50% vs 29%, p=0.05. Aggressive maintenance not necessary after etoposide induction but important after induction/ consolidation without etoposide	NR	
MRC AML15; ISRCTN17161961; 2002-2007 induction; 2002-2009 consolidation Burnett, 2011 (6); Burnett, 2013 (7); Pallis, 2011 (172) [p-glycoprotein]	3106. Induction, n=3106; consolidation, n=1440. Effect of GO induction, n=1113. Effect of GO consolidation, n=948. ADE vs FLAG-IDA, n=1268. ADE vs DA, n=1983 Age >15 y, Predominantly <60 y, untreated AML (de novo or secondary), APL excluded. Children age 0-14 y (n=87) allowed in some arms	Induction; consolidation Etoposide (GO) (Fludarabine + IDA vs DNR)	<u>Induction</u> DA (DNR + AraC) ± GO vs FLAG-IDA (fludarabine + AraC + GCSF + IDA) ± GO vs ADE (AraC + DNR + etoposide) [± GO starting 2005] DA 3+10 ± GO → DA 3+8: DNR (50 mg/m^2 d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-10) ± GO (3 mg/m^2 d 1) then 2nd cycle with DNR (50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-8) FLAG-IDA ± GO → FLAG-IDA: fludarabine (30 mg/m^2 iv, d 2-6) + AraC (2 g/m^2 over 4 h starting after fludarabine, d 2-6) + GCSF (lenograstin 263 µg sc daily, d 1-7) + IDA (8 mg/m^2 iv daily, d 4-6) ± GO (3 mg/m^2 d 1); then 2nd cycle same without GO ADE 10+3+5 → ADE 8+3+5: DNR (50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-10) + etoposide (100 mg/m^2 d 1-5) then 2nd cycle same except AraC d 1-8 Consolidation: See Table 4-14	<u>DA vs FLAG-IDA vs ADE</u> 78% DA vs 82% ADE, p=0.06 (OR/HR =1.24, 0.99-1.54) 84% FLAG-IDA vs 81% ADE, p=0.2 CR+CRi after 1 cycle: 63% DA vs 70% ADE, p=0.002; 77% FLAG-IDA vs 67% ADE, p<0.001 Subgroup Pgp-positive: 86% FLAG-IDA vs 78% DA/ADE; Subgroup Pgp-negative 86% FLAG-IDA vs 90% DA/ADE	<u>DA vs FLAG-IDA vs ADE</u> OS: ADE vs DA no difference (HR=1.00); 44% FLAG-IDA vs 37% ADE, HR=0.92 (0.79-1.06), p=0.2 RFS, relapse risk, death in remission similar for ADE vs DA (RFS 35% DA vs 32% ADE, p=0.8). FLAG-IDA (compared with ADE) reduced relapse (38% vs 55%, p<0.001), improved RFS (45% vs 34%, p=0.01), but increased death in remission (17% vs 11%, p=0.02)	<u>DA vs FLAG-IDA vs ADE</u> Induction deaths 6% DA vs 5% ADE, p=0.7; 7% FLAG-IDA vs 7% ADE, p=0.7. Grade 3-4 gastrointestinal toxicity greater with ADE compared with DA; other toxicities of modest clinical significance. FLAG-IDA compared with ADE had delay in recovery of neutrophils and platelets (p<0.001) resulting in more transfusions and antibiotics.	ITT Non-GO questions: At least 1000 pts per induction question to give 90% power to detect 10% survival difference at p<0.05 and 800 pts in consolidation to give 80% power to detect a 10% difference in OS	<u>DA vs FLAG-IDA vs ADE</u> FLAG-IDA is effective for induction

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[16]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
South Africa; 1981-1985 Jacobs, 1990 (233)	72 Age 12-71 y, median 36 y, untreated ANLL; excluded s-AML	Induction; maintenance Etoposide	CTRIII (AraC + DNR + etoposide) vs DAT (AraC + DNR + TG) CTRIII: AraC (80 mg/m^2 CI, d 1-5), DNR (50 mg/m^2 d 1), etoposide (80 mg/m^2 in ½-h infusion, d 1-5) DAT: AraC (100 mg/m^2 q12h as ½-h infusion, d 1-5), DNR (50 mg/m^2, d 1), TG (100 mg/m^2 po q12h, d 1-5) Patients with persistent leukemia on d 21 received 2nd course of induction; up to 4 cycles were given before pts classified as refractory and removed from the study Subset (n=29) randomized to receive *C. parvum* immunotherapy commencing with initiation of induction chemotherapy Pts in CR (n=32) randomized to short (6 m) or extended (15 m) maintenance Short: cyclophosphamide (iv q1m, m 1-3) then (methotrexate + VCR + AraC, q1m, m 4-6) Extended: (AraC + etoposide + DNR) monthly × 9 then same as short course for 6 m	52% vs 62%, p>0.05 (ns) *C. parvum* had no significant effect	Median 27 w CTRIII vs 34 w DAT, ns *C. parvum* had no significant effect	Median remission duration 27.5 w CTRIII vs 30 w DAT, ns *C. parvum* had no significant effect Median remission duration 24 w short course maintenance vs 35 w extended course, ns		
MRC AML10; 1988-1995 Hann, 1997 (70)	1857 AML, mostly age <56 y but older allowed if suitable for intensive therapy; included 286 children <15 y; allowed RAEB-t in children if AML-type therapy considered appropriate; de novo (93%) or secondary AML (7%); allowed all FAB types M0-M7	Induction Etoposide	DAT vs ADE (2 courses; double induction) DAT 3+10 → DAT 3+8: DNR (50 mg/m^2 slow iv, d 1, 3, 5) + AraC (100 mg/m^2 12-hourly iv, d 1-10) + TG (100 mg/m^2 12-hourly oral, d 1-10) then same but AraC and TG only d 1-8 ADE 10+3+5 → ADE 8+3+5: DNR (50 mg/m^2 slow iv, d 1, 3, 5) + AraC (100 mg/m^2 12-hourly iv, d 1-10) + etoposide (100 mg/m^2 iv 1-h infusion, d 1-5) then same but AraC, d 1-8 only Consolidation therapy (not randomized) given to pts with remission Transplant vs none if CR after 2 courses induction	81% DAT vs 83%, p=0.3	OS at 6 y: 40% both groups, p=0.9 DFS at 6 y from CR: 42% vs 43%, p=0.8; relapse rate: 50% vs 49%, p=0.6	8% vs 9% induction deaths, p=0.9 Deaths during consolidation: 6% vs 9%, p=0.06 ADE pts had slightly more severe non-hematologic toxicity (nausea, p=0.01; alopecia, p<0.0001; mucositis, p=0.002, diarrhea, p=0.008 after course 1; but only for alopecia after course 2. Slightly longer delay (1-2 d) with DAT in recovery of neutrophils and platelets	ITT	DAT and ADE both result in high remission rates and survival and are equally effective in pts up to age 55

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[16]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
JALSG AML92; 1991-1995 Miyawaki, 1999 (234)	667 Adult age 15+ y (median 49 y), newly diagnosed AML except M3; no preceding diagnosis of MDS	Induction Etoposide	BHAC + 6MP + DNR ± etoposide Etoposide (100 mg/m^2/d by 1-h infusion, d 1-5) All received DNR (40 mg/m^2/d iv, d 1-4) + behenoyl cytarabine (BHAC; 200 mg/m^2/d by 3-h infusion, 10 d) + 6MP (70 mg/m^2/d for 10 d; 300 mg/d of allopurinol for 10 d) Used response-oriented individual induction (duration determined by response). If marrow not severely hypoplastic on d 8 then DNR was added, d 8-9; if not severely hypoplastic on d 11 then added DNR + BHAC + 6MP on d 11-12 If CR then received 3 courses of consolidation with same agents followed by 6 courses of maintenance	75% vs 77% M4 pts: 69% vs 86% (p=0.009)	6-y OS: 38% vs 30%, p=0.925 DFS if CR: 35% vs 25%, (p=0.352	Etoposide group had shorter induction period and lower dose of DNR (p<0.001). Non-hematological toxicities equal except greater hair loss (p=0.024) and diarrhea (p=0.013) with etoposide.	NR	Etoposide showed no advantage when added to individualized induction
MRC AML11; 1990-1998 Goldstone, 2001 (69)	1314 Initially accepted age 56+ y; age ≥60 y starting end of 1994, although younger pts allowed if not suitable for more intensive chemo in AML10/AML12. 2% of pts age <56 y. Any de novo or secondary AML	Induction; consolidation; maintenance Etoposide (Anthracycline DNR vs MTZ) (GCSF)	2 courses induction: DAT vs ADE vs MAC (1:1:2 ratio) DAT 3+10 → DAT 2+5: DNR (50 mg/m^2 slow iv, d 1, 3, 5) + AraC (100 mg/m^2 12-hourly iv, d 1-10) + TG (100 mg/m^2 12-hourly po, d 1-10) then same but DNR, d 1, 3 and (AraC + TG), d 1-5 ADE 10+3+5 → ADE 5+2+5: DNR (50 mg/m^2 slow iv, d 1, 3, 5) + AraC (100 mg/m^2 12-hourly iv, d 1-10) + etoposide (100 mg/m^2 iv 1-h infusion, d 1-5) then same but DNR, d 1, 3, and AraC, d 1-5 MAC 3+5 → MAC 2+5: MTZ (12 mg/m^2 iv 30-min infusion, d 1-3) + AraC 100 mg/m^2 12-hourly iv, d 1-5) then same but MTZ, d 1, 3 A subset of pts (n=226) were randomized to receive GCSF (293 µg/d sc, d 8 of course 1 until neutrophil recovery or maximum of 10 d) or placebo Pts in remission (n=371) randomized to stop after a third course (DAT 2+7) or after 4 additional courses (DAT 2+7, COAP, DAT 2+5, COAP) Third randomization (n=362): IFN-α maintenance for 1 year vs none	62% DAT vs 50% ADE, p=0.002; Benefit of DAT in pts <70 and >70	5-y OS: 12% DAT vs 8% ADE, p=0.02; 8% ADE vs 10% MAC, p=0.2 5-y DFS: 18% DAT vs 15% ADE	No important differences in non-hematologic toxicity, or for number of days for neutrophil and platelet recovery	ITT	
Polish PALG; 1993 Holowiecki, 1994 (387) [Polish, English abstract]	56 Adult, ANLL	Induction Etoposide	IDA +AraC + etoposide [ICE] vs DNR + AraC IDA (d 1,3,5), AraC (1-7/10), etoposide (1-5), DNR (d 1-3) Additional HDAC C if insufficient cytoreduction in 6 day bone marrow biopsy and etoposide in M4-5 subtype	63% vs 61% After 1 cycle: 59% vs 34%, p<0.02		Side effects comparable in both groups; IDA arm needed more intensive supportive therapy		

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[16]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
USA; 1993-1997 Damon, 2004 (235)	138 Age >16 y, median 61 y, high-risk acute leukemia. Group II (n=39): secondary AML, median age 64 y; Group III (n=38): de novo AML, age ≥60 y (median 68 y). Group I (n=31): relapse. Group IV (n=30): induction failure or blast crisis of MDS. Group 1 belongs in relapse section; as toxicity is primary outcome, this study is just reported here	Induction + consolidation Etoposide administration	IDA + AraC + etoposide; etoposide administration randomized to bolus (experimental) vs CI (control) Groups I-III: IDA (8 mg/m^2/d iv, d 1-3), AraC (2000 mg/m^2 iv over 2h, d 1-6), etoposide (1600 mg/m^2 iv total dose). Group IV: as above but AraC intensified (q12h, d 1-6) Etoposide randomized to be either bolus iv over 10 h on d 7 or CI over, d 1-6 Pts with CR and not eligible to HSCT were eligible to 1 course of consolidation chemotherapy the same as the induction course; 27 of 34 pts in Group II/III with CR or hematologic remission received consolidation Pts who relapsed were permitted to enrol a second time and be re-randomized (n=7) Group IV (induction failure or blast crisis of myeloproliferative syndrome) doesn't appear to meet inclusion criteria but CR and OS includes all 4 groups; it is not included in mucositis outcomes in this table	All groups combined: 47% bolus vs 50% CI, p=0.7	Median 7.4 m overall and 2-y OS 18±3%; no significant difference between etoposide schedule, p=0.9	Significantly less oral mucositis in pts with bolus etoposide (grade 2+): Groups I-III combined 6% bolus vs 61% CI (p<0.0001); median duration 0 d vs 3 d (p<0.0001). Days of TPN and parenteral narcotic use were greater in continuous etoposide pts (p<0.01). No difference in skin or hepatic toxicities, hematologic recovery, AraC dose modification	Primary endpoint oral mucosal toxicity. Secondary endpoint tolerability. Sample size 17/arm in each group to detect minimum difference of 4 d mucositis with power of 0.8	Toxicity profile of high-dose etoposide is schedule-dependent
Russian; AML-01.01; 2001-2006 Parovichnikova, 2010 (177) [Russian, English abstract], (176) [abstract and poster]; Parovichnikova 2007 (236) [Russian, English abstract]; Parovitchnikova, 2003 (179) [abstract]	354 392 randomized	Induction + consolidation + maintenance Etoposide	[AraC + DNR + etoposide] ×4 + maintenance [n=124] vs [AraC + DNR + etoposide] ×2 then [AraC + DNR] ×2 + maintenance [n=130] vs [AraC + DNR (7+3) + etoposide] ×2 then [HDAC + DNR] ×2 (no maintenance) [n=126] AraC (100 mg/m^2 bid iv, d 1-7), DNR (45 mg/m^2, d 1-3), etoposide (120 mg/m^2 iv, d 17-21), HDAC (AraC 3 g/m^2 bid 1-3 d) Maintenance (5 or 6 courses): (7+3): AraC + 6MP (60 mg/m^2 bid 1-3 d) Total DNR dose 540 mg/m^2	52.1%, 56.0%, 56.9% after 1 course	2-y OS 38% vs 58% vs 65%; longer-term: 18% vs 30% vs 36% 2-y DFS 56% vs 52% vs 59%; longer-term RFS: 35%, 20%, 30%	Induction deaths 12.8% vs 8.6% vs 9.9%	NR	No significant difference in efficacy

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[16]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Slovakia; 2000-2011 Sabty, 2011 (166) [abstract]	128 Age 15-60 y, newly diagnosed AML	Induction Etoposide (AraC dose) Unequal numbers in groups not explained	DNR + AraC + etoposide (Group B) vs DNR + AraC (Group A) Group B (n=57): (AraC 100 mg/m^2/d CI, d 1-10) + DNR (50 mg/m^2/d, d 1, 3, 5) + etoposide (50 mg/m^2/d, d 1-5) Group A (conventional 3+7, n=27): DNR(60 mg/m^2/d, d 1-3) + AraC (200 mg/m^2/d CI, d 1-7) Note different AraC and DNR doses in the 2 arms	75.4% Group B vs 55.6% Group A, p=0.025	5-y OS: 41% vs 17%, p<0.00001 DFS: 44% vs 25%	Toxicity similar	NR	Etoposide can improve CR and outcome
Turkey; 1992-1995 Beksac, 1998 (204)	99 Age >14 y, previously untreated ANLL; also included pts with myelodysplastic features of <6 m duration. Median age Groups 1, 2, 3 were 40 y, 31 y, 36 y, p<0.05 (G1 vs G2); G3 had more pts age >60 y (n=7 vs n=2 in other groups)	Induction + consolidation IDA, MTZ, DNR + etoposide	Group 1: AraC + IDA vs Group 2: AraC + DNR + etoposide vs Group 3: AraC + MTZ Group 1: AraC (100 mg/m^2 CI, d 1-7) + IDA (12 mg/m^2/d iv, d 1-3; 10 mg/m^2 for pts age >50); 2nd course if >5% blasts on d 21; if CR then 2 courses of consolidation: IDA (15 mg/m^2 iv bolus, d 1; 12 mg/m^2 for age >50) + AraC (100 mg/m^2 q12h for 2-h infusion, d 1-6) Group 2: AraC (100 mg/m^2 iv q12h, d 1-10) + DNR (50 mg/m^2/d, d 1, 3, 5) + etoposide (100 mg/m^2/d, d 1-5); consolidation: 1 cycle AraC (100 mg/m^2 q12h, d 1-8) + DNR (50 mg/m^2/d, d 1, 3, 5) + etoposide (100 mg/m^2/d, d 1-5); 2nd cycle: AraC (200 mg/m^2/d CI, d 1-8) + AMSA (100 mg/m^2 1h infusion, d 1-5) + etoposide (100 mg/m^2/d, d 1-5); 3rd cycle: AraC (100 mg/m^2 q12h, d 1-3) + MTZ (10 mg/m^2 30 min infusion, d 1-5) Group 3: MTZ (12 mg/m^2/d iv bolus, d 1-3) + AraC (100 mg/m^2/d CI, d 1-10); consolidation: MTZ (15 mg/m^2 iv, d 1) + AraC (100 mg/m^2 2 h iv infusion q12h, d 1-6)	76.5%, 72.2%, 68.9%, p=0.79, ns 1st course: 34% vs 36% vs 52%	5-y OS: 26.5%, 18.9%, 14.8%, p=0.079 After 45 m follow-up, 3-y RFS 17 m, 9 m, 9 m; better for Group 1, p=0.014 5-y RFS: G1 better only when excluded pts with transplant (p=0.05)	Induction deaths 9.7%, 12.9%, 14.8% Median time to CR: 51 d vs 28 d vs 32 d, p<0.05 [may be due to age distribution]	NR	IDA-containing regimen superior
Finland; ≈1997-2000 Ruutu, 2004 (237)	68 (13 died prior to randomization) Age >65 y, median 72 y; de novo AML (n=65), subsequent to MDS (n=21), treatment related (n=6); excluded age <70 y if exceptionally fit; alive after 1 cycle induction	Induction (2nd and 3rd cycles) Etoposide vs AraC in 2nd cycle	ETI (oral) vs (AraC + IDA + 6-TG) ETI: [etoposide (80 mg/m^2) + thioguanine (100 mg/m^2)] q12h, d 1-5; plus IDA (15 mg/m^2, d 1-3) TAI: AraC (100 mg/m^2 iv, q12h, d 1-5); IDA (12 mg/m^2 iv, d 5); 6-TG (100 mg/m^2, po, q12h, d 1-5) All received a 6 d iv treatment with AraC (100 mg/m^2, 15 min iv infusion, twice a day, d 1-6) + IDA (12 mg/m^2, 10 min iv infusion, d 4 and 6) then randomized as above	ETI 67% vs TAI 72%, p=0.64	OS median 12 m vs 12 m, p=0.345; OS at 2 y, 33% ETI vs 21% TAI No difference in EFS (p=0.661) 2-y risk of relapse 67% vs 72%, p=0.617	ETI pts spent fewer days in hospital during induction (20 vs 41 d, p=0.010), less infections, shorter neutropenias and thrombocytopenias	NR	ETI and TAI similar; ETI less toxic and easier to administer (oral)

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[16]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Italian; 1981-1983 Bandini, 1987, 1991 (238,239)	156 Age <60 y, de novo AML	Induction + maintenance Etoposide + vindesine vs DNR	DNR + AraC + TG (DAT, arm A) vs DAT → (etoposide + AraC + vindesine) (arm B) Arm A, 1 cycle DAT 3+7 and 3 cycles DAT 1+5: DNR (45 mg/m^2 iv, d 1-3 or d 1), AraC (100 mg/m^2/12 h iv, d 1-7 or 1-5), TG (100 mg/m^2/12 h po, d 1-7 or 1-5) followed (if CR) by monthly maintenance (AraC + TG, 1+5) for 2 y • Pts who did not achieve CR after 2 cycles were considered induction failures and were treated with regimen B Arm B: alternate DAT and [etoposide (60 mg/m^2/12 h iv, d 1-5) + AraC (100 mg/m^2/12 h iv, d 1-5) + vindesine (2.5 mg/m^2 iv, d 1] for 4 cycles [M1, M2, M3 started with DAT; M4, M5 started with VAE], then maintenance (if CR) alternating (AraC + TG, 1+5) and (etoposide + AraC + vindesine) for 2 y • If CR not achieved after 2 cycles, treatment was determined by the treating centre. In all pts, DNR (at 40 mg/m^2 iv, d 1; max total dose 600 mg/m^2) was added to every 3rd cycle of maintenance	53% arm A vs 61% arm B, p=0.40 Including cross-over: 58% vs 61%, p=0.84	OS median 8-9 months, no difference between Arms; 7-y OS 15% (both arms combined) RFS at 4 y: 25% vs 21%	Early death: 24% vs 31%, ns Median CR duration 16 m and 15 m	200 pts to detect increase in CR from 60% to 80% and RF rate from 25% to 42% with 90% power; recruited only 168 pts	
Finland Ruutu, 1994, 1996 (240,241)	51 Age >65 y, median 73 y; de novo AML (n=38), after MDS (n=11) or treatment-related (n=2); fit enough to receive moderately intensive treatment but excluded pts fit enough to receive std intensive induction + consolidation	Induction + consolidation Etoposide + IDA vs DNR	Oral ETI vs conventional TAD ETI (oral): [etoposide (80 mg/m^2) + thioguanine (100 mg/m^2)] twice a day, d 1-5; plus IDA (15 mg/m^2, d 1-3) TAD: thioguanine (oral) + AraC (iv) (both 100 mg/m^2 twice a day, d 1-5) + DNR (60 mg/m^2, d 5) 1-2 cycles of crossover treatment if treatment failure Received 2 courses of induction then maintenance with 6MP + methotrexate	60% ETI vs 23%, p=0.007	OS median 9.9 m ETI vs 3.7 m, p=0.042 RFS 7.2 m vs 2.7 m, ns	No significant differences in side effects	NR	ETI higher remission and longer survival; ETI may also be preferred due to its oral administration

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[16]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
SWOG 9333; 4 years Anderson, 2002 (242)	328 Age >55 y, previously untreated AML, secondary AML allowed	Induction Etoposide + MTZ vs DNR	MTZ + etoposide vs AraC + DNR MTZ (10 mg/m^2/d iv over 30 min, d 1-5) + etoposide (100 mg/m^2/d iv over 30 min, d 1-5) vs AraC (200 mg/m^2/d CI, d 1-7) + DNR (45 mg/m^2/d iv, d 1-3) 2nd cycle if d 14 marrow showed 5+% blasts Pts with CR received post-remission therapy (DNR + AraC)	34% (26%-41%) vs 43% (35%-51%), adjusted p=0.96; p=0.089 for question of whether MTZ is worse	OS at 2 y: 11% (6%-15%) vs 19% (12%-25%), adjusted p=0.99, HR=1.32 (1.04-1.69); p=0.022 that survival was worse with MTZ RFS: median 7 m vs 9 m, 2-y RFS 16% vs 18%, adjusted p=0.83, HR=1.22 (0.80-1.87)	After accounting for prognostic factors, exploratory analysis suggested worse survival with MTZ, p=0.0066. Fatal toxicity higher with MTZ (23% vs 18%, p=0.90)	ITT. Null hypothesis that CR rates equal. 90% power to detect increased CR rate from 50% to 65% with 400 pts. 98% power to detect mortality hazard ratio of 0.67.	No benefit for MTZ/ etoposide. Terminated early by Data and Safety monitoring Committee because sufficient evidence to reject alternative hypotheses (p=0.0001 for CR, P<0.0001 for OS)
German AML Intergroup Study A: 2002-2008, NCT00146120 (AML HD 93A); NCT00209833 (AML 01/99) Buchner, 2012 (196)	828 Age 16-60 y, median 48 y	Induction + consolidation. [Induction for Study A; consolidation is same as std] Etoposide + IDA vs DNR	Study A (n=828): IDA + etoposide + AraC [ICE] vs common control arm 2 courses standard-dose AraC combination (IDA, AraC, etoposide) + 3 courses HDAC (3 g/m^2 q12h, d 1, 3, 5) First treatment with ICE + 2nd cycle if response; if no response then given A-HAM and search for unrelated donor Common control arm. Induction: AraC (100 mg/m^2/d CI, d 1-7) + DNR (60 mg/m^2/d iv over 2 h, d 3-5); 2nd course starting on d 22. Consolidation: 3 cycles at monthly intervals of HDAC (3 g/m^2 over 3 h q12h, d 1, 3, 5)	CR + CRi: 75% vs 70%, ns	5-y OS 41.4% vs 44.3%, p=0.826 5-y RFS 34.9% vs 44.8%, ns 5-y EFS 27.0% vs 31.5%, p=0.738	NR	NR	
Italian; 1999-2002 Russo, 2005 (8,9)	112 Age <60 y, newly diagnosed AML	Induction Etoposide vs fludarabine (Fludarabine vs etoposide)	FLAI vs ICE (one cycle) FLAI: fludarabine (25 mg/m^2/d, d 1-5) + AraC (2 g/m^2/d, d 1-5) + IDA (10 mg/m^2/d, d 1, 3, 5) ICE: IDA (10 mg/m^2/d, d 1, 3, 5) + AraC (100 mg/m^2/d CI, d 1-10) + etoposide (100 mg/m^2/d, d 1-5) Post-induction with HDAC (3 g/m^2/12 h/d, d 1-6) for all pts; if CR then received 2nd consolidation with MTZ + etoposide + AraC and/or stem cell transplant	74% FLAI vs 51%, p=0.01 After HDAC: 81% vs 69%, p=0.1	4-y OS: 32% vs 32%, p=0.7 4-y RFS 31.5% vs 44%, p=0.7	Death during induction 2% vs 9% (p=0.08); FLAI resulted in less hematological toxicities (p=0.002) and non-hematological toxicities (especially gastrointestinal (p=0.0001)	Primary endpoint CR rate. Required 55 pts/arm to detect 20% increment in CR rate with 70% power	FLAI more effective and less toxic for induction

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[16]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Sweden LGMS Bjorkholm, 1995 (243)	86 Age 15-60 y, median 44 y, previously untreated AML; excluded s-AML	Induction Etoposide + MTZ vs doxorubicin-DNA + VCR + prednisolone	MEA (MTZ + etoposide + AraC) vs doxorubicin-DNA + AraC + TG + VCR + prednisolone MEA: MTZ (12 mg/m^2/d by 1h infusion), etoposide (100 mg/m^2/d by 1h infusion), AraC (1 g/m^2 twice a day by 2h infusion), all on d 1-4 DNA group: doxorubicin-DNA (calf thymus DNA, 30 mg/m^2, 4h infusion, d 4-5), AraC (100 mg/m^2 CI, d 1-5), TG (50 mg/m^2 bid po, d 1-7), VCR (2 mg iv, d 1, 5), prednisolone (30 mg/m^2 bid po, d 107) Induction repeated if no CR or severe bone marrow hypoplasia. For MEA arm, 3rd course given if needed; if still no remission, AMSA + AraC were given For DNA arm, if no remission after 2 courses, doxorubicin-DNA was increased to 45 mg/m^2 on d 4-5 and VCR omitted in the 3rd course; if no remission, AMSA + AraC were given Post-remission: pts randomly assigned to R1 (16 monthly courses), or R2 and R3 (3 courses followed by bone marrow transplant) Study closed after interim analysis of 86 pts and post-remission part of study could not be evaluated	83% MEA vs 45%, p<0.001 After rescue therapy: 88% vs 64%, p<0.02	OS median 27.8 m MEA vs 13.1 m, p<0.03; 25% vs 5% at 60 m [from graph]	Non-hematologic toxicity was comparable in two arms, except gastrointestinal toxicity grade 3-4 which tended to be more frequent among the DNA arm, p=0.06.	Closed after interim analysis of 86 pts due to large difference in CR; consolidation study could not be evaluated	MEA regimen had high anti-leukemic activity; could not reproduce previous doxorubicin-DNA results with different source of DNA

6MP, 6-mercaptopurine (mercaptopurine); ADE, AraC + DNR + etoposide; A-HAM, ATRA + HAM = all-trans retinoic acid + high-dose cytarabine + mitoxantrone; ANLL, acute non-lymphoid leukemia; AMSA, amsacrine; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; ATRA, all-trans retinoic acid; BHAC, N4-behenoyl-1-β-D-arabinosylcytosine (widely used in Japan instead of AraC since 1979); CI, continuous iv infusion; COAP, cyclophosphamide, VCR, AraC, prednisone; CR, complete remission (complete response); CRi, complete remission with incomplete recovery; DA, DNR + AraC; DAT, DNR +AraC + 6-thioguanine (TG); DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; FLAG, fludarabine + high-dose AraC + GCSF; FLAI, Fludarabine + AraC + IDA; GCSF, granulocyte-colony stimulating factor; GO, gemtuzumab ozogamicin; HAM, high-dose cytarabine + mitoxantrone; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; ICE, idarubicin + cytarabine + etoposide; IDA, idarubicin; IFN, interferon; ITT, intention to treat; iv, intravenously; MAC, MTZ + AraC; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OR, odds ratio; OS, overall survival; po, oral administration (per os); RAEB-t, refractory anemia with excess of blasts in transformation; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; sc, subcutaneously; std, standard; TAD, thioguanine + cytarabine + daunorubicin; TG, 6-thioguanine; VCR, vincristine

Table 4-9. Induction, ATRA Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[17]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MD Anderson; 1995-1997 Estey, 1999 (244)	215 Median age 65 y (32% age >71 y). Newly diagnosed AML (n=153) or high-risk MDS (n=62), with poor prognosis (one of: age >71 y, abnormal blood counts, secondary AML/MDS, failure to respond to 1 course of AraC + anthracycline chemotherapy at other hospital, abnormal renal/hepatic function). 2/3 had an antecedent hematologic disorder, 26% s-AML, 11% refractory	Induction + post-remission ATRA (GCSF)	FAI (Fludarabine + AraC + IDA) vs FAI + ATRA vs FAI + GCSF vs FAI + ATRA + GCSF FAI: fludarabine (30 mg/m^2/d, d 1-4) + AraC (2 g/m^2, d 1-4) + IDA (12 mg/m^2, d 2-4) GCSF (200 µg/m^2 daily), ATRA (45 mg/m^2 daily in 2 doses) If white blood cell count <10, 000/µL then began ATRA on day -2 and GCSF on day -1; otherwise started both with chemotherapy ATRA continued until d 3; GCSF continued until neutrophil count exceeded 1000/µL 2nd course of induction in pts with persistent disease (not CR) Pts with CR received post-induction treatment for 6 months (4-5 courses) with AraC (100 mg/m^2/d, d 1-5) alternating with fludarabine (30 mg/m^2/d, d 1-2) + AraC (1 g/m^2/d, d 1-2) + IDA (8 mg/m^2, d 3); GCSF and/or ATRA (during chemo + 3 further days) given to pts who received them during induction at same dose as during induction	40% FAI, 51% FAI + ATRA, 55% FAI + GCSF, 59% FAI + ATRA + GCSF; Effect of ATRA ± GCSF vs no ATRA, p=0.264	All improved OS compared with FAI: FAI + GCSF, p=0.15; FAI + ATRA, p=0.023; FAI + ATRA + GCSF, p=0.055 After multivariate regression analysis with possible prognostic factors, OS differences not statistically significant EFS compared with FAI: FAI + ATRA, p=0.053; FAI + GCSF, p=0.32; FAI + GCSF + ATRA, p=0.095	NR	212 pts to detect 0.20 difference in probability of success (alive and in CR at 6 m) between baseline group (FAI) and each other group, power 0.80	Benefit of ATRA before but not after multivariate analysis. Authors suggest the study was too small for randomization to account for differences between groups. Results should not be generalized to other pt groups (e.g. AML pts with better prognosis) and other studies should be designed.
AMLSG AML HD98B (German); 1998-2001 Schlenk, 2004, 2009 (245,246)	242 Age 61+ y, median 66.6 y with de novo AML, RAEB-t, s-AML, or t-AML	Induction; consolidation. Randomized to 2nd consolidation ATRA	ICE (std arm) vs A-ICE ICE: IDA (12 mg/m^2 iv, d 1 and 3) + AraC (100 mg/m^2 CI, d 1-5) + etoposide (100 mg iv, d 1 and 3) A-ICE: ICE → ATRA started after administration of IDA and etoposide on d 3 at a dosage of 45 mg/m^2, d 3-5 and 15 mg/m^2, d 6-28 2nd cycle if CR or PR; if refractory then 2nd induction with A-HAE [AraC (0.5 g/m^2/12 h iv, d 1-3), etoposide (250 mg/m^2 iv, d 4 and 5), ATRA (45 mg/m^2, d 3-5 and 15 mg/m^2, d 6-28)] If CR after 2 cycles induction then consolidation with HAM vs A-HAM (along initial randomization). Randomized (n=61) to 2nd consolidation (if CR) with IEiv [IDA (12 mg/m^2 iv, d 1 and 3), etoposide (100 mg/m^2 iv, d 1-5)] or 1 year oral IEpo [IDA (5 mg po, d 1, 4, 7, 10, 13); etoposide (100 mg po, d 1 and 13); repeat on d 29 for 12 courses]	52% ATRA vs 39% std (ICE), p=0.05 1 cycle: 38% vs 27.5%	OS better with ATRA, median 11.3 m vs 7.0 m, p=0.01; 4-yr OS 10.8% ATRA vs 5%, p=0.003 EFS better with ATRA, p=0.03 4-y RFS 20.9% ATRA vs 4.8%, p=0.006	No difference in toxicity and supportive care for induction and first consolidation therapy between arms. Cumulative incidence of relapse (CIR): 39% IEiv vs 80% IEpo, p=0.002 Subgroup analysis: OS and RFS benefit of ATRA for mutant NPM1 without FLT3-ITD genotype only	ITT. Primary endpoint CR. 242 pts to detect 0.2 difference in CR between null hypothesis that both groups proportions are 0.5 and alternative that ATRA is 0.7, with 80% power.	ATRA added to induction and consolidation may improve CR, EFS, OS in elderly ATRA survival benefit may only apply to mutant NPM1 without FLT3-ITD, being validated in AMLSG 07-04 trial

[17] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[17]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
AMLSG 07-04 NCT00151242; 2004-2009 Schlenk,2011 2014 [abstract] (247,248)	1100 Younger adults with AML, age 18-60 y, 28% of those tested had a mutation in NPM1 (n=289)	Induction ATRA (+ VPA)	ICE ± ATRA (+ VPA) vs ICE ± ATRA ICE (2 cycles) ± ATRA (45 mg/m^2, d 6-8 and 15 mg/m^2, d 9-21) and VPA (first 372 pts) ICE (2 cycles) ± ATRA (rest of pts) Consolidation: Transplant if high risk, transplant or 3 cycles AraC if intermediate-risk, AraC for rest Randomized for VPA stopped at interim analysis (n=372) due to ineffectiveness.	ATRA had no significant effect by ITT. Per protocol, ATRA had benefit in NPM1 mutation subgroup (OR=2.07, p=0.03); wild-type OR=1.00, p=0.99	Median 5.1 y: ATRA benefit (ITT, p=0.09; per protocol, p=0.01); attributed to ELN-favourable subtypes (p=0.04) including core-binding factor AML, AML with CEBPAdm and AML with mutated NPM1 in the absence of FLT3-ITD	ATRA benefit for NPM1 mutation group on per protocol basis for CR (p=0.03) and EFS (p=0.04) EFS (median 3.3 y follow-up): NPM1-mutated HR=0.65, p=0.02, NPM1-wt HR=0.99, p=0.95	Primary endpoint EFS, 2nd endpoint CR, OS. ITT and per protocol analysis	
MRC AML12; ISRCTN17833622; 1994-2002 Burnett, 2010 (153,154)	2934 Age <60, median 41 y, de novo or secondary AML (including treatment-related or previous MDS, n=239) and high-risk MDS	Induction; consolidation ATRA	B. After Amendment (n=1193) DNR + AraC + TG: standard vs high (double) AraC dose Both groups randomized to ATRA (45 mg/m^2, d 1-60) vs none S-DAT 3+10 → S-DAT 3+8: DNR (50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2, q12h, d 1-10) + TG (100 mg/m^2 q12h, d 1-10); then same but AraC and TG, d 1-8 H-DAT 3+10 → H-DAT 3+8: DNR (50 mg/m^2, d 1, 3, 5) + AraC (200 mg/m^2, q12h, d 1-10) + TG (100 mg/m^2 q12h, d 1-10); then same but AraC and TG, d 1-8 Both Phases A & B Randomized Consolidation if CR (n=992): MACE then randomize to 1 (MidAC) or 2 further courses (ICE then MidAC)	68% ATRA vs 68% no ATRA, p=0.9	OS 33% ATRA vs 30% no ATRA, p=0.8 RFS 32% ATRA vs 29% no ATRA, p=0.8	Induction deaths 8% ATRA vs 8% no ATRA, p=0.9	NR	No benefit for increased AraC dose or for ATRA ATRA did not have significant benefit on any molecular subgroup (FLT3, NPM1, CEBPA, MN1) (154)
NCRI AML16; 2010-2012 Burnett, 2013 (249) [abstract]	616 Median age 67 y (53-82 y); 75% de novo AML, 16% secondary AML, 8% high-risk MDS	Induction ATRA (Etoposide)	Once accrued all patients for AraC vs clofarabine comparison, added new 2×2 induction comparison DA (DNR + AraC) ± ATRA vs ADE (DNR + AraC + etoposide) ± ATRA DNR (50 mg/m^2, d 1-3), AraC (100 mg/m^2 bid, d 1-10 course 1 or d 1-8 course 2), ATRA (45 mg/m^2/d for 60 d), etoposide (100 mg/m^2/d, d 1-5)	CR+CRi: 66% ATRA vs 73% no ATRA, OR=1.39 (0.98-1.95), p=0.06	OS at 2 y, ATRA 35% vs not 35%, HR=1.13 (0.91-1.40), p=0.3 RFS at 2 y: 31% ATRA vs 30% not, HR=0.93 (0.71-1.20), p=0.6	30-d mortality: 16% ATRA vs 8% no ATRA (p=0.005); 60-d mortality: 20% ATRA vs 12%, p=0.005	NR	

ADE, AraC + DNR + etoposide; A-HAM, ATRA + HAM = all-trans retinoic acid + high-dose cytarabine + mitoxantrone; A-ICE, ATRA + ICE; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; ATRA, all-trans retinoic acid; CI, continuous iv infusion; CR, complete remission (complete response); CRi, complete remission with incomplete recovery; DAT, DNR +AraC + 6-thioguanine (TG); DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; ELN, European LeukemiaNet; FAI, fludarabine + AraC + IDA; GCSF, granulocyte-colony stimulating factor; HAM, high-dose cytarabine + mitoxantrone; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; ICE, idarubicin + cytarabine + etoposide; IDA, idarubicin; IEiv, IDA + etoposide, iv; IEpo, IDA + etoposide, orally; ITT, intention to treat; iv, intravenously; MACE, amsacrine + AraC + etoposide; MDS, myelodysplastic syndromes; MidAC, MTZ + AraC; MTZ, mitoxantrone; NR, not reported; OR, odds ratio; OS, overall survival; po, oral administration (per os); PR, partial response/remission; RAEB-t, refractory anemia with excess of blasts in transformation; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; std, standard; t-AML, therapy-related AML following treatment of primary malignant disease; TG, 6-thioguanine; VPA, valproic acid

Table 4-10. Induction, gemtuzumab ozogamicin (GO) Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[18]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MRC AML15; ISRCTN17161961; 2002-2006 induction; 2002-2009 consolidation Burnett, 2011 (6)	1113 (3106). Induction, n=3106; consolidation, n=1440. Effect of GO induction, n=1113. Effect of GO consolidation, n=948. ADE vs FLAG-IDA, n=1268. ADE vs DA, n=1983 Age >15 y, predominantly <60 y, untreated AML (de novo or secondary), APL excluded	Induction; consolidation GO 3 mg/m^2 (Fludarabine + IDA vs DNR) (Etoposide)	Induction DA (DNR + AraC) ± GO vs FLAG-IDA (fludarabine + AraC + GCSF + IDA) ± GO vs ADE (AraC + DNR + etoposide) [± GO starting 2005] DA 3+10 ± GO → DA 3+8: DNR (50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-10) ± GO (3 mg/m^2, d 1) then 2nd cycle with DNR (50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-8) FLAG-IDA ± GO → FLAG-IDA: fludarabine (30 mg/m^2 iv, d 2-6) + AraC (2 g/m^2 over 4 h starting after fludarabine, d 2-6) + GCSF (lenograstin 263 µg sc daily, d 1-7) + IDA (8 mg/m^2 iv daily, d 4-6) ± GO (3 mg/m^2, d 1); then 2nd cycle same without GO ADE 10+3+5 → ADE 8+3+5: DNR (50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-10) + etoposide (100 mg/m^2, d 1-5) then 2nd cycle same except AraC d 1-8 Consolidation: See Table 4-14	GO Effect 82% GO vs 83%, p=0.8	GO Effect Induction 5-y OS: 45% GO vs 41%, p=0.16 ADE + GO vs ADE, OR=1.08 (0.71-1.63), ns DA + GO vs DA, OR=0.90 (0.71-1.15), ns FLAG-IDA + GO vs FLAG-IDA, OR=0.89 (0.70-1.14), ns Cytogenetic subgroup: favorable 80% GO vs 52% no GO, OR=0.32 (0.18-0.59); intermediate 48% vs 43%, OR=0.86 (0.70-1.07); adverse 10% vs 11%; non-high risk 53% vs 45%, p=0.009 No OS difference with GO consolidation 5-y RFS 39% GO vs 35% No RFS difference with GO consolidation Cumulative incidence of relapse at 5 y: 49% vs 44%, p=0.09	GO Effect Induction deaths 7% GO vs 6%, p=0.6; 30-d mortality 11% GO vs 10%. No difference in non-hematologic toxicity; GO pts required more platelets (p<0.001) and antibiotics (p=0.02) after course 1.	ITT Non-GO questions: At least 1000 pts per induction question to give 90% power to detect 10% survival difference at p<0.05 and 800 pts in consolidation to give 80% power to detect a 10% difference in OS	GO Effect GO well tolerated. Significant survival benefit of GO during induction for pts with favourable cytogenetics and a trend for benefit for intermediate-risk pts; significant for these two groups combined No benefit of GO during consolidation
MRC AML15+16 meta-analysis Burnett, 2012 (58)	2228 Median age 61 y, range 51-84 y	Induction; consolidation; maintenance. [meta-analysis of induction with GO] GO 3 mg/m^2	See AML15 and AML16 entries		Improved survival with GO, HR=0.88 (0.79-0.98), p=0.02	Overall reduction in relapse risk with GO, HR=0.82 (0.72-0.93), p=0.002	NR	

[18] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[18]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
NCRI AML16; 2006-2010 Burnett, 2012 (58) [GO vs none]; Burnett, 2012 (149) [abstract]	1115 Older pts suitable for intensive chemotherapy. Generally age >60 y, median 67 y (range 51-84 y); some younger pts if not suitable for trial for younger pts. Untreated de novo AML (72%), secondary AML (17%), or high-risk MDS (10%)	Induction; consolidation; maintenance GO 3 mg/m^2 (Clofarabine)	DNR + AraC (DA arm) ± GO vs DNR + clofarabine (DClo arm) ± GO GO given only in 1st of 2 induction cycles; GO vs no GO (n=1115) After 800 pts enrolled, subsequent pts received DNR/AraC ± GO DNR + AraC (3+10) ± GO → DNR + AraC (3+8): DNR (50 mg/m^2/d, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-10) ± GO (3 mg/m^2, d 1), then 2nd cycle DNR (50 mg/m^2/d, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-8) DNR + clofarabine ± GO → DNR + clofarabine: DNR (50 mg/m^2/d, d 1, 3, 5) + clofarabine (20 mg/m^2/d, d 1-5) ± GO; then 2nd cycle same without GO Post-induction, pts with CR were randomized to DNR (50 mg/m^2, d 1, 3) + AraC (100 mg/m^2 q12h, d 1-5) vs none; Maintenance: Pts not planned for allograft were then randomized to AZA (75 mg/m^2/d for 5 d; repeat q6w ×9) vs none	62% GO vs 58%, p=0.14 CR+CRi 70% vs 68%, p=0.3	3-y OS 25% GO vs 20% no GO, p=0.05 OS by cytogenetic risk: adverse risk 8% vs 3%, intermediate 28% vs 24%, 3-y RFS 21% vs 16%, p=0.04 3-y cumulative incidence of relapse 68% vs 76%, p0.007	GO group had more grade 3-4 nausea/vomiting (9% vs 4%, p=0.002), bilirubin (7% vs 6%, p=0.001)	ITT. Primary outcome OS. Powered to detect difference of 10% in 2-y OS from 25% to 35% (equivalent to HR=0.76) with 90% power. 800 pts and 552 deaths required.	Addition of GO to chemo did not increase rate or speed of remission but improved survival; similar toxicity DA and DClo resulted in similar outcomes In pts with CR, no significant benefit for 3rd course (consolidation)
NCRI AML17; 2009-2011 Burnett, 2014 (62) [abstract]	788 Median 50 y (range 0-81y, 29 pts <16 y), 86% de novo AML, 9% secondary AML, 5% MDS	Induction GO dose	90 mg/m^2/d DNR + AraC vs 60 mg/m^2/d DNR + AraC [± GO ± etoposide] GO 6 mg/m^2 vs GO 3 mg/m^2 on d 1 DA (3+10) or ADE (10+3+5); all children received ADE	CR+CRi: 85% for 6 mg vs 89%, OR=1.34 (0.88-2.04), p=0.17	OS at 3 y: 50% vs 53%, OR=1.12 (0.91-1.36), p=0.3 RFS at 3 y: 42% vs 45%, OR=1.11 (0.91-1.35), p=0.3	30-d mortality 7% vs 3%, OR=2.04 (1.10-3.80), p=0.02 60-d mortality 9% vs 5%, OR=1.99 (1.17-3.39), p=0.01 More transfusions and antibiotics required for 6 mg group; no difference in grade 3+ toxicity in course 2	NR	No benefit of 6 mg/m^{2}GO compared with 3 mg/m^2

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[18]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ALFA-0701, NCT00927498; 2008-2010 Castaigne, 2014, [abstract] (60); Castaigne, 2012 (61); Renneville, 2014 (5)	278 Age 50-70 y, median 62 y, previously untreated de novo AML, excluded s-AML/ t-AML	Induction + consolidation GO 3 mg/m^2/d (×3 d induction + ×2 d consolidation)	DNR + AraC ± GO DNR (60 mg/m^2 for 3 d) + AraC (200 mg/m^2 for 7 d) ± GO (fractionated doses, 3 mg/m^2 [max dose 5 mg] on d 1, 4, 7 plus d 1 of each of 2 courses of consolidation) 2nd course of induction if bone marrow aspirate on d 15 had >10% persistent leukemic blasts: DNR (60 mg/m^2/d, 2 d) + AraC (1 g/m^2 q12h over 2 h, 3 d). GO not given in 2nd course.	CR+CRi 80.5% vs 74.1%, p=0.25; In multivariate analysis, CR/CRp: OR=2.01 (0.99-4.08), p=0.053	3-y OS: 44% vs 36%, p=0.18; 2-y OS overall: 53.2% vs 41.9%, p=0.0368; unfavourable genetics: 0% vs 16%, p=0.24; 2-y OS, favourable/ intermediate genetics: 65% vs 53%, p=0.057; 2-y OS, CN pts: 69% vs 52%, p=0.024; 2-y OS, abnormal cytogenetics: 31% vs 34%, p=0.61 In multivariate analysis, OS HR=0.75 (0.49-1.13) all pts; HR=0.51 (0.27-0.98), p=0.043 CN-AML 3-y EFS: 31% vs 19% (p=0.0026); 3-y RFS: 38% vs 25% (p=0.006)	Induction deaths 6% vs 4%, p=0.41; SAEs: 57% vs 43%	80% power to detect 15% difference in 2-yr EFS; ITT	GO improved EFS and RFS but not OS
SWOG S0106; NCT00085709; 2004-2009 Petersdorf, 2013 (63)	595 Age 18-60 y, AML; excluded AML from prior hematological malignancy; 1 dose of prior intrathecal chemo for acute leukemia permitted. Induction stratified by age <35 y, 35+ y	Induction; maintenance GO 6 mg/m^2	DNR + AraC + GO vs DNR + AraC [note different DNR dose] DNR + AraC + GO: DNR (45 mg/m^2/d, d 1-3), AraC (100 mg/m^2/d CI, d 1-7), GO (6 mg/m^2, d 4) Standard induction (DNR + AraC): DNR (60 mg/m^2, d 1-3), AraC (100 mg/m^2 CI, d 1-7) 2nd course using standard DNR + AraC if >20% cellularity and >40% blasts on d 14 or >5% blasts subsequently Pts with CR received consolidation with AraC (3 g/m^2 by 3h CI q12h, d 1, 3, 5; administered monthly) Post-consolidation randomization (n=169) stratified by prior GO use: GO (5 mg/m^2, 3 doses at least 28 d apart) vs observation	69% GO vs 70%, p=0.59. 1 course: 61% vs 59% Based on preplanned interim analysis after 456 pts the accrual stopped as hypothesis rejected at predefined significance level of p<0.0025	5-y OS 46% GO vs 50%, p=0.85; median 41 m vs 61 m, p=0.59 5-y RFS 43% GO vs 42%, p=0.40 DFS not improved with post-consolidation GO, HR=1.48, p=0.97	Early deaths (30 d): 5.5% GO vs 1.4%, p=0.0062 [authors note that GO rate is comparable for chemotherapy in other trials; 1.4% for non-GO arm is extremely low] Grade 4 or fatal non-hematologic induction toxicity higher in GO group, 21% vs 12%, p=0.0054; about 80% of pts in both groups had grade 3+ toxicity.	Primary outcome CR for induction. Assuming ½ pts go on to consolidation, 684 pts for first objective would allow 11% difference (81% GO vs 70% without) in CR at 90% power. Primary outcome DFS for post-consolidation; 342 evaluable pts required to determine if true DFS HR=0.67 (GO vs observation) at 90% power.	GO in induction or post-consolidation failed to show improvement in CR, DFS, OS. GO withdrawn from US market based on this trial but other trials were ongoing.

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[18]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
GOELAM; AML 2006 IR; 2007-2010 Delaunay, 2011 (3) [abstract]	254 Age 18-60 y, de novo AML with intermediate cytogenetics not eligible for allogeneic transplant	Induction + consolidation GO 6 mg/m^2	Std 3+7 ± GO (6 mg/m^2) Consolidation: MTZ + intermediate AraC ± GO	91.6% GO vs 86.5%, ns	3-y OS 53% vs 46%, ns Subgroup without allogeneic transplant, ns 3-y EFS 51% vs 33%, ns Subgroup without allogeneic transplant: EFS 53.7% vs 27%, p=0.0308	Early death 10% vs 4.5%, ns; more major toxicity with GO: 23% vs 13% grade 3-4 hepatic toxicities (p=0.031),	NR	
EORTC/GIMEMA AML-17; 2002-2007 Amadori, 2013 (64)	472 Age 60-75 y (median 67 y), newly diagnosed AML (de novo or secondary)	Induction + consolidation GO 6 mg/m^2/d (×2d)	GO → MTZ + AraC + etoposide (MICE) vs MICE GO (6 mg/m^2, d 1, 15), MTZ (7 mg/m^2 iv, d 1, 3, 5), etoposide (100 mg/m^2 iv, d 1-3), AraC (100 mg/m^2/d CI, d 1-7) 2nd course of MICE if PR 2nd dose of GO (d 15) omitted if progression and started MICE Those with CR or CRp received consolidation with 2 courses ICE (IDA + AraC) ± GO according to previous randomization	36% vs 41%; 44% vs 41% age 61-69; 22% vs 41% age 70-75 CR+CRp: 45% GO vs 49%, OR=0.86 (0.6-1.23), p=0.46	OS at median 5.2 y follow-up: median 7.1 m GO vs 10 m, HR=1.2 (0.99-1.45), p=0.07 OS 16% vs 21.7%; pts age 60-69 HR=1.05, p=0.69; pts age ≥70: HR=1.79, p=0.009; s-AML age <70: HR=0.57 (0.30-1.09), p=0.02 EFS HR=1.08, p=0.36 DFS HR=1.08, p=0.61	Induction mortality 17% GO vs 12%; 60-d mortality 22% vs 18% Grade 3-4 hematologic and liver toxicities greater with GO 17% of GO pts and 31% of other pts completed planned treatment	ITT. OS primary outcome. Powered to detect 10% difference in survival rate at 2.5 y, from 20% to 30%, HR=0.75, 450 pts and 378 deaths required	GO provided no additional benefit and was more toxic in pts age ≥70; possible benefit in pts age <70 with s-AML
German; 2005-2009 Brunnberg, 2012 (4)	115 Age ≥60 y, median age 69 y; de novo AML (n=80), or secondary AML (treatment-related or MDS history; n=32), or high-risk MDS (n=3)	Induction GO vs DNR	AraC + GO (7+GO) vs AraC + DNR (7+3) AraC (100 mg/m^2/24 h CI, d 1-7); DNR (60 mg/m^2 iv, d 3-5); GO (6 mg/m^2 iv, d 1; 4 mg/m^2 iv, d 8) 2nd course of induction with 7+3 in pts of both groups without blast clearance; 2 courses of HDAC consolidation upon CR Therapeutic prophase with 100 mg/m^2/d AraC iv was allowed for early stabilization	54.4% vs 55.2%, ns	OS median 10 months GO vs 9 months, ns No difference in CR, EFS, remission duration	Both arms equal in blast clearance; more induction deaths with GO (11 vs 3, p=0.021) including 2 GO pts from hepatic toxicity (veno-occlusive disease)	ITT; powered for increase of median EFS from 90 to 160 d; median OS from 9 to >16 m with a power of 80%	Did not show superiority of GO in elderly; may consider if anthracycline contraindicated

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[18]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MRC AML10 + 12 + 15 + NCRI AML17; 1988-2012 Burnett, 2013 (250) [abstract]	896 Core-binding factor AML, age 16-60 y	Induction or consolidation GO, FLAG	Prognostic factor analysis, including use of GO or FLAG-IDA in induction, HDAC in consolidation	NR	OS at median 8.24 y follow-up: 89% using GO in induction and HDAC consolidation Significant prognostic factors for RFS: log WBC (HR=1.86, 1.53-2.25, p<0.0001), FLAG-IDA (HR=0.38, 0.24-0.61, p<0.0001) and high-dose AraC (HR=0.76, 0.60-0.96, p=0.02)	Significant factors in multivariate analysis of survival: use of GO in induction (HR=0.40, 0.26-0.61, p<0.0001); performance status (HR=1.20, 1.07-1.34, p=0.001); age (HR per decade=1.18, 1.07-1.30, p=0.001); log WBC (HR per unit increase=1.38, 1.12-1.70, p=0.002).	NR	Core-binding factor AML is highly curable; most important factor is GO induction and HDAC consolidation

ADE, AraC + DNR + etoposide; AMSA, amsacrine; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; AZA, azacitidine; CI, continuous iv infusion; CR, complete remission (complete response); CRi, complete remission with incomplete recovery; CRp, complete remission without full platelet recovery; DA, DNR + AraC; DClo, DNR + clofarabine; DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; FLAG, fludarabine + high-dose AraC + GCSF; GCSF, granulocyte-colony stimulating factor; GO, gemtuzumab ozogamicin; HAM, high-dose cytarabine + mitoxantrone; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; ICE, idarubicin + cytarabine + etoposide; IDA, idarubicin; ITT, intention to treat; iv, intravenously; MICE, MTZ + AraC + etoposide; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OR, odds ratio; OS, overall survival; PR, partial response/remission; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; SAE, severe adverse effect; sc, subcutaneously; std, standard; WBC, white blood cell

Table 4-11. Induction, GCSF or GM-CSF

Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
EORTC/HOVON; 1995-1999 Lowenberg, 2003 (251)	640 Age 18-60 y, newly diagnosed AML	Induction GCSF GCSF	[AraC + IDA (cycle 1) then AraC + AMSA (cycle 2)] ± GCSF GCSF (lenograstim, Aventis; 150 µg/m^2 sc or iv, d 0-8 for cycle 1; d 0-6 for cycle 2) AraC (200 mg/m^2 CI, d 1-7) + IDA (12 mg/m^2 iv over 5-10 min, d 6-8) → AraC (1000 mg/m^2 iv over 2 h q12h, d 1-6) + AMSA (120 mg/m^2 iv over 1 h, d 4-6) Pts with CR randomly assigned to a third cycle with etoposide + MTZ or high-dose chemo with busulfan + AraC followed by autologous SCT. Allogenic SCT if age <55 with a suitable donor	79% GCSF vs 83%, p=0.24	4-y OS: 40% vs 35%, p=0.16 Std-risk AML: 45% vs 35%, p=0.02 4-y EFS 33% vs 28%, p=0.17 4-y DFS 42% vs 33%, p=0.02 Std-risk AML: EFS 39% vs 29%, p=0.01; DFS 45% vs 33%, p=0.006	Grade 3-4 adverse effects similar. More early deaths (within 50 d) with GCSF (n=55 vs n=34, p=0.02)	ITT. 600 pts over 5 y + 2 y follow-up to give power of 78% to show increase of 10% in CR (from 70% to 80%) with GCSF; power of 75% to show 10% increase in OS (35% to 45%) at 3 y; power of 81% to show 10% increase in EFS	OS and EFS benefit in std-risk but not unfavourable-risk AML; DFS benefit in all
AMLSG; 1992-1994 Heil, 1997, 2006 (258,259)	521 Age 16+ y, de novo AML	Induction GCSF + consolidation GCSF	Filgrastim vs placebo Filgrastim (5 µg/kg/d sc) vs placebo after std induction (DNR + AraC + etoposide 1 or 2 cycles) as well as consolidation (1-2 cycles) if CR From 24 h after chemotherapy until neutrophil count ≥10^9/L for 3 d	69% vs 68%, p=0.47 Age <50: 76% vs 71% Age ≥50: 64% vs 65%	5-y OS 19% vs 17%; median OS 12.5 m vs 13.6 m, p=0.97 5-y DFS 19% vs 14%; median DFS 10.3 m vs 9.5 m, p=0.52	Filgrastim group experienced shorter neutrophil recovery (20 d vs 25 d, p<0.0001), shorter duration of fever (7 d vs 8.5 d, p=0.009), less antibiotics (15 d vs 18.5 d, p=0.0001) and hospitalization (20 d vs 25 d, p=0.0001), and less antifungal therapy (34% vs 43%, p=0.04. Early (30 d) deaths: 8.1% vs 9.5%, ns (except due to infections (3.5% vs 6.9%)	ITT (except DFS). Designed to detect 15% change in CR rate from 65% to 80% with power of 90%.	Filgrastim is safe and has clinical early benefit but no significant long-term effect

[19] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MD Anderson; 1995-1997 Estey, 1999 (244)	215 Median age 65 y (32% age >71 y). Newly diagnosed AML (n=153) or high-risk MDS (n=62), with poor prognosis (one of: age >71 y, abnormal blood counts, secondary AML/MDS, failure to respond to 1 course of AraC + anthracycline chemotherapy at other hospital, abnormal renal/hepatic function). 2/3 had an antecedent hematologic disorder, 26% s-AML, 11% refractory	Induction + post-remission GCSF (ATRA)	FAI (Fludarabine + AraC + IDA) vs FAI + ATRA vs FAI + GCSF vs FAI + ATRA + GCSF FAI: fludarabine (30 mg/m^2/d, d 1-4) + AraC (2 g/m^2, d 1-4) + IDA (12 mg/m^2, d 2-4) GCSF (200 µg/m^2 daily), ATRA (45 mg/m^2 daily in 2 doses) If white blood cell count <10, 000/µL then began ATRA on day -2 and GCSF on day -1; otherwise started both with chemotherapy ATRA continued until d 3; GCSF continued until neutrophil count exceeded 1000/µL 2nd course of induction in pts with persistent disease (not CR) Pts with CR received post-induction treatment for 6 months (4-5 courses) with AraC (100 mg/m^2/d, d 1-5) alternating with fludarabine (30 mg/m^2/d, d 1-2) + AraC (1 g/m^2/d, d 1-2) + IDA (8 mg/m^2, d 3); GCSF and/or ATRA (during chemo + 3 further days) given to pts who received them during induction at same dose as during induction	40% FAI, 55% FAI + GCSF, 51% FAI + ATRA, 59% FAI + ATRA + GCSF Effect of GCSF ± ATRA vs no GCSF, p=0.018 Effect of ATRA ± GCSF vs no ATRA, p=0.264	All improved OS compared with FAI: FAI + GCSF, p=0.15; FAI + ATRA, p=0.023; FAI + ATRA + GCSF, p=0.055 After multivariate regression analysis with possible prognostic factors, differences were not statistically significant EFS compared with FAI: FAI + GCSF, p=0.32; FAI + ATRA, p=0.053; FAI + GCSF + ATRA, p=0.095	NR	212 pts to detect 0.20 difference in probability of success (alive and in CR at 6 m) between baseline group (FAI) and each other group, power 0.80	Benefit of ATRA before but not after multivariate analysis. Authors suggest the study was too small for randomization to account for differences between groups. Results should not be generalized to other pt groups (e.g. AML pts with better prognosis) and other studies should be designed.
Turkey; Turkish Leukemia Study Group (TLG) AML trial (95-002); NCT00820976; 1995-1998 Beksac, 2011 (257)	260 Age 16+ y, median 38.5 y, de novo AML	Induction GCSF GCSF	AraC + IDA ± GCSF AraC (100 mg/m^2/d, 10 d), IDA (12 mg/m^2/d, 3 d) GCSF (Filgrastim, Neupogen®, Roche Ltd., Basel, Switzerland): 5 µg/kg iv over 30 min, d 8 until the absolute neutrophil count (ANC) exceeded 0.5×10^9/L for 2 consecutive days 2nd course (same as 1st course) according to guidelines if not CR Pts with CR after 1 or 2 cycles received consolidation (AraC + IDA) then stem cell transplantation or 2nd consolidation	62.5% vs 64.6%, p=0.72 After 1 cycle: 58.3% vs 55.6%	3-y OS 31.8% vs 25.6% (p=0.049 multivariate analysis); median 239 d vs 184 d, p=0.38 Mortality rate 47.9% vs 43.0%, p=0.42. Relapse rate 29.8% vs 36.6%, p=0.36	Severity and duration of leukopenia improved with GCSF. Other adverse effects similar in both arms.	NR	GCSF does not worsen outcome. It may decrease time for neutrophil recovery and hospitalization.

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
German AMLCG 1999 [AMLCG 99]; NCT00266136; 1999-2011 Buchner, 2004, 2006 (223,224) [GCSF: letter, abstract]; see Buchner, 2006 (222) for induction; several subsequent abstracts on subgroups by age or other factors (225-229)	895 (3350). 3232 evaluable pts to this study, plus 118 to standard arm Age 16-85 y, de novo AML; also s-AML or high-risk MDS (18% age <60 y, 32% age ≥60 y)	Induction GCSF + consolidation GCSF + maintenance GCSF (Anthracycline TAD/HAM)	TAD → HAM vs HAM → HAM At 32/52 centres, ½ patients were randomly assigned to receive GCSF (150 µg/m^2 sc daily) from 48 hours before until the last dose of each chemotherapy course during the first year (n=895 in GCSF substudy) All pts with CR received consolidation (same as TAD induction) + monthly maintenance for 3 y with AraC (100 mg/m^2 q12h sc, d 1-5) + second agent in rotating sequence: DNR (45 mg/m^2 by 1-h infusion, d 3-4) or TG (100 mg/m^2 po q12h, d 1-5) or cyclophosphamide (1 g/m^2 iv injection, d 3)	Identical CR rate with or without GCSF	Identical OS with or without GCSF; HR 0.99 (0.77-1.30) age 16-60; HR=1.08 (0.84-1.38) age >60 Identical DFS (RFS) with or without GCSF; HR=0.96 (0.68-1.35) age 16-60; HR=1.17 (0.83-1.65) age >60	No trend for difference in OS, RFS, or RD according to GCSF administration	ITT analysis	
AMLCG; 1990-1992 Dombret, 1995 (252)	173 Age ≥65 y, newly diagnosed AML; exclude pts with history of MDS for >3 m	Induction GCSF GCSF	Lenograstim or placebo Induction with DNR (45 mg/m^2/d, 4 d) + AraC (200 mg/m^2/d, 7 d) then randomized on d 8 to either lenograstim (5 µg/kg body weight/d) or placebo starting on d 9 until neutrophil recovery or treatment failure, or max of 28 d Salvage chemotherapy (AraC + MTZ) for resistant disease at d 21 was also followed by lenograstim or placebo (starting d 5) Pts with CR (to induction or salvage) received 2 courses consolidation without lenograstim or placebo	70% vs 47%, p=0.002 1 course: 61% vs 34%, p=0.006 Age ≤70: 74% vs 50%, p=0.03 Age >70: 67% vs 44%, p=0.05	12-m OS: 45% vs 40%, p=0.76, RR=0.95 EFS: 94% vs 95%, p=0.39	Mortality at 8 w 23% lenograstim vs 27% placebo, p=0.60 Similar incidence of severe infections. Neutropenia (in pts with CR) 21 d vs 27 d, p<0.001 Mean time to CR: 24 d vs 33 d, p=0.0015	ITT. Main outcome 8-w mortality. Sample size to detect 50% reduction assuming 30% mortality in placebo. Closed by data-monitoring committee after 5th analysis (n=150) as no benefit in 8-w mortality	Lenograstim improved CR but did not have significant survival effect
Korea; Lee, 2011 (253)	34 Age 15-64 y, newly diagnosed AML	Induction GCSF GCSF	IDA + AraC ± GCSF [note AraC doses different] GCSF group: IDA (12 mg/m^2/d iv over 15 min, d 1-3) + AraC (500 mg/m^2/12 h iv over 3 h, d 4-8) + GCSF (lenograstim; 250 µg/m^2/d iv, d 3-7) vs Control: IDA (12 mg/m^2/d, d 1-3) + AraC (100 mg/m^2/12 h, d 1-7) IDA reduced to 8 mg/m^2/d (both groups) and AraC to 350 mg/m^2/12 h (GCSF group) for pts over age 50 Both groups received GCSF during nadir periods after chemotherapy	88.2% vs 82.4%, p=0.31	3-y OS 45.6% vs 64.7%, p=0.984 3-y EFS 37.6% vs 64.7%, p=0.551	Median time to neutrophil recovery 26 d vs 26 d, p=0.338; time to platelet recovery 21 d vs 16 d, p=0.190. Febrile neutropenia 70.6% vs 76.5%, p=0.679	Primary outcome CR	No improved clinical outcomes with GCSF priming

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Turkey Kutlay, 2003 (256)	101 Age 15-60 y, newly diagnosed de novo AML	Induction GCSF GCSF	AraC + IDA ± GCSF AraC (100 mg/m^2/d CI, 10 d), IDA (10 mg/m^2/d, 3 d) Randomized after 7 d chemotherapy to GCSF use GCSF (lenograstim, Roche): 5 µg/kg/d sc, d 7 until absolute neutrophil count was >10^9/L for 3 consecutive d or 10^{10}/L for 1 d. Pts in CR received consolidation with AraC + IDA	75% vs 62% <u>By GCSF receptor expression</u>: GCSFr + pts (n=86): 76% vs 63%, p>0.05 GCSFr- pts (n=15): 67% vs 56%, p>0.05	NR	GCSF pts had shorter recovery times for neutrophils to recover to >10^9/L (24 vs 28 d, p<0.001) and less febrile days (22 d vs 27 d, p<0.001)	NR	GCSF presence or intensity does not influence clinical benefit
MRC AML11 + MRC AML12; 1994-1997 Wheatley, 2009 (254); see individual trials elsewhere in table for results other than GCSF (69,153,154)	803 AML11 (n=226) mainly age ≥60 y; AML12 (n=577) mainly age <60 y; de novo or s-AML, including APL	Induction GCSF GCSF	GCSF (263 µg/d sc) vs placebo from d 8 from the end of induction chemotherapy until neutrophil recovery to >0.5×10^9/L or up to 10 d; given after 1st induction course only Induction varied in the two trials: AML11: ADE, DAT, or MAC; see Goldstone, 2001 (69) AML12: ADE 10+3+5 or MAE 3+10+5; see Burnett, 2010 (153,154) GCSF: glycosylated GCSF, lenograstim, Chugai Pharmaceuticals	73% vs 75%, p=0.5 Age <40: 81% vs 93%, p=0.006 By treatment received: 81% vs 82%, p=0.8; age <40: 89% vs 95%, p=0.2	5-y OS: 29% vs 36%, p=0.10 Age <40: GCSF worse, HR=1.64, p=0.006 Age 40+: HR=1.01, p=0.9 5-y DFS: 34% vs 38%, p=0.3 By treatment received: DFS 34% vs 40%, p=0.13;	Days in hospital less with GCSF, 30 d vs 32 d, p=0.01. Neutrophil recovery shorter with GCSF, 15 vs 20 d, p<0.0001	Principle analyses ITT; subsidiary analysis excluding patients who did not start assigned treatment	GCSF reduced neutrophil recovery time and shortened hospitalization. No overall difference in CR, DFS. Pts age <40 did worse with GCSF. Well-powered individual patient meta-analysis (not published, details not reported) found neither benefit nor harm for endpoints of CR, DFS, OS

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
SWOG 9031; 1992-1994 Godwin, 1998 (255)	211 Age 56+ y, median 68 y, de novo AML or s-AML	Induction GCSF GCSF	Std induction regimen + GCSF or placebo Induction: DNR (45 mg/m^2 iv, d 1-3), AraC (200 mg/m^2 CI, d 1-7) GCSF (400 µg/m^2/d iv over 30 min) or placebo given starting on d 11 if the d 10 bone marrow biopsy was hypocellular with blasts <5% GCSF (*E coli*-derived recombinant human GCSF, r-metHuG-CSF, Neupogen, Filgrastim, Amgen Inc) continued until absolute neutrophil count was 1000/µL then tapered over 3 d. 2nd induction if d 10 blasts 5+% and d 14 marrow showed residual leukemia; GCSF received according to group in 1st cycle Pts with CR received 2 courses post-remission therapy: DNR (30 mg/m^2 iv, d 1-2) + AraC (200 mg/m^2/d CI, d 1-7); plus GCSF or placebo as in the initial assignment starting on d 8	41% GCSF vs 50%, p=0.89 Age 56-64: 38% vs 56% Age ≥65: 42% vs 45%	OS 6 m vs 9 m, p=0.71 RFS median 8 m vs 9 m, ns	Time to neutrophil recovery 15% shorter in GCSF arm, p=0.014 (median 24 d vs 27 d). Shorter duration of infection with GCSF but no difference in incidence (73% vs 64%). Non-hematologic toxicities were similar.	ITT. 182 evaluable patients to give 82% power to detect an increase in CR from 40% to 60%. With 2 y accrual and 1 y additional follow-up would give 82% power to detect HR (placebo: GCSF) of 1.5 in OS, assuming median OS placebo of 7 m age 56-64 and 1.4 m age ≥65	GCSF improved clinical parameters of duration of neutropenia and antibiotic use but not CR or survival
EORTC/GIMEMA AML-13; 1995-2001 Amadori, 2005 (262)	722 Age 61-80 y, median 68 y, newly diagnosed AML (including s-AML)	Induction GCSF; consolidation GCSF	4 arms, 2×2 design: GCSF or not during induction (MICE), then GCSF or not after chemotherapy A: no GCSF B: GCSF during chemotherapy C: GCSF after chemotherapy until d 28 or recover of PMNL D: GCSF during and after chemotherapy GCSF at 150 µg/m^2/d by 30 min iv infusion MICE: MTZ (7 mg/m^2 iv, d 1, 3, 5), AraC (100 mg/m^2/d CI, d 1-7), etoposide (100 mg/m^2 as 1-h infusion, d 1-3) Pts with PR received 2nd induction course. Pts with CR were randomized (n=346) to 1 course consolidation with either iv or oral mini-ICE. This was followed by a 2nd course or myeloablative chemotherapy with autoPBSC support in the younger cohort (<70 years of age) as chosen by the centre prior to the trial start date iv mini-ICE: IDA (8 mg/m^2/d iv, d 1, 3, 5), AraC, (100 mg/m^2/d CI, d 1-5), etoposide (100 mg/m^2 as 1-h infusion, d 1-3) Oral Mini-ICE: IDA (20 mg/m^2/d po, d 1, 3, 5), AraC (50 mg/m^2 q12h sc, d 1-5), etoposide (100 mg/m^2 q12h po, d 1-3)	48.9% vs 52.2% vs 48.3% vs 64.4% B vs A, p=0.53; D vs C, p=0.003; C vs A, p=0.92; D vs B, p=0.024 Group B+D vs A+C: 58.3% vs 48.6%, p=0.009 Group A+B vs C+D: 50.6% vs 56.4%, p=0.12	3-y OS: 15.2% vs 18.3% vs 14.4% vs 7.6% No significant differences; B+D vs A+C, p=0.24; C+D vs A+B, p=0.81 Median after 4.7 y follow-up: 7.9 m vs 9.2 m vs 8.4 m vs 11.5 m 3-y EFS: 10.5% vs 9.2% vs 9.0% vs 9.3% DFS: 21.5% vs 17.6% vs 18.6% vs 14.5%	GCSF after chemo resulted in shorter time to neutrophil recovery (median 20 vs 25 d, p<0.001) Severe hypotension more frequent in groups receiving GCSF after chemo: 4.3% C+D vs 1.2% A+B Was 613 deaths at time of final analysis, giving power of >90% to detect significant differences Consolidation: instantaneous risk of death or relapse 17% higher in oral group, HR=1.18 (0.94-1.49)	ITT. Primary outcome was OS. Sample size of 500 pts and 425 deaths to detect increase in OS of 8% at 3 y, HR=0.74. For 2nd randomization, 330 pts required and therefore 720 pts at initial randomization. Allowed detection in CR rate between pairs of groups with 70% power, OR=1.86	GCSF priming can improve CR but has no effect on long-term outcome

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MRC AML11; 1990-1998 Goldstone, 2001 (69)	226 (1314) Initially accepted age 56+ y; age ≥60 y starting end of 1994, although younger pts allowed if not suitable for more intensive chemo in AML10/AML12. 2% of pts age <56 y. Any de novo or secondary AML	Induction; consolidation; maintenance GCSF (Etoposide) (Anthracycline DNR vs MTZ)	2 courses induction: DAT vs ADE vs MAC (1:1:2 ratio) DAT 3+10 → DAT 2+5: DNR (50 mg/m^2 slow iv, d 1, 3, 5) + AraC (100 mg/m^2 12-hourly iv, d 1-10) + TG (100 mg/m^2 12-hourly po, d 1-10) then same but DNR, d 1, 3 and (AraC + TG), d 1-5 ADE 10+3+5 → ADE 5+2+5: DNR (50 mg/m^2 slow iv, d 1, 3, 5) + AraC (100 mg/m^2 12-hourly iv, d 1-10) + etoposide (100 mg/m^2 iv 1-h infusion, d 1-5) then same but DNR, d 1, 3, and AraC, d 1-5 MAC 3+5 → MAC 2+5: MTZ (12 mg/m^2 iv 30-min infusion, d 1-3) + AraC 100 mg/m^2 12-hourly iv, d 1-5) then same but MTZ, d 1, 3 A subset of pts (n=226) were randomized to receive GCSF (293 µg/d sc, d 8 of course 1 until neutrophil recovery or maximum of 10 d) or placebo Pts in remission (n=371) randomized to stop after a third course (DAT 2+7) or after 4 additional courses (DAT 2+7, COAP, DAT 2+5, COAP) Third randomization (n=362): IFN-α maintenance for 1 year vs none	58% GCSF vs 51% placebo, p=0.4	3-y OS: 15% GCSF vs 18% placebo, p=1.0 5	No important differences in non-hematologic toxicity, or for number of days for neutrophil and platelet recovery	ITT	
Japan; Gran AML; 1993-1996 Usuki, 2002 (260)	245 Age 15+ y, newly diagnosed de novo AML; <20% blasts at d 1 after completion of remission induction therapy	Induction GCSF + consolidation GCSF GCSF	GCSF or not after induction GCSF (Filgrastim, Kirin Brewery Co; 200 µg/m^2 iv from 48 h after chemotherapy until neutrophil count exceeded 1.5×10^9/L; GCSF in control group only if severe infection occurred) Induction regimen was determined by each hospital (mostly BHAC + DNR or with additional agents); randomized to GCSF or not 1 d after completion of induction therapy Pts without CR based on bone marrow at time of neutrophil recovery or d 35 if persistent neutropenia discontinued GCSF (If in GCSF group) and received a 2nd course of induction the same as the first course If CR, then post-remission therapy according to institution policy, including GCSF according to initial randomization	80.8% vs 76.8%, p=0.532 Excluding control pts who received GCSF: 80.8% vs 68.4%	5-y OS 42.7% vs 35.6%, p=0.5918; median 20.8 m vs 18.8 m 5-y DFS 34.5% vs 33.6%, p=0.9407; median 14.0 m vs 12.5 m	Neutrophil recovery faster in GCSF group, 12 d vs 18 d, p=0.0001. Median duration febrile neutropenia 3 d vs 4 d, p=0.0001. No difference in incidence of fever, infection, iv antibiotics	NR	GCSF is safe and useful, did not influence DFS. Should be confirmed in large RCT

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
EORTC/GIMEMA AML8 (GM-CSF amendment); 1990-1992 Zittoun, 1996 (267)	102 Newly diagnosed AML, age 15-60 y. AML 8A trial: Age 15-45 y. AML 8B trial: age 46-60 y. Excluded blast crisis of CML, AML after other myeloproliferative disease or after MDS longer than 6 m	Induction GM-CSF GM-CSF	GM-CSF or not during induction (subprotocol of main study) Induction with DNR + AraC: DNR (45 mg/m^2/d iv push, d 1-3), AraC (200 mg/m^2/d CI, d 1-7) 4 arms for GM-CSF comparison: (1) no GM-CSF (2) GM-CSF starting 24 h before induction and continuing until completion on d 7 (3) GM-CSF immediately after completion of chemotherapy on d 8 until d 28 or PMN count at least 0.5 ×10^9/L (4) GM-CSF 24 h before induction until d 28or PMN count at least 0.5 ×10^9/L 2nd course if PR by d 28, with GM-CSF as for the first cycle GM-CSF (recombinant human *E coli*-derived, Sandoz/Schering Plough): 5 µg/kg/d CI No GM-CSF during salvage treatment (mainly AraC + IDA or AMSA)	77% vs 72% vs 48% vs 46% Arms 3+4 lower than 1+2, p=0.008 After 1 course: 77% vs 60% vs 44% vs 42%	3-y OS 62% vs 32% vs 30% vs 29%; p=0.07 for arms 1+2 vs 3+4; p=0.37 for arms 2+4 vs 1+3 EFS shorter with post-induction chemo, p=0.02; no significant difference (p=0.16) with GM-CSF before induction or not	Trend towards accelerated neutrophil recovery with GM-CSF after induction, but no fewer infections or induction deaths. Continued CR 70% vs 28% vs 38% vs 45%	ITT. Initial aim: 600 pts to detect an improvement in CR from 65% to 75% (OR=0.63, alpha=0.05, beta=0.15). After 103 pts (93 evaluated) determined OR >1 (p=0.01) and stopped trial early.	GM-CSF did not improve CR; GCSF and post-induction appeared to increase risk of resistance
German; 1990-1991 Heil, 1995 (272)	82 Age 15-75 y, de novo AML	Induction GM-CSF + consolidation GM-CSF GM-CSF	AraC + DNR + etoposide + [GM-CSF (cycle 2-3) or placebo] 1st induction (not randomized): AraC (100 mg/m^2 CI, d 1-8) + DNR (60 mg/m^2 iv bolus, d 3-5) + etoposide (100 mg/m^2 by 2-h infusion, d 4-8) 2nd induction (GM-CSF randomized): AraC (100 mg/m^2 CI, d 1-7) + DNR (45 mg/m^2 bolus iv, d 3-4) + etoposide (100 mg/m^2 by 2-h infusion, d 3-7) Pts with CR after 2nd cycle received 3rd cycle (early consolidation) identical to 2nd cycle Late consolidation at 4 w after 3rd induction (1 cycle): AraC (3 g/m^2 by 2-h infusion, 12 doses; reduced to 0.6 g/m^2 for pts age >50 y) + DNR (30 mg/m^2 bolus iv, d 7-9) + [GM-CSF or placebo] GM-CSF (rhu GM-CSF, *E coli*): 250 µg/m^2/d sc, starting 48 h prior to induction in courses 2 and later, continued until neutrophil count >500/µL for 3 d	81% vs 79%, p=0.57 Age ≤50: 82% vs 76% Age >50: 79% vs 83%	OS at 43 m: 45% vs 49%, p=0.66 OS age ≤50: 70% vs 50%, p=0.26 OS age >50: 24% vs 50%, p=0.08 RFS at 41 m: 42% vs 41%, p=0.89; median remission duration 24 m vs 17 m RFS age ≤50: 65% vs 58%, p=0.31 RFS age >50: 20% vs 31%, p=0.28	Duration of thrombocytopenia was longer in the GM-CSF group;	Study closed prematurely due to unavailability of drug	GM-CSF is feasible but no significant effect found.

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
HOVON/SAKK; About 1992-1995 [Years not stated but median follow-up 42 m and some data reported to 48 m] Lowenberg, 1997 (264)	253 Age 15-60, median 43 y, newly diagnosed AML; excluded preceding myelodysplasia or myeloproliferative disorders	Induction GM-CSF GM-CSF	GM-CSF or not during induction* and GM-CSF or not after induction chemotherapy (2×2 factorial design) (+/-) GM-CSF during chemo but not after (+/+) GM-CSF during chemo and after chemo (-/-) no GM-CSF during or after chemo (-/+) no GM-CSF during chemo; GM-CSF given after chemo GM-CSF (*E coli*-derived GM-CSF; Molgrastim; Sandoz) 5 µg/kg CI or sc daily. During chemo, GM-CSF administration was started 1 d before initiation of chemo and continued until completion of chemo in cycles 1 and 2 (not given in cycle 3) After chemo, GM-CSF administration was begun following completion of chemo until granulocyte recovery to 0.5×10^9/L for at least 3 d but not extending beyond, d 28; GM-CSF was discontinued in case of progressive leukemia. If WBC count was $>3\times10^{10}$/L at start of treatment then GM-CSF was postponed until WBC count was $\leq2\times10^{10}$/L; if WBC increase to $\geq5\times10^{10}$/L then GM-CSF was interrupted. *Induction chemo: 1st cycle DNR (45 mg/m^2 iv, d 1-3) + AraC (200 mg/m^2 CI, d 1-7); 2nd cycle AMSA (120 mg/m^2 iv, d 4-6) + AraC (1 g/m^2 iv q12h, d 1-6); pts with CR received 3rd cycle with MTZ (10 mg/m^2 iv) + etoposide (100 mg/m^2 iv, d 1-5)	80% vs 77% vs 75% vs 77%, no significant differences After 1st cycle: 42% vs 50% vs 43% vs 60% During chemo (+/- or + /+) vs not (-/- or -/+): 79% vs 76%, OR=1.07, ns After chemo (+/ + or -/+) vs not (+/- or -/-): 77% vs 77%, OR=0.99, ns	3-y OS: 30% vs 37% vs 41% vs 46%, no significant differences During chemo (+/- or + /+) vs not (-/- or -/+): 33% vs 44%, HR=1.21, ns After chemo (+/ + or -/+) vs not (+/- or -/-): 41% vs 35%, HR=0.94, ns 3-y DFS: 25% vs 40% vs 43% vs 42%, no significant differences During chemo (+/- or + /+) vs not (-/- or -/+): 32% vs 42%, HR=1.23, ns After chemo (+/ + or -/+) vs not (+/- or -/-): 41% vs 33%, HR=0.76 (0.53-1.08), ns	During chemo (+/- or + /+) vs not (-/- or -/+): time to neutrophil recovery after 1 cycle 29 d vs 27 d, ns After chemo (+/ + or -/+) vs not (+/- or -/-): time to neutrophil recovery after 1 cycle 26 d vs 30 d, p=0.001; monocyte recovery 26 d vs 30 d, p=0.005 Groups with GM-CSF during chemo had more fluid retention (64% vs 40%, p<0.001), grade 2-4 renal toxicity (15% vs 2%, p=0.002), grade 2-4 liver abnormalities, 30% vs 19%, p=0.04), hypotension (23% vs 3%, p<0.0001). More fever with GM-CSF during chemo (p=0.002) or after chemo (p=0.03)	ITT. 50 pts to detect 5 d reduction in neutropenia with 80% power; 172 pts to detect reduction in infections from 60% to 40%; 170 pts to detect 20% increase in CR rate after 1 cycle; 500 pts to detect 10% increase in CR rate. Expect accrual of 350 pts in 3 y (actual 274 pts in 4 y). Will pool with other study for CR endpoint.	GM-CSF had no effect on CR, OS, DFS. GM-CSF during induction had no effect on hematologic recovery GM-CSF after induction reduced neutrophil and monocyte recovery time
ECOG E3993; 1993-1997 Rowe, 2004 (190)	254 (348) Age >55 y, previously untreated AML	Induction GM-CSF (Anthracycline IDA, MTZ, DNR)	DNR vs IDA vs MTZ all received AraC (100 mg/m^2/d CI for 7 d) DNR (45 mg/m^2/d iv, d 1, 2, 3); IDA 12 mg/m^2/d, d 1, 2, 3); MTZ 12 mg/m^2/d, d 1, 2, 3) 2nd induction cycle if residual leukemia Starting 1994 was also randomization to GM-CSF (250 µg/m^2/d sc) vs placebo starting 2 d before induction	GM-CSF vs placebo: 38% vs 40%, ns	OS, GM-CSF vs placebo: median 5.3 m vs 8.5 m, p=0.11 DFS: GM-CSF vs placebo, median 6.9 m vs 5.1 m, p=0.73	NR	Priming: 92% power to detect 20% improvement in CR with GM-CSF; 82% power to detect DFS by cure rate model (25% to 40%)	Pts in GM-CSF priming substudy had delay in start of induction and worse outcome

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Australasian LLG AML7; 1995-1997 Bradstock, 2001 (261); see Bradstock, 2005 (87) for consolidation	112 Age 15-60 y, median 43 y, untreated AML, no previous hematological disorders	Induction GCSF; consolidation GCSF	Lenograstim (glycosylated recombinant human GCSF) vs none Chemotherapy: AraC (3g/m^2 q12h, d 1, 3, 5, 7), IDA (12 mg/m^2, d 1-3; reduced to 9 mg/m^2 after 44 pts randomized due to toxicity), etoposide (75 mg/m^2, d 1-7) GCSF (5 µg/kg/d sc, from d 8 until neutrophil recovery) One cycle ICE; 2nd cycle if not CR at physician's discretion; pts with CR randomized to either ICE or 2 courses consolidation with lower-dose: AraC (100 mg/m^2 iv, d 1-5), IDA (12 or 9 mg/m^2, d 1-2), etoposide (75 mg/m^2, d 1-5); all received lenograstim	81% vs 75%, p=0.5	Relative death rate at median 3.6 y follow-up: 0.83, p=0.48	Shorter neutropenia duration (median 18 vs 22 d, p=0.0005), leucopenia (17 d vs 19 d, p=0.0002), reduced antibiotics (20 vs 24 d, p=0.015); no difference in non-hematologic toxicity	Designed to have 90% power to pick a clinically important decrease of 2 d in duration of neutropenia. Used triangular sequential design to monitor and allow early stopping if large advantage found.	Improvement in clinically important parameters with no major adverse effects
German; NCT00199147; 2000-2005 Bug, 2014 (263)	183 Age >60 y, Median 67 y, previously untreated AML; s-AML allowed	Induction GCSF GCSF timing	GCSF priming (before chemo + during) vs GCSF after induction chemo Chemo: cycle 1: AraC (100 mg/m^2 CI, d 1-7), IDA (10 mg/m^2 iv, d 2, 4, 6), etoposide (100 mg/m^2 iv, d 3-7); cycle 2: AraC (100 mg/m^2 CI<d 1-5), IDA (10 mg/m^2, d 1, 3), etoposide 100 mg/m^2, d 1-5) GCSF (Filgrastim, Neupogen, Amgen; sc in one daily dose of 5 µg/kg from d 0 in priming group or day after chemo [d 6 or d 8] in after group until absolute neutrophil count of 1000/µL for 3 consecutive days) If CR after 2 cycles, pts judged able to tolerate it received intensive post-remission therapy: fludarabine (30 mg/m^2, d 1-4), AraC (600 mg/m^2, d 1-4), IDA (8 mg/m^2, d 1-3), GCSF (5 µg/kg, starting d 0)	57% vs 67%, p=0.153	10-y OS 14% vs 17%; median 12.0 m vs 13.2 m, p=0.205 Median RFS 12.3 m vs 12.3 m, p=0.407; 10-y RFS 25% vs 14% Normal karyotype (NK) AML: 10-y RFS 44% vs 22%, p=0.074	Induction mortality 23% vs 10%, p=0.014; subgroup of NK AML 25% vs 2%, p=0.003. Higher rate of severe mucositis and more life-threatening infectious complications in the GCSF priming arm (41% vs 28%, p=0.04). Time for neutrophil recovery did not differ.	NR	GCSF priming increased early death and failed to improve OS compared with GCSF after induction
German; 1990-about 1994 Rottmann, 1994 (268); Buchner, 1993 (269)	72 (interim) Age 15-75 y, median 51, de novo AML	Induction GM-CSF GM-CSF	Method of administering GM-CSF along with induction: GM-CSF randomized to continuous iv (CI), sc 1×/d, sc 2×/d; additional control group (n=32) without GM-CSF (not clear if randomized or not) GM-CSF: 250 µg/m^2/d, 24 h prior to chemotherapy and until neutrophil recovery; randomized to CI or sc 1×/d, sc 2×/d Induction was TAD 9-HAM (age 15-60) or TAD 9 (age ≥60); consolidation TAD, maintenance monthly TAD	GCSF vs control: 78% vs 81%	NR	No difference in hematologic effects by method of administration <5% blasts on d 16: 59% GM-CSF vs 40% control.	NR	

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Denmark; 1990-1992 Hansen, 1995 (265,266)	18 De novo AML age 40+ y (14 pts); or other advanced, age 18+ y (n=4; 1 pt with MDS, 1 s-AML, 1 relapsed AML, 1 CML)	Induction GM-CSF GM-CSF	GM-CSF or not, starting prior to induction Induction: ACR (75 mg/m^2 iv as 1-h infusion, d 1-3; 50 mg/m^2/d in pts age >60), AraC (100 mg/m^2/d CI, d 1-7) GM-CSF (*E coli* synthesized recombinant human GM-CSF, Schering-Plough/Sandoz): 10 µg/kg/d iv over 3 h (increased to 6 h after first 3 pts due to adverse effects); started 3 d before chemo in pts with hypoplastic bone marrow and 1 d before in others, given until blood neutrophil count of 1.5×10^9/L for 3 d or total WBC count of 10^{10}/L for 1 d or until max 21 d after start of induction	30% vs 50%	NR	No significant differences in time to neutrophil recovery, platelet recovery, transfusions. Death during induction: 30% vs 12%. Increased hepatotoxicity with GM-CSF	NR	Small number of pts does not permit definite conclusions but suggest GM-CSF is unlikely to be of benefit
CALGB 8923; 1990-1993 Stone, 1995, 2001 (278,279)	388 Age ≥60 y, newly diagnosed de novo AML. Included M0 after March 1991; excluded APL after October 1992; excluded pts with prior MDS	Induction GM-CSF; post-remission GM-CSF	DNR (3 d) + AraC (7 d) with GM-CSF vs placebo DNR (45 mg/m^2/d, d 1-3), AraC (200 mg/m^2/d CI, d 1-7) GM-CSF (*E coli*-derived GM-CSF, Schering): 5 µg/kg/d iv over 6 h, from d 8 until neutrophil count was 1000/µL, regrowth of leukemia, or severe toxicity 2nd cycle with DNR (2 d) and AraC (5 d) if bone marrow at 22 d revealed >5% leukemia cells and cellularity >15%. Once the study drug was stopped, it was not restarted even if a second course of chemotherapy was required. However, if the patient was still receiving the study infusion when the second course of induction chemotherapy was given, the growth factor or placebo was continued until one of the three specified events occurred. Second randomization (n=169) if stable remission and physician judged the pt could tolerate highly myelosuppressive therapy: AraC (100 mg/m^2/d CI, 5 d; for 4 monthly courses) vs AraC (500 mg/m^2 q12h [250 mg/m^2 over 15 min then 250 mg/m^2 over 3 h] + MTZ (5 mg/m^2 q12h) for 6 doses; given 2 courses 60 d apart GM-CSF not given after post-remission therapy	51% GM-CSF vs 54%, p=0.61	OS median 0.7 y vs 0.9 y; 16% vs 23%, p=0.10 OS median from 2nd randomization: 1.6 y AraC vs 1.3 y AraC + MTZ 5-y OS, GM-CSF: 11% AraC vs 21% AraC + MTZ; placebo: 16% AraC vs 18% AraC + MTZ, all ns 2nd randomization: Median DFS 11 m AraC vs 10 m AraC + MTZ, p=0.67; relapse rates 77% vs 82% 5-y DFS, GM-CSF: 5% AraC vs 14% AraC + MTZ; placebo: 16% AraC vs 11% AraC + MTZ, all ns	Duration of neutropenia shorter with GM- CSF (15 d vs 17 d, p=0.02).	ITT. 384 pts for induction, 80% power to detect improvement in CR from 50 to 65%. Would also give 163 pts for post-CR regimens with 80% power to detect a failure rate ratio of 1.67 with 1.5 y follow-up	Clinical importance of GM-CSF minimal because it did no lower treatment-related mortality or CR AraC/MTZ more toxic but not more effective and therefore has no benefit post-remission in pts age ≥60

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
GOELAM SA3; 1992-1994 Witz, 1998 (270)	240 Age 55-75 y, newly diagnosed AML	Induction GM-CSF GM-CSF	IDA + AraC plus [GM-CSF vs placebo] IDA (8 mg/m^2/d, d 1-5), AraC (100 mg/m^2/d CI, d 1-7) GM-CSF (human recombinant *E coli*-derived GM-CSF, Pharmacia & Upjohn Laboratories): 5 µg/kg/d by 6-h infusion from d 1 until recovery of neutrophils or regrowth of leukemia, max 28 d Consolidation (n=48): Pts with CR age 55-64 y randomized to receive consolidation + maintenance or maintenance alone (see Table 4-14) Pts age 65-75 y with CR received maintenance (TG + AraC, lomustine + mitoguazone) for 1 y (without GM-CSF)	63% vs 60.5%, p=0.79	2-y OS: 39% vs 27%, p=0.082 2-y OS age 55-64: better with GM-CSF, p=0.014 2-y OS age 65-75: p=0.97 2-y DFS 48% vs 21%, p=0.003 overall; median 23 m vs 11 m DFS age 55-64: 57% vs 20%, p=0.002 DFS age ≥65: 39% vs 21%, p=0.22	Time to neutrophil recovery shorter with GM-CSF (24 d vs 29 d, p=0.0001)	240 pts required to demonstrate 20% improvement in CR (50% to 70%) or 20% increase in DFS (20% to 24%). Included all pts who started assigned treatment in the analysis.	GM-CSF shortened neutrophil recovery and improved survival for pts age 55-64 but did not affect CR
ECOG E1490 1990-1992 Rowe, 1995 (271)	124 Age 55-70 y, median 64 y, AML, no antecedent myelodysplasia	Induction GM-CSF + consolidation GM-CSF GM-CSF	DNR + AraC; GM-CSF or placebo if aplastic bone marrow DNR (60 mg/m^2/d iv, d 1-3), AraC (25 mg/m^2 iv push, d 1 then 100 mg/m^2/d CI, d 1-7). Bone marrow examined on d 10, if aspirate was aplastic without leukemia then pts received GM-CSF or placebo on d 11. If bone marrow showed residual leukemia then a 2nd induction cycle was given; if bone marrow on d 3 showed residual leukemia, pts were off the study; if free of leukemia pts received GM-CSF or placebo. GM-CSF (yeast-derived recombinant GM-CSF, Sargramostim, Leukine, Immunex Corp): 250 µg/m^2 iv over 4 h daily until absolute neutrophil count at least 1500/µL for 3 d or for a max of 42 d. <u>Consolidation (n=49) if CR after GM-CSF or placebo</u> AraC (1.5 g/m^2 iv over 1 h q12h for 12 doses); GM-CSF or placebo on d 11 (according to initial randomization)	60% vs 44%, p=0.08 Age 55-65: 68% vs 48%, p=0.08 Age 66-70: 45% vs 31% [not enough pts to determine significance]	OS median 10.6 m vs 4.8 m, p=0.048 (p=0.021 adjusted) DFS 8.5 m vs 9.6 m, p=0.95	For induction, GM-CSF arm had less overall treatment – related toxicity (p=0.049; grade 3+ pneumonia 14% vs 54%, p=0.046) and infectious toxicity (p=0.015). GM-CSF arm had shorter neutrophil recovery time during induction (14 vs 21 d, p=0.001) but not consolidation (14.5 d vs 15 d, p=0.17)	ITT. The sample size for this study was calculated to provide greater than 80% power to detect a 7- to 9-d reduction in the median duration of neutropenia	GM-CSF safe and efficacious. Trend for improved CR; improved OS and less toxicity with GM-CSF

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ALFA-9802; 1999-2003 Thomas, 2007, 2010 (276,277)	259 Age 15-50 y, de novo AML (not previously treated); excluded s-AML or other active cancer	Induction GM-CSF; consolidation + maintenance GCSF and other GM-CSF	GM-CSF or not with all cycles of chemo GM-CSF (recombinant human GM-CSF, Leucomax, Schering Plough): 5 µg/kg/d iv over 6 h, d 1 until last day of chemotherapy of each course except salvage Induction: DNR (80 mg/m^2/d iv, d 1-3), AraC (500 mg/m^2/d CI, d 1-3), MTZ (12 mg/m^2/d iv, d 8-9), AraC (500 mg/m^2/12 h iv over 3 h, d 8-10) ± GCSF Salvage therapy if required (no CR): HDAC (3 g/m^2/12 h iv, d 1, 3, 5, 7), AMSA (100 mg/m^2/d iv, d 1-3) Post-remission (pts with CR): GM-CSF according to initial randomization 4 cycles HDAC → maintenance [see CALGB trial] vs 1 cycle [AMSA + AraC] → 1 cycle [MTZ + etoposide + AraC] [see ALFA 9000 trial] [± GCSF as in induction for all stages] HDAC (3 g/m^2/12 h iv over 3 h, d 1, 3, 5), AMSA + AraC: AMSA (90 mg/m^2 iv, d 1), AraC (60 mg/m^2/12 h sc, d 1-5) Maintenance (4 cycles): DNR (45 mg/m^2 iv, d 1) + AraC (100 mg/m^2/12 h sc, d 1-5) MTZ + etoposide + AraC: MTZ (12 mg/m^2/d iv, d 1-3), etoposide (200 mg/m^2/d CI, d 8-10), AraC (500 mg/m^2/d CI, d 1-3 and d 8-10) Good risk group including favourable cytogenetics, constituted by core binding factor (CBF) leukemias and the good risk-2 subset (normal karyotypes with favourable genotypes)	88% vs 78%, p<0.04 After salvage: 91% vs 87%, p=0.25 By MRC definition: Favourable 96% vs 86%, p=0.20; intermediate 86% vs 78%, p=0.19; unfavourable 89% vs 67%, p=0.04 By Risk group: Good 98% vs 90%, p=0.18; poor 84% vs 72%, p=0.04 Molecular biology: initial high white blood cell count + FLT3-ITD or MLL rearrange-ment: 83% vs 73%, p=0.42	5-y OS 51% vs 42%, p=0.21 By MRC definition: Favourable 72% vs 75%, p=0.99; intermediate 52% vs 41%, p=0.24; unfavourable 16% vs 20%, p=0.62 By Risk group: Good 70% vs 80%, p=0.27; poor 37% vs 30%, p=0.27 Molecular biology: initial high white blood cell count + FLT3-ITD or MLL rearrange-ment: 43% vs 13%, p=0.02 5-y EFS 43% vs 34%, p=0.04 By MRC definition: Favourable 61% vs 62%, p=0.90; intermediate46% vs 35%, p=0.19; unfavourable 16% vs 10%, p=0.21 By Risk group: Good 63% vs 64%, p=0.73; poor 32% vs 24%, p=0.06 Molecular biology: initial high white blood cell count + FLT3-ITD or MLL rearrange-ment: 39% vs 8%, p=0.007	Death during induction 3% vs 7%. Severe adverse effects after induction and time to hematopoietic recover were similar. The frequencies of severe adverse effects after consolidation therapy and the times to hematopoietic recovery after consolidation therapy did not differ significantly	Planned accrual 344 pts; actual 262 pts due to interruption of GM-CSF production. Primary endpoint EFS. Planned 5 y enrollment + 2 additional years follow-up to detect increase of 20% in EFS (from 40% to 60%) at 3 years, given 123 expected events. Within 4 years, 259 patients were evaluated. As of May 2005, 155 EFS events had occurred.	GCSF improved CR rate and EFS but OS to lesser extent (ns). The EFS benefit was only in poor-risk pts

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ALFA-9802; 1999-2003 Thomas, 2007 (277)	259 Age 15-50 y, de novo AML (not previously treated); excluded s-AML or other active cancer	Induction GM-CSF; consolidation + maintenance GM-CSF and other GM-CSF	Results according to consolidation/maintenance See results under Induction GM-CSF for treatment details (276,277) EMA: etoposide + MTZ + AraC arm Hazard Ratios and significance compared with EMA without GM-CSF	See other tables	3-y OS, all pts HDAC HR=1.04, p=0.9; EMA + GCSF HR=0.8, p=0.56; HDAC + GM-CSF HR=0.82, p=0.62 OS, intermediate risk cytogenetics: HDAC HR=0.38, p=0.06; EMA + GCSF HR=0.44, p=0.11; HDAC + GM-CSF HR=0.26, p=0.01 3-y EFS, all pts HDAC HR=1.01, p=0.96; EMA + GCSF HR=0.77, p=0.44; HDAC + GM-CSF HR=0.74, p=0.38 EFS, intermediate risk cytogenetics: HDAC HR=0.41, p=0.04; EMA + GCSF HR=0.37, p=0.03; HDAC + GM-CSF HR=0.29, p=0.008	The frequencies of severe adverse effects after consolidation therapy and the times to hematopoietic recovery after consolidation therapy did not differ significantly	NR	Overall no difference with GM-CSF, but improved survival for intermediate-risk group. Overall EMA and HDAC similar, but HDAC better in intermediate-risk group
Sweden; 1994-1998 Hast, 2003 (274)	93 35-90 y, median 72 y, RAEB-t (n=25) or s-AML (AML after MDS, n=68)	Induction GM-CSF + consolidation GM-CSF GM-CSF	TAD ± GM-CSF TAD: DNR (60 mg/m^2 iv, d 1-2) + AraC (100 mg/m^2 iv, d 1-7) + TG (200 mg/m^2 po, d 1-7) GM-CSF (molgramostim, Schering-Plough AB, Stockholm): 200 µg/d sc, starting 2 d before chemotherapy if white blood cell (WBC) count <50×10^9/L otherwise concomitantly with chemotherapy; continued for maximum of 3 w or until absolute neutrophil count (ANC) reached >10^9/L in recovery phase after chemotherapy Pts in CR could receive maximum of 3 consolidation courses with TAD (1+5) with or without GM-CSF according to initial randomization	43% vs 43%, no difference	No significant difference in OS, p=0.95 Relapse at 34 m follow-up 85% vs 84%; RFS median 364 d vs 330 d, p=0.45	Severe non-hematological adverse events (fluid retention, exanthema, cardiac complications) more common with GM-CSF (p=0.01) Early deaths 15.2% vs 8.5%, p=0.33	The study was designed to detect a 30% difference in CR rate with 80% power.	GM-CSF provided no clinical benefit but increased risk of side effects in s-AML and RAET-t

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[19]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
EORTC/HOVON AML-11; 1990-1994 Lowenberg, 1997 (199); Uyl-de Groot, 1998 (273)	318 Age 61+ y, median 68 y, untreated newly diagnosed AML	Induction GM-CSF + consolidation GM-CSF; maintenance GM-CSF	DNR + AraC ± GM-CSF induction DNR + AraC consolidation ± GM-CSF according to induction group Induction: DNR (30 mg/m^2 iv bolus, d 1-3) + AraC (200 mg CI, d 1-7), with or without GM-CSF (5 µg/kg CI, d 0-28 or until granulocytes 0.5×10^9/L for 3 d); 2nd cycle if PR Consolidation (if CR): same as induction but DNR for 1 d Maintenance (if continuing CR): 2nd randomization to AraC (10 mg/m^2 sc q12h for 12 d; 8 cycles at 6 w intervals) or none	56% vs 55%, p=0.98	2-y OS 22% vs 22%, p=0.55 2-y DFS 14% vs 19%, p=0.69	Median time for neutrophil recovery 23 d vs 25 d, p=0.0002.	ITT. 310 pts to detect CR increase from 50-65% and increase in 2-y OS from 15% to 25%. Final analysis after 256 deaths	GM-CSF does not improve clinical outcome (except for faster neutrophil recovery)
Sweden; 1992-1999 Lofgren, 2004 (275)	110 Age 64+ y, median 77 y, untreated de novo AML, antecedent MDS excluded	Induction GM-CSF + consolidation GM-CSF; maintenance GM-CSF	AraC + MTZ + etoposide ± GM-CSF AraC (1 g/m^2 as 2-h infusion q12h, 3 d), MTZ (12 mg/m^2/d as 1-h infusion, 3 d), etoposide (200 mg/m^2 as 1-h infusion, 3 d), GM-CSF (200 µg/m^2/d sc, starting 1 d before chemo until neutrophil count >10^9/L) 2nd cycle induction if PR Pts with CR received 2 cycles consolidation: 1st cycle AraC + MTZ + etoposide (as for induction except MTZ for 1 d); 2nd cycle AMSA (90 mg/m^2 as 1-h infusion, 4 d). GM-CSF given (or not) according to initial randomization Maintenance (n=30): 2nd randomization to low-dose TG (160 mg/wk) or none	64% vs 65%, ns	OS median 9 m vs 14 m; 6-y OS: 8% vs 10%, p=0.07 For pts randomized to maintenance: median OS 28 m TG vs 16.5 m none	Median time to neutrophil recovery 17 d vs 25 d (p=0.03). Less signs of liver damage with GM-CSF (11% vs 27%). Median duration remission 6 m vs 13 m. For pts randomized to maintenance: median 18 m remission with TG vs 16 m none, ns	Primary outcome CR. 110 pts to detect 30% difference in CR	GM-CSF reduced neutrophil recovery time but did not improve OS No conclusions regarding maintenance due to low number of pts

ACR, aclarubicin; ADE, AraC + DNR + etoposide; AMSA, amsacrine; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; ATRA, all-trans retinoic acid; BHAC, N^4-behenoyl-1-β-D-arabinosylcytosine; CI, continuous iv infusion; COAP, cyclophosphamide, VCR, AraC, prednisone; CR, complete remission (complete response); DAT, DNR +AraC + 6-thioguanine (TG); DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; EMA, etoposide + MTZ + AraC; GCSF, granulocyte-colony stimulating factor; FAI, fludarabine + AraC + IDA; GM-CSF, granulocyte-macrophage colony-stimulating factor; HAM, high-dose cytarabine + mitoxantrone; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; ICE, idarubicin + cytarabine + etoposide; IDA, idarubicin; IFN, interferon; ITT, intention to treat; iv, intravenously; MAC, MTZ + AraC; MDS, myelodysplastic syndromes; MAE, MTZ + AraC + etoposide; MICE, MTZ + AraC + etoposide; MTZ, mitoxantrone; NR, not reported; OR, odds ratio; OS, overall survival; po, oral administration (per os); PR, partial response/remission; RAEB-t, refractory anemia with excess of blasts in transformation; RD, remission duration; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; sc, subcutaneously; SCT, stem cell transplant; std, standard; TAD, thioguanine + cytarabine + daunorubicin; TG, 6-thioguanine; VCR, vincristine; WBC, white blood cell

Table 4-12. Induction, agents not in other tables Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[20]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
AZA-AML-001 NCT01074047; 2010-2014 Dombret, 2015 (145); Dohner, 2015 (146)	87 (488) Age ≥65, median 71 y, newly diagnosed AML (de novo or s-AML), >30% bone marrow blasts, not eligible for hematopoietic stem cell transplant, intermediate- or poor-risk cytogenetics, ECOG PS ≤2	Induction Intensive (AraC + DNR/IDA) vs azacitidine	Before randomization, a convention care regimen was chosen (standard induction, low-dose AraC, or supportive care) and then pts randomized to azacitidine or conventional care; only subgroup initially randomized to standard induction is relevant to this review Azacitidine, 75 mg/m^2/d sc, 7 consecutive days per 28-d treatment cycle, at least 6 cycles Standard induction: [AraC (100-200 mg/m^2/d CI, 7 d) + either DNR (45-60 mg/m^2/d)or IDA (9-12 mg/m^2/d)] for one cycle then up to 2 cycles consolidation with same regimen but for AraC given for 3-7 d for pts with CR or partial response	CR 30% vs 36%; CR+CRi: 42% azacitidine vs 47.7% standard induction	OS median 13.3 m azacitidine vs 12.2 m standard induction, p=0.5032; 1-y OS 55.8% vs 50.9%, ns	RBC transfusion independence rates with AZA vs IC were 57% vs 35% Grade 3-4 treatment-emergent adverse events in the AZA and IC groups: anemia 12% vs 14%; neutropenia 30% vs 33%; febrile neutropenia 33% vs 31%; thrombocytopenia 23% vs 21%; and (any) infections 49% vs 50%	Primary endpoint OS, secondary endpoint 1-y survival rate and OS in subgroups. Study not powered to demonstrate significant differences within preselection groups.	Low intensity azacitidine may benefit older pts eligible for intensive induction who choose to forego it
AMLSG 12-09 NCT01180322; 2010-2012 [Phase II trial] Schlenk, 2012 (280) [abstract]	252; (104 stage 1) AML not candidate for genotype-adapted treatment approaches; median age 62 y (18-82)	Induction AZA	ICE vs AZA → IDA + etoposide vs AZA + IDA + etoposide vs IDA + etoposide → AZA Std arm: ICE: IDA (12 mg/m^2/d iv, d 1, 3, 5) + AraC (100 mg/m^2/d CI, d 1-7) + etoposide (100 mg/m^2/d iv, d 1, 2, 3) AZA-prior arm: AZA (100 mg/m^2/d sc, d 1-5) + IDA (12 mg/m^2/d iv, d 6, 8, 10) + etoposide (100 mg/m^2/d iv, d 6, 7, 8) AZA-concurrent arm: AZA (100 mg/m^2 d sc, d 1-5) + IDA (12 mg/m^2/d iv, d 1, 3, 5) + etoposide (100 mg/m^2/d iv, d 1, 2, 3) AZA-after arm: IDA (12 mg/m^2/d iv, d 1, 3, 5) + etoposide (100 mg/m^2/d iv, d 1, 2, 3) + AZA (100 mg/m^2/d, sc, d 4–8) Induction for 2 cycles; if CR then consolidation (not randomized) by HSCT or 3 courses of HDAC followed by 2 y maintenance with AZA (50 mg/m^2/d sc d 1-5 q4w) Terminated AZA-prior and AZA-concurrent arms after 104 pts; continued other 2 arms until 100 pts per arm	AZA-prior and AZA-concurrent: 42% and 38% so arms stopped. ICE 59% vs AZA-after 52%, p=0.39	NR	NR	NR	ICE and AZA-after appear equally effective and will be studied in subsequent Phase III trial

[20] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[20]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
German SAL AML-AZA Müller-Tidow, 2014 (281) [abstract]	214 Older pts with AML (de novo or secondary), median age 70 y	Induction + consolidation + maintenance AZA	(AZA → std induction) → (AZA → std consolidation) → AZA maintenance vs std induction and maintenance All pts received AraC (100 mg/m^2) + DNR (60 mg/m^2) [7+3 induction], and up to 2 cycles consolidation with AraC (1 g/m^2 q12h, d 1, 3, 5) AZA: 75 mg/m^2 for 5 d for induction or consolidation, up to one year for maintenance	48% vs 52%, p=0.58	OS median 16 m vs 21 m, p=0.35 Median EFS, 6 m vs 6 m, p=0.96; median RFS 12 m vs 12 m, p=0.95	At least one SAE: 51% AZA vs 31%, p=0.005; cardiac disorders, n=15 vs n=6, ns;	ITT	AZA does not improve EFS or OS in unselected pts and is more toxic; trends in DNMT3A subgroup should be explored
Greece (Hellenic Society of Hematology) Matsouka, 2006 (74)	55 Secondary AML (post-MDS), age >60 y, median 69 y	Induction CsA	(IDA + AraC + etoposide) ± CsA Group A: IDA (8 mg/m^2, 15 min iv infusion, d 1-3), etoposide (75 mg/m^2, 2h iv infusion, d 1-5), AraC (100 mg/m^2 CI, d 1-5) Group B: IDA (6 mg/m^2, 15 min iv infusion, d 1-3), etoposide (60 mg/m^2, 2h iv infusion, d 1-5), AraC (100 mg/m^2 CI, d 1-5), CsA (5 mg/kg/d po, divided into 2 doses/d, d -1 to +5) If CR (or PR in 2 pts), gave 2nd cycle IDA + AraC for 5 d then consolidation Note different doses in each arm as CsA modulates plasma/cell concentration	52% vs 27%, p=0.01	OS median 7 m vs 6 m, p=0.3; OS at 25 m: estimated 14% vs 8%, p=0.18; actual 17% vs 8%, p=0.02 Median DFS 12 m vs 7 m, p=0.03; DFS at 12 m: 40% vs 0%, p=0.01	NR	28 pts per arm to detect a clinically important difference in success of 35% (20 to 55%), 80% power	CsA may improve outcome in elderly pts with s-AML
SWOG 9126; 1993-1998 List, 2001 (75)	226 Age 18-70 y, median 53 y, poor-risk AML: refractory/ relapsed (78%); untreated s-AML or t-AML (17%); or RAEB-t (5%). Stratified by age (≤55 y, >55 y) and disease type. Note: mainly relapsed/ refractory AML	Induction + consolidation CsA	AraC + DNR ± CsA AraC (3 g/m^2 daily by 3h infusion, d 1-5), DNR (45 mg/m^2/d CI, d 6-8), CsA (2h iv loading of 6 mg/kg + 6-h infusion of 4 mg/kg on d 6; then 16 mg/kg/d CI, 72h concurrently with DNR) 2nd induction in pts with persistent leukemia and >50% blast reduction Pts with CR received 1 course consolidation (n=57) with DNR ± CsA according to induction assignment, but at shorter schedule: AraC (d 1-3), DNR ± CsA (d 4-6)	39% vs 33%, p=0.14 One course: 38% vs 26%, p=0.032	2-y OS 22% vs 12%, RR=0.78, p=0.046 Previously untreated (s-AML or RAEB-t): median 9 m vs 4 m; 2-y OS 26% vs 5%, RR=0.41 (0.22-0.76) 2-y RFS 34% vs 9%, RR=0.59 (0.34-1.03) Previously untreated pts: 2-y RFS 60% vs 5%, RR=0.20 (0.05-0.84)	Induction deaths 15% vs 18%. CsA group had more grade 4 hyperbilirubinemia (31% vs 4%, p<0.0001) and grade 3 nausea (11% vs 3%, p=0.016); other toxicities similar	ITT. 220 pts to give 82% power to detect 50% increase in CR from 35% to 53% and 90% power to detect mortality HR=0.67	CsA reduced frequency of resistance to DNR and probability of relapse; improved OS

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[20]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ACCEDE trial; NCT00715637; 2008-2010 Stone, 2015 (282)	433 Age 18+ y, newly diagnosed, previously untreated s-AML/t-AML	Induction Amonafide	AS1413 (amonafide L-malate) + AraC vs DNR + AraC AraC (200 mg/m^2 CI, d 1-7), amonafide (600 mg/m^2 iv over 4 h daily, d 1-5), DNR (45 mg/m^2 iv over 30 min daily, d 1-3) Pts with persistent leukemia based on d 14 bone marrow assessment received 2nd course	46% vs 45%, p=0.81 Age ≥60: 41% vs 44%, p=0.60 Age <60: 54% vs 45%, p=0.27 Age <56 (exploratory): 64% vs 40%, p=0.016	HR=1.209, p=0.168 Median 7.0 m both arms; 1-y OS 36% vs 31%; 18 m OS: 21% vs 19% Age <56 y: median 16.1 m vs 7.1 m, p=0.03	30-d mortality 19% vs 13%; 60-d mortality 28% vs 21%. Pts with Amonafide had more grade 4+ toxicity, especially gastrointestinal grade 4 and cardiac and neurologic grade 5	Planned 420 pts to yield 89% power to detect a 15% improvement in CR from 30% to 45%	Amonafide did not improve CR or OS except in exploratory analysis of pts age <56 y
HOVON 81 AML; NTR904; 2007-2009 Ossenkoppele, 2012 (283)	171 Age ≥60 y, de novo AML or refractory anemia with excess blasts	Induction Bevacizumab	1st cycle: std chemotherapy 3+7 ± bevacizumab 2nd cycle: AraC ± bevacizumab 3+7: DNR (45 mg/m^2 iv over 3 h, d 1-3) + AraC (200 mg/m^2 CI, 7 d) Bevacizumab (dose 5 mg/kg in part A, 10 mg/kg iv for 60 min, d 1 and 15 in Part B) 2nd cycle: AraC (1000 mg/m^2 q12h iv over 6 h, d 1-6) ± bevacizumab as randomized for 1st cycle	65% both arms, ns	OS at 24 m: 29% vs 28%, p=0.82 EFS at 12 m 30% vs 33%; EFS at 24 m 16% vs 22%, p=0.42	SAE higher in bevacizumab arm (n=63 vs n=28, p=0.043); but percentages of death or life-threatening SAE were lower (60% vs 75%)	ITT. The upper limit of the 80% confidence interval for the true difference in CR rate was lower than 10% (9.8%), which according to the protocol, indicates evidence for inefficacy	Bevacizumab does not improve outcome for older AML pts
NCT00407966, USA; 2008-2010 Karp, 2012 (284)	78 Age 18+ y, newly diagnosed, poor-risk AML (secondary AML, age ≥50 y, or adverse cytogenetics); prior treatment for MDS allowed	Induction Flavopiridol	Flavopiridol → AraC + MTZ vs hybrid flavopiridol → AraC + MTZ Arm A: flavopiridol (50 mg/m^2 bolus daily, d 1-3) Arm B: flavopiridol (30 mg/m^2 as 30 min bolus followed by 4h infusion of 40 mg/m^2; total daily dose 70 mg/m^2) AraC (2 g/m^2; 667 mg/m^2/24h, d 6-8), MTZ (40 mg/m^2 iv bolus over 1-2 h, d 9, 12 h after completing AraC) Pts with CR were eligible for 2nd cycle	CR+CRi: bolus 62% vs 74%	OS median 11.4 m vs 13.0 m, p=0.38 Estimated 12 m survival from CR: 58% vs 66% Median DFS 13.6 m vs 12.0 m	NR	Phase II pick the winner. Primary outcome CR. Number of pts based on null hypothesis of 30% CR and alternative is 55%	Comparable results, future study is planned

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NCT01349972; 2011-2013 Zeidner, 2015 (285)	165 Newly diagnosed AML, age 18-70 y, excluded CBF positive. 47% had s-AML	Induction Flavopiridol + MTZ vs DNR	FLAM vs AraC + DNR (7+3) FLAM: flavopiridol (50 mg/m^2 iv, d 1-3) + AraC (667 mg/m^2/d CI, d 6-8) + MTZ (40 mg/m^2 iv, d 9) 7+3 AraC/DNR: AraC (100 mg/m^2/d CI, d 1-7), DNR (90 mg/m^2 iv, d 1-3). IDA (12 mg/m^2 iv, d 1-3) substituted as need for lack of DNR availability Randomization 2:1 FLAM vs 7+3, stratified by age, secondary AML and/or known adverse cytogenetics, leukocyte count Pts with residual leukemia on d 14 received 5+2 on the 7+3 arm, whereas pts on FLAM were not retreated. However, only 13/24 pts (54%) with residual disease received the 2nd induction cycle Post-induction treatment according to physician preference: 46% FLAM and 28% HDAC for the FLAM group and 81% HDAC for the 7+3 group	CR/CRi: 70% vs 46% 7+3, p=0.003; 70% vs 57% 7+3 → 5+2 (if needed), p=0.08 s-AML: 60% vs 35%, p=0.05; de novo AML 79% vs 57%, p<0.05 age <60: 79% vs 52%, p=0.02 1 cycle, age <50 96% vs 57%; age ≥50: 61% vs 43%	OS median 17.5 m vs 22.2 m, p=0.39 2-y OS 50% vs 59% Trial not powered to detect OS difference Relapse: 43% vs 50% at median 553 d follow-up Median EFS 9.7 m vs 3.4 m, p=0.15	Grade 3+ toxicities similar. 60-d mortality 10% FLAM (5-17%) vs 4% (0-12%), p=0.22; with majority of deaths in pts age 60+ Overall deaths 60% vs 57%; follow-up median 553 d	Phase II trial; CR primary endpoint; OS, DFS, toxicity are secondary outcomes. A sample size of 165 pts yielded 85% power to detect an increase in CR from 55% with 7+3 to 75% with FLAM	FLAM induction gives higher CR without increased toxicity. Phase III trial is under development. FLAM better than 1 cycle 7+3 for CR in all subgroups (age, non-adverse, adverse, complex, secondary, de novo, poor-risk, not poor-risk) although some not statistically significant due to low pt numbers Benefit of FLAM compared with 2 cycles was lower than for 1 cycle, and unclear for elderly or pts with adverse genetics

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China; 2007-2011 ChiCTR-TRC-06000054 Jin, 2013 (56)	620 Untreated AML, age 14-59 y	Induction Homoharringtonine (Anthracycline ACR, DNR)	Homoharringtonine + ACR vs homoharringtonine + DNR vs DNR; all had AraC (100 mg/m^2, d 1-7) HAA: homoharringtonine (2 mg/m^2/d, d 1-7) + AraC + ACR (20 mg/d, d 1-7) HAD: homoharringtonine (2 mg/m^2/d, d 1-7) + AraC + DNR (40 mg/m^2/d, d 1-3) DA: DNR (40-45 mg/m^2/d, d 1-3) + AraC	73% HAA vs 61% DA, p=0.011 67% HAD (p=0.20 vs DA)	OS unadjusted (ns); adjusted for prognostic factors: HAA vs DA, HR=0.68 (p=0.213) 3-y EFS: 35.4% HAA vs 23.1% DA, p=0.0023; 32.7% HAD (p=0.08 vs DA) RFS unadjusted (ns); adjusted HAA vs DA HR=0.59 (p=0.0080)	Adverse events similar, except more early deaths compared with DA: HAA (5.8%; p=0.0067) and HAD (6.6%, p=0.0030), DA (1%) Benefit of HAA and HAD greatest in subgroup with favourable cytogenetics	ITT; primary endpoint CR + EFS. 200 pts/arm to detect 3-y EFS difference of 12% (23% vs 35%) and HR=0.70. Adequate power for CR	HAA is an option
MD Anderson Giles, 2005 (73)	100 Age ≥50 y (median 67 y), newly diagnosed AML (72%) or high-risk MDS (26% RAEB or RAEB-t); karyotype other than inv(16), t(8;21) or t(15:17)	Induction Interleukin-11	Bayesian design to adaptively randomize to the treatment arm IDA + AraC + interleukin-11 (IL-11) vs IDA + AraC IDA (12 mg/m^2/d iv bolus, d 1-3), AraC (1.5 g/m^2/d CI, d 1-4 age <65 or d 1-3 age >64), IL-11 (15 µg/kg/d sc, d 3-28)	IL-11 53% vs 53%, ns	OS median 21 vs 59 w (p=0.271)	No significant difference in grade 3-4 adverse events. TTF median 37 w vs 46 w, ns	Once the probability of randomization to an arm became >95%, the other arm would close. Maximum 100 pts	Study closed after 100 pts (prespecified maximum); probability was low that IL-11 would show superior TTF
NCRI AML15 + AML17; 2007-2012 Knapper, 2014 (286) [abstract]	500 FLT3-Mutated AML: 74% FLT3-ITD mutations, 23% FLT3-TKD mutations, 2% both. Age 5-68 y, median 49 y (5 pts <16 y), newly diagnosed, 94% de novo AML, 5% secondary AML, 1% high-risk MDS	Induction Lestaurtinib	Std chemo followed by lestaurtinib or none Lestaurtinib (80 mg bid or placebo, up to 28 d after each of 4 courses of chemotherapy); dose reduction to 40 mg bid for patients on concomitant azole antifungal drugs	CR+CRi: Lestaurtinib 92% vs control 94%, OR=1.37 (0.68-2.78), p=0.4	5-y OS: 46% vs 43%, HR=0.89 (0.68-1.13), p=0.3 Subgroup on GO + azole: 61% vs 28%, p=0.02 5-y RFS 40% vs 37%, HR=0.87 (0.68-1.12), p=0.3	Minimal differences in toxicity, except excess nausea/ diarrhea with lestaurtinib in course 2. In subgroup analysis, some evidence of benefit in pts receiving GO or GO + azole	NR	Lestaurtinib may be safely used in younger pts with FLT3-mutated AML; Use with GO needs validation

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MD Anderson; 1995-1997 Estey, 1999 (287)	70 Age <71 y (median 48 y; stratified below or above age 65 y), newly diagnosed de novo AML (89%), RAEB-t or RAEB	Induction Lisofylline	IDA + AraC ± lisofylline (or placebo) IDA (12 mg/m^2/d iv over 0.5 h, d 1-3), AraC (1.5 g/m^2/d CI, d 1-4), lisofylline or placebo (3 mg/kg iv every 6 h, from -6 h to recovery of neutrophil or platelet counts) 2nd induction course if persistence of blasts in bone marrow Pts with CR given one course AraC alternating with one course IDA + AraC every 4-5 weeks for 1 y	77% vs 74%	OS: p=0.92, median 56 w DFS once in CR, p=0.52; remission duration median 42 w all patients, p=0.29	Infection rate: 37% vs 49%, p=0.46 expert panel; 43% vs 51%, p=0.63 by study physicians Serious infections: 17% vs 34%, p=0.11 Severe nausea/ vomiting and mucositis more frequent in lisofylline group Early mortality (60 d): 17% vs 20%	Primary endpoint was infection; CR, serious infections, and survival were secondary endpoints. Powered at 77% to detect decrease in infection rate from 50% to 20% with 35 pts/arm	Larger studies of lisofylline in this population not warranted
GOELAM: BGMT-95; 1995-2001 Pigneux, 2007 (82); Pigneux, 2010 (83)	364 Age ≥60 y, de novo AML; excluded s-AML	Induction; consolidation (post-remission) Lomustine	IDA + AraC + lomustine vs IDA + AraC IDA (8 mg/m^2, d 1-5), AraC (100 mg/m^2, d 1-7), lomustine (200 mg/m^2 po, d 1) 2nd course if not CR If CR, received IDA + AraC sc; if stable then 2nd randomized (n=101) to intermediated-dose AraC (500 mg/m^2 q12h over 2h, d 1-4) + IDA + maintenance or maintenance alone	67% lomustine vs 58%, p=0.104 After 1 course: 65% vs 54%, p=0.055 Subgroup with adverse cytogenetic features: 59% vs 40%, p=0.074; favourable/ intermediate features: 71% vs 64%, p=0.286	OS median 12 m vs 7 m, p=0.05. 2-y OS 31±7% vs 24±6%, ns Median EFS was 7 m vs 4 m, p=0.06; 2-y EFS 22% vs 18%, ns. 2-y DFS 31% vs 31%	Induction deaths 20% vs 19%, ns. Lomustine group had more grade 3-4 liver toxicity (p=0.01), and hematologic effects (platelet and neutrophils recovery, p=0.001 and p=0.004; units of blood and platelets transfused, p=0.03 and p=0.006)	ITT. Primary outcome CR and OS. Sample size of 350 pts to detect increase of 15% in CR and 20% in 2-y survival with power of 90%	Adding lomustine did not improve survival; adding intermediate-dose AraC to consolidation did not improve outcome Further trial of lomustine for consolidation is being planned (see LAMSA 2007 trial)

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CALGB 9720; 1998-1999 Baer, 2002 (79)	120 Age ≥60 y, de novo AML	Induction PSC-833	ADE vs ADEP ADE: AraC (100 mg/m^2/d by 7 d infusion) + [DNR (60 mg/m^2) + etoposide (100 mg/m^2 daily)] for 3 d ADEP: AraC (as above) + [DNR (40 mg/m^2) + etoposide (60 mg/m^2)] for 3 d + PSC-833 (2.8 mg/kg over 2 h then 10 mg/kg/d by 3-d infusion) ADEP (PSC-833) arm closed due to excessive early mortality	46% ADE vs 39% ADEP, p=0.008	OS 33% at one year, both groups, p=0.48 DFS: median 7 m vs 8 m, p=0.38	Interim analysis at 120 pts. Deaths 12 (20%) ADE vs 26 (44%) ADEP. Early deaths (30 d): 7 ADE vs 19 ADEP	Original target 400 pts giving 0.84 power to detect increase in CR from 0.50 to 0.65; power reduced to 0.31	ADEP arm closed early (120 pts) due to excessive early mortality.
HOVON + UK MRC; 1997-1999 Van der Holt, 2005 (80)	419 Untreated primary or secondary AML, age ≥60 y	Induction PSC-833	DNR + AraC ± PSC-833 Arm A: DNR (45 mg/m^2, 15 min infusion, d 1-3), AraC (200 mg/m^2/d CI, d 1-7) Arm B: DNR (35 mg/m^2), AraC (200 mg/m^2), PSC-833 (2 mg/kg in 2 h then 10 mg/kg CI every 24 for 72 h, d 1-3) 2nd cycle given if achieved normocellular marrow with <5% blasts Consolidation if achieved CR	54% vs 48%, p=0.22	OS 10% in both arms, p=0.52 5-y EFS 7% vs 8%, p=0.53; DFS 13% vs 17%, p=0.06	Adverse effects affecting central and peripheral nervous system and liver and biliary disorders more frequent with PSC-833	ITT, EFS primary outcome. 80% power to detect increase in 2-y EFS from 9.5% to 18%; 400 pts and 331 events required	
CALGB 19808; NCT00006363; 2001-2003 Kolitz, 2010 (78)	302 Age <60 y	Induction PSC-833	ADE (AraC + DNR + etoposide) vs ADEP (AraC + DNR + etoposide + PSC-833) ADE: AraC (100 mg/m^2 CI, d 1-7), DNR (90 mg/m^2 iv), etoposide (100 mg/m^2 iv over 2 h, d 1, 2, 3) ADEP: PSC-833 (2.8 mg/kg iv over 2 h, d 1; 10 mg/kg CI for 72 h) then AraC (100 mg/m^2 CI, d 1-7), DNR (40 mg/m^2 iv, d 1-3), etoposide (40 mg/m^2 iv over 2 h, d 1-3) 2nd course if CR not achieved: ADE had AraC over 5 d, DNR and etoposide for 2 d each; ADEP identical to 1st course except PSC-833 infused between hours 2 and 50	75% both regimens	OS median 1.86 y ADE vs 1.69 y ADEP (p=0.82) Median DFS 1.34 y ADE vs 1.09 y ADEP (p=0.74)	More reversible grade 3+ liver and mucosal toxicities with ADEP PSC-833 withdrawn from clinical development Aug 2003 so enrolment ended early	ITT. Required 600 pts and 374 deaths to detect HR=1.4 for OS. Closed early at 302 pts (power =0.64 instead of planned 0.90)	PSC-833 does not improve outcome.

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MRC AML14; LRF AML14; ISRCTN62207270; 1998-2005 Burnett, 2009 (76); Burnett, 2005 (77) [abstract]	1273 Predominantly ≥60 y (younger pts permitted if not fit to enter other trials for younger pts), AML (de novo or secondary) or high-risk MDS	Induction; consolidation PSC-833 (Anthracycline DNR dose, AraC dose). See anthracycline section for full data	DNR (50 vs 35 mg/m^2) + AraC (200 vs 400 mg/m^2) Subgroup receiving DNR 35 mg/m^2 ± PSC-833 DNR (50 or 35 mg/m^2 iv, d 1-3) + AraC (100 or 200 mg/m^2 iv q12h, d 1-10) + TG (100 mg/m^2 po q12h, d 1-10). Course 2 same except AraC + TG, d 1-8 - Subgroup of 601 pts randomized to DNR 50, DNR 35, or DNR 35 + PSC-833 (2 mg/kg iv over 2 h with simultaneous CI 10 mg/kg/24 h for 72 h; in both courses)	52% DNR_{50} vs 57% DNR_{35} vs 47% DNR_{35}+ PSC, p=0.06 (PSC vs not)	5-y OS: 13% DNR_{50} vs 15% DNR_{35} vs 9% DNR_{35} + PSC, p=0.02 (PSC vs not) <u>5-year relapse</u> 85% DNR_{50} vs 82% DNR_{35} vs 84% DNR_{35} + PSC, p=0.9 (PSC vs not)	Induction death 16% DNR_{50} vs 14% DNR_{35} vs 27% DNR_{35} + PSC, p=0.0003 (PSC vs not) No important differences in non-hematological toxicity or hematologic recovery	ITT analysis	Pts did worse with PSC-833
GOELAM 2; 1995-1999 Solary, 2003 (288); Harousseau, 2000 (289)	425 Age 15-60 y, de novo AML	Induction + consolidation Quinine	(IDA + AraC) ± quinine AraC (200 mg/m^2/d, d 1-7), IDA (8 mg/m^2/d iv, d 1-5), quinine (30 mg/kg/d CI, starting 12 h before first dose of IDA, ending 12 h after last IDA infusion) 2nd induction cycle if not CR using AraC (3 g/m^2 as 3-h infusion, q12h, d 1-4) + MTZ (12 mg/m^2 iv, d 5-6) ± quinine (d 4-6) according to initial randomization Consolidation: course 1 with AraC + MTZ as in induction 2; 2nd course with AMSA (150 mg/m^2 as 1-h infusion, 5 d) + etoposide (100 mg/m^2 as 2-h infusion, 5 d); quinine according to initial randomization	81.2% quinine vs 80.6%, ns Subgroup with rhodamine 123 efflux ex vivo: 82.8% vs 48.0%, p=0.01	OS, 43.7% vs 39.3%, p=0.3 DFS at 4 y: 45.3% vs 41.1%, p=0.29	Grade 3+ toxicity: mucositis 17.2% vs 10.2%, p=0.05; no significant difference for other toxicities	128 pts/arm to detect increase of 4-y survival from 40% to 55%. ITT analysis	Quinine does not improve survival
SAL SORAML; NCT00893373; 2009-2011 Röllig, 2014 (290) [abstract] Rollig, 2015 (291) [published after external review]	267 Age 18-60 y, newly diagnosed AML	Induction + consolidation Sorafenib	(induction + consolidation) ± sorafenib (or placebo) 1st induction cycle: (DNR 60 mg/m^2, d 3-5; AraC 100 mg/m^2/d CI, d 1-7) ± sorafenib (400 mg q12h, d 10-19) 2nd cycle same if response on day 16 assessment of bone marrow Pts without response received 2nd induction with HAM (AraC 3 g/m^2 q12h, d 1-3; MTZ 10 mg/m^2, d 3-5) ± sorafenib as in cycle 1 Consolidation (42% sorafenib pts and 49% placebo pts) if CR*: 3 cycles with HDAC (3 g/m^2 q12h, d 1, 3, 5) ± sorafenib (400 mg q12h, d 8 to 3 d before next consolidation, Maintenance: sorafenib (400 mg q12h for 12 m) or placebo [reduced dose if grade 3+ toxicity] *Intermediate-risk pts with sibling donor and high-risk pts with matched donor were offered allogeneic SCT	60% vs 59%, p=0.764	3-y OS 63% vs 56%, p=0.382 Median EFS (censored at transplant): 21 m vs 9 m; 3-y EFS 40% vs 22%, p=0.013. Median RFS >36 m vs 23 m, 3-y RFS 56% vs 38%, p=0.017. Cumulative incidence of relapse after 3 y: 34% vs 49%, p=0.033	Risk of fever, bleeding and cardiac events, rash, and hand-foot syndrome significantly higher in sorafenib arm. More withdrawal from study due to adverse effects in sorafenib arm: 41 pts vs 19 pts Exploratory analysis in pts with FLT3 mutations (n=46): no difference in EFS; better RFS (18 m vs 6 m) and OS (>36 m vs 19 m); all ns	Primary endpoint EFS. Assuming EFS would increase from 9 m to 13.5 m; 80% power with 276 pts and 191 events; p adjusted to 0.046 due to pre-planned interim analysis Secondary endpoints RFS, OS, CR, toxicity	Prolonged EFS and RFS but not OS with sorafenib . Study authors concluded need OS results after long-term follow-up and a confirmatory trial

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NCT00373373 (Study Alliance Leukemia, Germany); 2006-2008 Serve, 2013 (292)	201 Age >60 y, de novo or secondary AML; pretreatment with hydroxyurea or up to 2 d AraC (≤100 mg/m^2/d) allowed. Induction stratified by NPM1 and FLT3 status	Induction + consolidation + maintenance Sorafenib	Sorafenib vs placebo, administered between chemotherapy cycles and up to 1 year after start of therapy. All received AraC + DNR (7+3) and up to 2 cycles intermediate-dose AraC consolidation Sorafenib (400 mg q12h, d 3 until 3 d before next chemo course) AraC (100 mg/m^2/d CI, d 1-7), DNR (60 mg/m^2/d iv, d 3-5) 2nd induction course if blasts 5+% Pts with CR received consolidation (n=80) with 2 courses AraC (1 g/m^2 q12h, d 1, 3, 5) + sorafenib or placebo as above Maintenance: sorafenib (400 mg twice daily from d 3 after consolidation until 1 year after start of induction) or placebo	48% vs 60%, p=0.12 CR+CRi: 57% vs 64%, p=0.34	OS median 13 m vs 15 m, HR=1.03 (0.73-1.44), ns EFS median 5 m vs 7 m, HR=1.26 (0.94-1.70), ns	Sorafenib arm had more adverse effects during induction; grade 3+ infections greater with sorafenib. Early death 17% vs 7%, p=0.052. 60-d mortality: 23% vs 10%, p=0.035. Of pts with CR, more pts in sorafenib arm did not receive the 1st cycle of consolidation (p=0.007)	ITT. EFS primary outcome. Powered to detect increase in median EFS from 3 to 5 months with 80% power after 127 events, planned 200 pts	Adding sorafenib in induction + consolidation is not beneficial for elderly
MD Anderson; 1999-2000 Cortes, 2003 (296)	84 Adults age >16 y (median 65 y) with AML or high-risk MDS (30% had RAEB or RAEB-t) and cytogenetic abnormalities other than other than inv (16), t(18;21), -Y, -X; no previous therapy or max 1 cycle with AraC, anthracycline and/or topotecan with no response	Induction + post-remission Bayesian selection design Topotecan, thalidomide	(DNX + AraC) ± thalidomide vs (DNX + topotecan) ± thalidomide Topotecan arms closed after 11 pts due to no response Thalidomide (400 mg/d po; increased to 600 mg/d if no toxicity after 1 week; reduced to 200 mg if Grade 3+ toxicity), continued until remission DNX + AraC: DNX (100 mg/m^2/d iv over 2 h, d 1-3) + AraC (1 g/m^2/d over 24 h CI, d 1-4) DNX + topotecan: DNX (75 mg/m^2/d iv over 2 h, d 1-3) + topotecan (1.25 mg/m^2/d iv CI, d 1-3) Pts without early CR (by d 50) were removed from study; pts in remission received 2 more courses of same regimen with altered dose (DNX 50 mg/m^2 iv, d 1-2; AraC 0.75 g/m^2/d CI, d 1-2; topotecan 0.6 mg/m^2/d CI, d 1-3; thalidomide 400 mg/d)	42% DNX + AraC + thalidomide vs 46% DNX + AraC, p=0.71	Median survival 28 w vs 35 w, p=0.15	Median CR duration 34 w vs 38 w, p=0.57 Given the CR the posterior probability that DA produced an CR rate ≥20% higher than the historical was 0.007; the posterior probability that it produced an CR rate≥10% higher was 0.11	Max 20 pts/arm. Accrual into any arm was to stop if, given the CR rate when the next patient was to be accrued, the posterior probability was <0.05 that the CR rate with that arm was at least 0.66 (20% improvement over historic data).	Addition of thalidomide does not result in clinical benefit.

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[20]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
JALSG AML87; 1987-1989 Ohno, 1993 (297)	265 Age 16+ y, (15-79 y, median 48 y) newly diagnosed AML, not previously diagnosed with MDS	Induction; maintenance Vincristine	BDMP ± VCR, stratified by age (≤60 y, >60 y) and FAB class (M3 or non-M3) BDMP: behenoyl cytarabine (200 mg/m^2, 3h infusion) + 6MP (daily, 70 mg/m^2 po with 300 mg/d allopurinol) + prednisolone (40 mg/m^2 3h infusion, d 1-4) + DNR (40 mg/m^2 iv, d 1-3, plus d 7, 8, 11, 12 if necessary) VCR (0.35 mg/m^2, 3h infusion, d 1-4) all received same consolidation, then re-randomized (n=131) to either 4 or 12 courses maintenance	70% VCR vs 84%, p=0.007	OS NR DFS similar, p=0.898 EFS worse with VCR, 26% vs 28%, p=0.0122 Maintenance: DFS better with 12 courses, (48% vs 34%), p=0.0663	NR	Randomization stopped after interim analysis showed statistical difference in CR between groups	Vincristine in induction was harmful Intensive maintenance results in better DFS
AMLSG 06-04, NCT00151255; 2004-2006 Tassara, 2014 (298)	186 Newly diagnosed AML (de novo or secondary to MDS or therapy-related, age >60 y, median 68 y	Induction VPA	(IDA + AraC + ATRA) ± VPA 2 cycles IDA 12 mg/m^2 iv, d 1-3 + AraC 100 mg/m^2 iv, d 1-5 + ATRA po 45 mg/m^2, d 3-5 and 15 mg/m^2, d 6-28 with or without valproic acid (VPA) 400 mg po twice per day then adapted according to serum levels from d 3 to give 100 mg/L (60-150 mg/L) on d 1-28 2nd cycle given only to pts with CR or PR (88/186 pts) Due to toxicity at interim analysis after 77 pts: modified VPA arm to use VPA only in first cycle reduced dose of IDA (given only d 1 and d 3) in both cycles Most of pts receiving 2 cycles induction received consolidation (not randomized) with 1 cycle A-HAM [AraC, 0.5 g/m^2 per 12 hours iv, d 1 to 3; MTZ, 10 mg/m^2 intravenously, d 2 and 3] then 1 cycle A-IE: [IDA, 12 mg/m^2 intravenously, d 1 and 3; etoposide, 100 mg/m^2 intravenously, d 1 to 5; ATRA, 15 mg/m^2 by mouth, d 4 to 28]	CR+Cri+PR, VPA vs std (no VPA): 47.3% vs 52.7% after 1 cycle (ns) 40% vs 52% after 2 cycles, p=0.14	OS median 84 m: no difference, p=0.57 5-y EFS 7.6% vs 2.3%, p=0.95 RFS: 24.0% vs 6.4%, p=0.02	Early death 26% vs 14%, p=0.06 From exploratory analysis, pts with mutated NPM1 may benefit from VPA	Primary endpoint EFS. Sample size based on HD98B trial results; success defined as increase in 2-y EFS from 10% to 25%, 500 pts required. ITT survival analysis	Terminated early after planned interim analysis due to lack of efficacy of VPA.
ECOG 3999; NCT00046930 Cripe, 2010 (81)	449 Age >60 y, newly diagnosed AML (de novo or secondary) or high-risk MDS (RAEB-t or high-risk RAEB). Stratified by age (<70 y, ≥70 y) and leukemia type	Induction + consolidation Zosuquidar	AraC + DNR ± zosuquidar (or placebo) AraC (100 mg/m^2/d CI, d 1-7), DNR (45 mg/m^2/d over 10-15 min iv, d 1-3), zosuquidar (550 mg iv, 1 hr prior to each dose of DNR and continued for additional 5 h) or placebo 2nd induction cycle in patients with persistent AML in bone marrow 2 cycles consolidation therapy if CR or CRp: 1st cycle AraC (1500 mg/m^2, 1-h infusion q12h, d 1-6 if age <70; q24h, d 1-6 if age ≥70); 2nd cycle identical to induction regimen	CR+CRp: 51.9% vs 48.9% CR: 46.2% vs 43.4%, p=0.617	Median 7.2 m vs 9.4 m; 2-y OS 20% vs 23%, p=0.281	Early mortality (42 d) 22.2% vs 16.3%, p=0.158; PFS median 3.0 m vs 2.0 m, p=0.165. Increased frequency of gastrointestinal events with zosuquidar, no other differences	Primary outcome OS. 80% power to detect difference in OS, n=450 with 354 deaths; included 2 interim analyses	Zosuquidar did not improve outcome

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[20]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
AMLSG 07-04 NCT00151242; 2004-2009 Schlenk, 2014 [abstract] (247)	1100 Younger adults with AML, age 18-60 y, 29% had a mutation in NPM1	Induction VPA (ATRA)	ICE ± ATRA (+ VPA) vs ICE ± ATRA ICE (2 cycles) ± ATRA 45 mg/m^2 d 6-8 and 15 mg/m^2 d 9-21 and VPA (first 372 pts) ICE (2 cycles) ± ATRA (rest of pts) Consolidation: Transplant if high risk, transplant or 3 cycles AraC if intermediate-risk, AraC for rest	Randomization for VPA stopped at interim analysis on CR (n=372) due to ineffectiveness.	NR	NR	Primary endpoint EFS, 2nd endpoint CR, OS. ITT and per protocol analysis	
China Wei, 2003, 2005 (293,294) [Chinese, English abstract]	65 Acute leukemia, not previously treated	Induction Shengfu	Chemotherapy ± shengfu injection (shenqui fuzheng injection; SFI) Note: chemotherapy type not indicated in abstract	SFI higher but p>0.05	NR	Restoring of peripheral mature neutrophils higher in SFI group, p<0.05; greater increase in CD 4 and CD 4/CD 8 ratio (p<0.05)	NR	SFI could improve immune function
China Xu, 2004 (295) [Chinese, English abstract]	114 AML	Induction TCM	Chemotherapy ± TCM* Chemotherapy: DNR + AraC, homoharringtonine + AraC, IDA + AraC Chemotherapy for M3 pts: ATRA + arsenic trioxide *TCM: traditional Chinese medicine: supplementing Qi, nourishing Yin, and clearing heat principle (SQNYCH)	Significant difference	NR	TCM group: more increase in hemoglobin (p<0.05), platelet (p<0.01); CD 4, CD 4/CD 8 ratio (p<0.05), NK cells (p<0.01)	NR	

6MP, 6-mercaptopurine (mercaptopurine); ADE, AraC + DNR + etoposide; A-HAM, ATRA + HAM = all-trans retinoic acid + high-dose cytarabine + mitoxantrone; ACR, aclarubicin; AMSA, amsacrine; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; ATRA, all-trans retinoic acid; AZA, azacitidine; CI, continuous iv infusion; CR, complete remission (complete response); CRi, complete remission with incomplete recovery; CRp, complete remission without full platelet recovery; CsA, cyclosporin A (cyclosporine); DA, DNR + AraC; DFS, disease-free survival; DNR, daunorubicin; DNX, DaunoXome, a liposomal formulation of daunorubicin; EFS, event-free survival; FLAM, flavopiridol + AraC + MTZ; GO, gemtuzumab ozogamicin; HAA, homoharringtonine + AraC + ACR; HAD, homoharringtonine + AraC + DNR; HAM, high-dose cytarabine + mitoxantrone; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; IDA, idarubicin; ITT, intention to treat; iv, intravenously; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OR, odds ratio; OS, overall survival; po, oral administration (per os); PR, partial response/remission; RAEB-t, refractory anemia with excess of blasts in transformation; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; SAE, severe adverse effect; sc, subcutaneously; std, standard; t-AML, therapy-related AML following treatment of primary malignant disease; TG, 6-thioguanine; TTF, time to treatment failure; VCR, vincristine; VPA, valproic acid

Table 4-13. Induction, planned or ongoing trials Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[21]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
NCT01145846, South Korea; 2010- 2014 Interim analysis; final analysis expected late 2015 Lee, 2012 (299) [abstract] Note: Results presented at ASH, Dec 2015 . Lee, 2015 (300) [abstract]	299 Newly diagnosed AML, age ≤65 y	Induction IDA vs DNR	IDA + AraC vs DNR + AraC IDA (12 mg/m^2/d, 3 d), DNR (90 mg/m^2/d, 3 d), AraC (200 mg/m^2/d, 7 d) 2nd induction cycle if no CR: IDA (12 mg/m^2/d, 2 d) or DNR (45 mg/m^2/d, 2 d); plus AraC (5 d) Consolidation if CR with 4 doses HDAC (3 g/m^2×6d) if good/intermediate-risk cytogenetics, otherwise AraC (1 g/m^2×6d) + etoposide (150 mg/m^2×3d)	80.5% vs 74.7%, p=0.224	OS at median 1046 d follow-up: 4-y OS 51.1% vs 54.7%, p=0.756 4-y RFS 63.5% vs 74.2%, p=0.181 4-y EFS: 44.8% vs 50.7%, p=0.738	Toxicity profiles similar In subset (n=44 pts) with FLT-ITD mutants OS 30.8% vs 61.9%, p=0.030; EFS 31.4% vs 61.9%, p=0.025		No significant differences at interim or final analysis
Polish PALG 2000 Wierzbowska, 2003 (301) [Polish, English abstract; preliminary analysis of first 120 pts]	138 Age >60 y, de novo AML or following MDS	Induction Etoposide	MTZ + AraC + etoposide vs DNR + AraC 2 courses MTZ (6 mg/m^2 iv, d 1-3) + AraC (10 mg/m^2 q12h sc, 7 d) + etoposide (100 mg/d for 7 d) [3rd course if PR or no response; not included in CR results] DNR (45 mg/m^2 iv, d 1-3) + AraC (100 mg/m^2/24 h iv, d 1-7), 1 course [2nd course if PR; not included in CR results]	50% vs 29%; by ITT: 22% vs 23% CR+PR: 69% vs 52%; by ITT 30% vs 41%	OS: no difference, p=0.59 DFS: no difference, p=0.88	Short-term mortality (30 d): 27% vs 19%	Low ITT numbers as data only available for 44% of pts after 2 courses MTZ	
CALGB 10603 (RATIFY); NCT00651261; 2008-2011 (ongoing; expected completion July 2015) Stone, 2011 (302) [abstract] Note: Results presented at ASH, Dec 2015. Stone, 2015 (303) [abstract]	717 Untreated FLT3mut AML, age 18-59 y	Induction + post-remission Midostaurin	Induction: DNR/AraC ± midostaurin DNR (60 mg/m^2/d iv, d 1-3), AraC (200 mg/m^2/d CI, d 1-7), midostaurin (50 mg po twice a day, d 8-21) Consolidation (4 cycles): High dose AraC (3 g/m^2 iv over 3 h q12h, d 1, 3, 5) ± midostaurin (same group as previously); dexamethasone ophthalmic solution along with AraC infusions Maintenance: midostaurin or placebo for 12 cycles	59% vs 54%, p=0.18	Median OS 74.7 m vs 26.0 m, p=0.007 (on-sided); 5-y OS 50.8% vs 43.1%, HR=0.77 (0.63-0.95) EFS: median 8.0 m vs 3.0 m, p=0.0044, 5-y EFS 26.7% vs 19.1%, HR=0.80 (0.67-0.95)	Grade 5 adverse events 5.3% vs 5.0%No statistically significant difference in grade 3+ adverse events	84% power to detect OS improvement from 16.3 m to 20.9 m (HR=0.78), with 509 deaths but analyzed at 359 deaths	Improved EFS and OS in TKD or ITD (low or high mutation burden) types of FLT3 AML

[21] Results for agents in parentheses are reported in the relevant tables

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison for induction[21]	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MD Anderson; ≈2011- ongoing (continues to accrue) Mathisen, 2012 (106) [abstract] Note: Interim results presented at ASH, Dec 2015. Koller, 2015 (304) [abstract]	158 Median age 55 y, newly diagnosed AML	Reinduction Clofarabine vs fludarabine	IDA + AraC plus either clofarabine or fludarabine IDA (10 mg/m^2/d, 3 d), AraC (1 g/m^2/d, 5 d), clofarabine (15 mg/m^2/d, 5 d), fludarabine (30 mg/m^2/d, 5 d) 1 cycle induction + up to 6 cycles consolidation using same drugs with attenuated schedule	72% clofarabine vs 67% fludarabine	2-y OS 48% vs 53%, p=0.45 Median EFS 14 m vs 11 m, p=0.81 Relapse 32% vs 27% Events 53% vs 51%	8-w mortality 1% vs 2% MRD negativity 74% vs 35%, p=0.049	Primary outcome overall response rate (CR + CRp + CRi)	Both effective, better outcome compared to IDA + AraC alone (not included in study)
LAMSA 2007 GOELAMS trial NCT00590837; 2008-2011 https://clinicaltrials.gov/ct2/show/NCT00590837 complete but not published; Note: Results presented at ASH, Dec 2015. Pigneux, 2015 (305) [abstract]	459 (429 evaluable) Age > 60 y, de novo AML and non-poor cytogenetic features, excluded previous MDS	Induction + consolidation (post-remission) Lomustine	IDA + AraC (5+7) ± lomustine IDA (8 mg/m^2/d iv, d 1-5), AraC (100 mg/m^2/d iv , d 1-7), lomustine (200 mg/m^2 po , d 1) Pts in CR or CRi were randomized to consolidation with IDA (8 mg/m2/d iv, d 1-3) + AraC (100 mg/m2/d s/cut, d 1-5) ± lomustine (80 mg po, d 1) according to the initial randomization; then 6 courses reduced dose consolidation with IDA (8 mg/m2/d iv, d1) + AraC (100 mg/m2/d s/cut, d 1-5) ± lomustine (40 mg po, d1). Maintenance for 6 m with alternating purinethol and methotrexate	CR + CRi 84.7% vs 74.9%, p=0.01 Primary resistance 7.7% vs 21.4%, p<0.0001	2-y OS 56% vs 48% 2-y EFS 41% vs 26%, p=0.01 CIR 41.2% vs 60.9%, p=0.003	Induction deaths 7.7% vs 3.7%, p=0.11 Grade 3-4 toxicities higher with lomustine after induction and consolidation: neutropenia 23 d vs 21 d (p=0.0001) and 11 d vs 7 d (p<0.0001); thrombopenia 19 d vs 14 d (p<0.001) and 11 d vs 4 d (p<0.001)	Primary outcome OS; secondary outcome response rate, CIR, EFS, safety	

AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; CI, continuous iv infusion; CIR, cumulative incidence of relapse; CR, complete remission (complete response); CRi, complete remission with incomplete recovery; CRp, complete remission without full platelet recovery; DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; HAM, high-dose cytarabine + mitoxantrone; HCT, hematopoietic cell transplantation; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; IDA, idarubicin; ITT, intention to treat; iv, intravenously; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OS, overall survival; po, oral administration (per os); PR, partial response/remission; RFS, recurrence-free survival; sc, subcutaneously; std, standard

Table 4-14. Consolidation trials (Including those with Induction plus second randomization)

Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
HOVON 43 AML; SAKK 30/01; ISRCTN77039377; NTR212; 2000-2006 Lowenberg, 2009, 2010 (45,46)	232 (813) Age 60-83 y, median 67 y; AML (including 169 with s-AML) or high-risk refractory anemia (n=39, 5%)	Consolidation (Induction) GO vs none	Induction: (see Table 4-3): AraC + DNR (escalated) vs AraC + DNR (conventional dose) If CR, then either transplant or 2nd randomization to GO (6 mg/m^2; 25% of pts) or none (60% of pts). GO for up to 3 cycles, only 58% received all 3 cycles	59%	5-y OS: 28% GO vs 21%; 2-y OS 45% vs 45%, both ns 5-y DFS 17% GO vs 16%, ns; 2-y DFS 34% vs 26%	NR	ITT. GO post-remission: DFS primary endpoint. 240 pts to give 78% power to detect DFS HR=0.67 from 2nd randomization, increase in 12 m DFS from 40% to 54%	Post-remission treatment with GO did not provide benefit
GOELAM SA3; 1992-1994 Witz, 1998 (270)	240 Age 55-75 y, newly diagnosed AML	Consolidation + maintenance vs maintenance (Induction GM-CSF)	Induction: IDA + AraC plus [GM-CSF vs placebo] (see Table 4-11) Consolidation (n=48): Pts with CR age 55-64 y randomized to receive consolidation course [AraC (1 g/m^2 as 3-h infusion q12h, d 1-4) + AMSA (100 mg/m^2 iv, d 5-7)] followed by maintenance or maintenance alone (both arms without GM-CSF)	62%	OS, consolidation vs none: 76% vs 46%, p=0.052 Consolidation subgroup: DFS 67% GM-CSF vs 25% no GM-CSF, p=0.031 No consolidation subgroup: 57% GM-CSF vs 0% no GM-CSF, p=0.0002	NA	Only for induction	
MRC AML14; LRF AML14; ISRCTN62207270; 1998-2005 Burnett, 2009 (76); Burnett, 2005 (77) [abstract]	250 (1273) Predominantly ≥60 y (younger pts permitted if not fit to enter other trials for younger pts), AML (de novo or secondary) or high-risk MDS	Consolidation (Induction) Common then IDA + AraC + etoposide (4th course) vs no more	Induction (see Tables 4-1, 4-3, 4-12): DNR (50 vs 35 mg/m^2) + AraC (200 vs 400 mg/m^2) Subgroup of 601 pts randomized to DNR 50, DNR 35, or DNR 35 + PSC-833 Pts with CR received MTZ (d 1-3) + AraC (q12h, d 1-3) then randomized to no further treatment or a 4th course consisting of IDA (10 mg/m^2 slow iv, d 1, 3) + AraC (100 mg/m^2 by 2h infusion q12h, d 1-3) + etoposide (100 mg/m^2 by 1h infusion daily, d 1-3)	54%	OS, 4th course vs only 3 courses: 22% vs 20%, p=0.7 5-year relapse, 4th course vs only 3 courses: 80% vs 84%, p=0.3	NR	ITT analysis	No difference between 3 and 4 courses

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Finland; 1986-1992 Elonen, 1998 (84)	139 (248) Age 16-65 y, median 46 y, de novo AML	Consolidation Common then 4 more courses (various) or no more	2 courses induction (DAT or AMSA-HDAC) Pts in CR randomized to 2 additional (short arm) or 6 additional (long arm) cycles after induction First 4 courses (2 courses induction + 2 courses consolidation) were same in both arms: Cycle 1, DAT: DNR (50 mg/m^2 iv, d 1, 3, 5) + AraC (50 mg/m^2 iv bolus, d 1 plus 100 mg/m^2 CI, d 1-9) + TG (75 mg/m^2 po q12h, d 1-9) Cycle 2: as cycle 1 unless no response and then given HDAC + AMSA Cycle 3: AMSA (115 mg/m^2 iv, d 1-5) + AraC (3 g/m^2 iv as 3-h infusion q12h, d 1-2) Cycle 4: AraC (2 g/m^2 as 3-h infusion, q12h, d 1-5) + DNR (30 mg/m^2 iv, d 6-8) <u>In Long Arm:</u> Cycles 5 and 6: ACR (25 mg/m^2 iv, d 1-7) + etoposide (60 mg/m^2 iv q12h, d 1-5) + VCR (1 mg/m^2 iv, d 1-5) + prednisone (60 mg/m^2 po, d 1-8) Cycle 7: DNR (30 mg/m^2 iv, d 1-3) + AraC (500 mg/m^2/d CI, d 1-3 and 10-12) Cycle 8: AMSA (115 mg/m^2 iv, d 1-5) + AraC (2 g/m^2 as 3-h infusion q12h, d 1-2)	77%	OS median 43 m vs 39 m, p=0.421 RFS median 21 m vs 17 m, p=0.777	The median time from diagnosis to the recovery of neutrophil counts after the last (fourth) cycle in the short arm was 155 d (range 113–330 d), and to the recovery after the last (eighth) cycle in the long arm was 339 d (range 253–519 d)	NR	8 cycles were not better than 4 cycles
Hokuriku Hematology Oncology Study Group; 2002-2006 Fukushima, 2012 (306)	21 (26) Newly diagnosed AML; excluded s-AML, t-AML	Consolidation AraC dose in 2 cycles (6-8 cycles common)	Induction: BHAC + MTZ + etoposide + 6MP (repeated if not CR) For pts with CR: 4 or 5 courses of consolidation and 4 or 5 courses intensification, of which there was a difference in the two arms for only one course, as follows Intermediate vs high-dose AraC for consolidation cycle 2 and intensification cycle 3 Intermediate: AraC (1 g/m^2 in 1-h infusion q12h, 5 d) HDAC: AraC (2 g/m^2 in 1-h infusion q12h, 5 d)	84.6%	OS NR 4-y RFS 49% vs 56%, p=0.86	Severe leukocytopenia with HDAC, no difference in grade 3+ infections	NR	Larger scale trials comparing AraC dose should be conducted

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
CALGB 8525; 1985-1990 Mayer, 1994 (34); Bloomfield, 1998 (35)	596 (1088) Age 16+ y, median 52 y, newly diagnosed AML	Consolidation AraC dose	Induction: DNR (45 g/m^2, d 1-3; 30 mg/m^2 age 60+) + AraC (200 mg/m^2, 7 d); 2nd course if not CR Pts with CR: 4 courses AraC at 100 mg/m^2 vs 400 mg/m^2 vs 3 g/m^2 AraC (100 mg/m^2 CI, 5 d); AraC (400 mg/m^2 CI, 5 d); AraC (3 g/m^2 by 3-h infusion q12h, d 1, 3, 5) All received 4 courses monthly maintenance (DNR + AraC) Due to toxicity, starting in 1989 patients age >60 y were not given the highest dose	64%	4-y OS after randomization: 31%, 35%, 46%, p=0.04; HR =0.74 (0.57-0.96) 3 g vs 100 mg; HR=0.78 (0.61-1.00) 400 mg vs 100 mg Subgroup age ≤60 y: 35%, 40%, 52%, p=0.02 Survival for subgroup age 60+: was 9% Median follow-up 52 m: 4-y DFS 21%, 25%, 39%, p=0.003; 3 g vs 100 mg HR=0.67 (0.53-0.86); 400 mg vs 100 mg HR=0.75 (0.60-0.94) Subset age ≤60 y: DFS 24%, 29%, 44%, p=0.002 Age >60 y: DFS: <16% all groups, p=0.19	Probability of remaining in continuous CR after 4 y: age ≤60 y, 24%, 29%, 44%, p=0.002; age >60 y, 16% or less in each group. Only 29% of pts age >60 y could tolerate high-dose AraC; 32% of these pts age >60 had serious central nervous system abnormalities compared with none with lower doses Courses requiring hospitalization: 16%, 59%, 71%; courses requiring platelet transfusion: 28%, 80%, 86%; serious central nervous system toxicity: 0%, 0%, 12%. <u>Cytogenetic subgroups</u> (n=285) continuous CR after 5 y: CBF AML16%, 57%, 78%, p<0.001; normal karyotype AML 20%, 37%, 40%, p=0.01; other types, 13%, 13%, 21%	NR	Dose response effect for pts age <60 y

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
GOELAM; BGMT-95; 1995-2001 Pigneux, 2007 (82); Pigneux, 2010 (83)	101 (364) Age ≥60 y, de novo AML; excluded s-AML	Consolidation (Induction) Common then AraC + IDA vs no more	Induction (see Table 4-12): IDA + AraC + lomustine vs IDA + AraC Pts with CR received IDA + AraC sc; if stable then 2nd randomization (n=101) to intermediate-dose AraC (500 mg/m^2 q12h over 2h, d 1-4) + IDA + maintenance or maintenance alone	62%	2-y OS 47% AraC vs 46.5%, p=0.96	NR	ITT. Primary outcome CR and OS. Sample size of 350 pts to detect increase of 15% in CR and 20% in 2-y survival with power of 90%	Adding intermediate-dose AraC to consolidation did not improve outcome
Egypt Ahmad, 2011 (307)	71 (89) Age 18-60 y, median 37 y, de novo AML with known K-RAS status (mutant or wild type)	Consolidation AraC dose	Induction: DNR (45 mg/m^2/d iv, 3 d) + AraC (200 mg/m^2/d CI, 7 d) Pts with CR: 4 cycles HDAC vs low-dose AraC HDAC: (400 mg/m^2 CI, 5 d), low-dose AraC (100 mg/m^2 CI, 5 d) All received maintenance with 4 monthly treatments AraC (100 mg/m^2 q12h, 5 d) + DNR (45 mg/m^2, d 1)	83%	4-y OS, mut RAS: 90.9% HDAC vs 21.4%, p=0.001 4-y OS, wild RAS: 57.3% vs 61.4%, p=0.258 4-y DFS, mut RAS: 69.2% vs 20.0%, p=0.001 4-y DFS, wild RAS: 73.1% vs 27.3%, p=0.031	NR	NR	HDAC better than low dose; effect greater in mut RAS AML
Switzerland SAKK; 1985-1992 Fopp, 1997 (85)	137 (276) Age 15-65 y, previously untreated de novo AML	Consolidation AraC dose (DNR in both)	Induction (2 courses): DNR (45 mg/m^2, d 1-3) + AraC (100 mg/m^2 CI, 7 d) + VCR (0.8 mg/m^2 iv, d 10) then AMSA (120 mg/m^2/d iv, 5 d) + etoposide (80 mg/m^2/d CI, 5 d) Pts in remission (CR or PR) randomized to 1 course consolidation with std vs high-dose AraC Std: AraC (100 mg/m^2 CI, 7 d) + DNR 45 mg/m^2/d, d 1-3) High: AraC (3 g/m^2 as 1-h infusion, q12h, 6 d) + DNR 45 mg/m^2/d, d 1-3)	61% CR; 14% PR	4-y OS 34% vs 45%, p=0.07; Median OS 24.6 m vs 32.6 m 4-y OS in pts with CR: 38% vs 48%, p=0.10; median 27.5 m vs 43.3 m 4-y EFS 22% vs 31% (p=0.018 in text, p=0.12 in table); median EFS 10.8 m vs 12.2 m 4-y DFS in pts with CR: 25% vs 37%, p=0.09; median 8.5 m vs 15.2 m; pts age <40 y median 8.1 m vs 10 m, p=0.98; pts age ≥40 y median 9.4 m vs 16.6 m, p=0.04	Grade 3+ toxicities 21% vs 58%, p<0.0001 (infections, gastrointestinal, neurologic, vomiting, diarrhea, mucositis). HDAC reduced hazard of progression (HR=0.69, p=0.08) and death (HR=0.70, p=0.13)	ITT. Planned to assess absolute 30% increase in EFS at 3 y (15% vs 45% EFS) with 80% power, required minimum 50 pts/arm	HDAC is superior

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
SWOG 8600; 1986-1991 Weick, 1996 (161); see Appelbaum 1997 (162) for long-term survival	245 (723) Age <65 y, previously untreated AML, de novo or secondary. Stratified by age (<50 y, 50-64 y)	Consolidation (Induction) AraC dose (DNR in both)	Induction (see Table 4-1): HDAC + DNR vs std-dose AraC (SDAC, 200 mg/m^2/d) + DNR Those with CR to SDAC were randomized to 2 additional courses SDAC + DNR (d 6-7), or to one course HDAC (d 1-5) + DNR (d 6-7). DNR dose was reduced to 30 mg/m^2 for ages 50-64. Initially pts age <50 y on HDAC received AraC at 3 g/m^2 (HDAC-3) but after 2 years the monitoring committee determined neurotoxicity was too high and HDAC was reduced to 2 g/m^2 for all ages. Near the end of the study they decided HDAC (2 g/m^2) + DNR was also too toxic and induction randomization was stopped early.	54%	4-y OS: Age <50: 28% (9%-46%) HDAC-3 vs 23% (11%-35%) HDAC-2 vs 34% (23%-45%) SDAC Age 50-64: 19% (7-31%) HDAC-2 vs 14% (4-24%) SDAC 4-y DFS Age <50: 20% (4%-36%) HDAC-3 vs 14% (4%-25%) HDAC-2 vs 24% (15%-34%) SDAC Age 50-64: 17% (5-28%) HDAC vs 4% (0%-10%) SDAC	NR	600 pts for induction to ensure sufficient pts for consolidation study; study size increased Dec 1988 when HDAC dose reduced (485 pts SDAC, 188 pts HDAC) to give 220 pts for consolidation randomization in ratio 130:90 to give 86% power to detect HR of 1.5 for DFS. Induction portion closed slightly early due to toxicity.	Differences not significant due to small numbers of pts per group and wide confidence intervals
German SAL AML96; 1996-2003 Schaich, 2011 (88)	447 (933) Age 15-60 y, median 47 y, untreated AML	Consolidation AraC dose (MTZ in both)	Induction with MTZ (10 mg/m^2, d 4-8) + AraC (100 mg/m^2 CI, d 1-8) + etoposide (100 mg/m^2, d 4-8) → AraC (1g/m^2, q12h, d 1-5) + AMSA (100 mg/m^2, d 1-5) Pts with CR randomized to intermediate-dose AraC (1 g/m^2 q12h, d 1-6) + MTZ (10 mg/m^2, d 4-6) vs HDAC (3 g/m^2 q12h, d 1-6) + MTZ (10 mg/m^2, d 4-6) Pts within good-risk group received additional cycle of AraC + AMSA as in 2nd cycle of induction	66%	5-y OS 30% vs 33%, p=0.77 As treated: 5-y OS 48% vs 56%, p=0.12 5-y DFS 37% vs 38%, p=0.86 As treated: 5-y DFS 41% vs 45%, p=0.32	Prolonged neutropenia and higher transfusion demands with HDAC, otherwise comparable adverse events	ITT. DFS primary endpoint. Assuming 2-y DFS of 40%, study was powered to identify a 10% difference in survival with power of 80%. Planned 400 pts with CR and no HSCT	HDAC did not improve outcome compared with intermediate dose

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Russian AML-01.10; (AML-10); NCT01587430; 2010-2014 Savchenko, 2014 (308) [abstract, interim results]; Parovichnikova, 2014 (309) [in Russian]	145 (250) Age 16-60 y, de novo AML	Consolidation AraC and IDA dose (MTZ in both)	Randomized before treatment start Induction (2 courses): DNR (60 mg/m^2, 3 d) + AraC (100 mg/m^2 bid iv, d 1-7 in the 1st course; 200 mg/m^2/d CI, d 1-7 in the 2nd course) Consolidation (2 courses): IDA (12 mg/m^2 × 3 + MTZ (10 mg/m^2 ×3 + AraC (100 mg/m^2 bid iv, d 1-7) vs HDAC (AraC 1 g/m^2 bid iv, d 1-3) + IDA (8 mg/m^2, d 3-5) + MTZ (10 mg/m^2, d 3-5) After consolidation all received maintenance with AraC (100 mg/m^2 bid iv, d 1-5) + 6MP (50 mg/m^2, d 1-5)	72.9%	3-y OS 43% vs 38%, ns 3-y DFS 62% vs 51%, ns DFS in pts who completed consolidation: favourable cytogenetics 85% vs 85%, intermediate 65% vs 57%, poor 20% vs 22%	NR	ITT	
Australasian LLG AML7; 1995-2000 Bradstock, 2005 (87); See Bradstock, 2001 (261) for induction	202 (292) Age 15-60 y, de novo AML	Consolidation (Induction GCSF) AraC dose (IDA + etoposide in both; ICE vs IcE)	Induction (see Table 4-11): ICE [AraC (3g/m^2 q12h, d 1, 3, 5, 7), IDA (12 mg/m^2, d 1-3; reduced to 9 mg/m^2 after 44 pts randomized due to toxicity), etoposide (75 mg/m^2, d 1-7)]; initial 114 pts randomized to GCSF or not Pts with CR randomized to further ICE (1 cycle) or 2 attenuated cycles IcE (AraC 100 mg/m^2/d × 5; IDA × 2, etoposide × 5)	80%	After randomization, 3-y OS: 61% vs 62%, p=0.91 3-y RFS 49% vs 46%, p=0.66	Cumulative incidence of relapse 43% vs 51%, p=0.31. ICE more toxic than IcE: increase in neutropenia duration, diarrhea, nausea and vomiting, stomatitis; gastrointestinal, cerebellar, renal, ocular toxicities	ITT. Target of 200 in consolidation, 80% power to detect increase in 3-y RFS from 47% to 71%	No additional benefit to intensive consolidation (HDAC)
German AML Intergroup Study C: 2000-2005, NCT00209833 (AML 01/99) Buchner, 2012 (196)	235 Age 16-60 y, median 47 y, primary AML or s-AML	Consolidation DNR (AraC in both)	Study C (n=235): double induction with standard-dose AraC combination + early consolidation by intermediate-dose AraC (1 g/m^2 q12h, d 1-4) + DNR Late consolidation randomized to HDAC (3 g/m^2 q12h, d 1-6) + DNR vs autologous SCT If bad response to induction or high-risk karyotype: FLAG-IDA Common control arm AraC (100 mg/m^2/d CI, d 1-7) + DNR (60 mg/m^2/d iv over 2 h, d 3-5); 2nd course starting on d 22; 3 cycles consolidation at monthly intervals: HDAC (3 g/m^2 over 3 h q12h, d 1, 3, 5)	76%	OS 47.5% vs 44.3% (common arm), p=0.583 5-y RFS 47.0% vs 44.8% (common arm), ns EFS 38.5% vs 31.5%, p=0.106	NR	NR	

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
CALGB 8923; 1990-1993 Stone, 1995, 2001 (278,279)	169 (388) Age ≥60 y, newly diagnosed de novo AML; included M0 after March 1991; excluded APL after October 1992; excluded pts with prior MDS	Consolidation (Induction GM-CSF) AraC + MTZ vs AraC (lower dose)	Induction (see Table 4-11): DNR (3 d) + AraC (7 d) with GM-CSF vs placebo Second randomization (n=169) if stable remission and physician judged the pt could tolerate highly myelosuppressive therapy: AraC (100 mg/m^2/d CI, 5 d; for 4 monthly courses) vs AraC (500 mg/m^2 q12h [250 mg/m^2 over 15 min then 250 mg/m^2 over 3 h]) + MTZ (5 mg/m^2 q12h) for 6 doses; given 2 courses 60 d apart GM-CSF not given after post-remission therapy	53%	Median OS from 2nd randomization: 1.6 y AraC vs 1.3 y AraC + MTZ 5-y OS, GM-CSF: 11% AraC vs 21% AraC + MTZ; placebo: 16% AraC vs 18% AraC + MTZ, all ns 2nd randomization: Median DFS 11 m AraC vs 10 m AraC + MTZ, p=0.67; relapse rates 77% vs 82% 5-y DFS, GM-CSF: 5% AraC vs 14% AraC + MTZ; placebo: 16% AraC vs 11% AraC + MTZ, all ns	NR	ITT. 163 pts for post-CR regimens with 80% power to detect a failure rate ratio of 1.67 with 1.5 y follow-up	AraC/MTZ more toxic but not more effective and therefore has no benefit post-remission in pts age ≥60
German SAL AML2003; 2003-2009 Schaich, 2013 (89)	442 (1179) Age 16-60 y, median 48 y, untreated AML. De novo AML, s-AML, or RAEB2	Consolidation AMSA + MTZ + AraC vs HDAC alone	Induction (2 cycles): AraC (100 mg/m^2 CI, d 1-7) + DNR (60 mg/m^2, d 3-5) Pts with CR were treated with std HDAC vs multi-agent consolidation; randomization was done upfront (prior to induction) HDAC (3 cycles) (3 g/m^2 q12h, d 1, 3, 5) Multi-agent (3 cycles): 2 cycles MTZ (10 mg/m^2/d, d 4-6) + AraC (1 g/m^2 q12h, d 1-6) then 1 cycle AMSA (100 mg/m^2/d, d 1-5) + AraC (1 g/m^2 q12h, d 1-5)	65%	3-y OS 69% vs 64%, p=0.18 Per protocol: 72% vs 63%, p=0.04 3-y DFS 46% vs 48%, p=0.99; per protocol p=0.29 (HDAC better)	Multi-agent group had more gastrointestinal and hepatic toxicity, higher rate of infection and bleeding, longer time to neutrophil and platelet recovery	ITT. Sample size for consolidation calculated post-hoc. Based on 269 events a HR=0.68 would have been detected with 80% power; 3-y DFS difference of 13% (58% vs 45%).	Multi-agent consolidation did not improve outcome and was more toxic
CALGB 9222; Moore, 2005 (90)	309 (474) Age <60 y, untreated de novo AML	Consolidation Multiple agents vs HDAC	Induction: DNR (45 mg/m^2, 3 d) + AraC (200 mg/m^2/d, 7 d) Pts in CR randomized to: HDAC → etoposide + cyclophosphamide → diaziquone + MTZ + GCSF vs 3 courses HDAC HDAC (3 g/m^2 iv over 3 h q12h, d 1, 3, 5), etoposide (1800 mg/m^2 CI over 25-26 h), cyclophosphamide (50 mg/kg as 2-h infusion, d 2, 3), diaziquone (28 mg/m^2 CI, 3 d), MTZ (12 mg/m^2 slow iv, 3 d), GCSF (5 µg/kg/d sc, d 4 until recovery)	72%	5-y OS 46% vs 44%, p=0.89 DFS, median from randomization 1.0 y vs 1.1 y, p=0.66; 5-y DFS 30% vs 35%	Toxicity greater with multi-agent chemotherapy	ITT. Accrual of 3 y, follow-up of 1.5 y with 450 (180 randomized) pts to give 0.80 power to find difference in DFS	Similar outcomes but multiagent regimen more toxic

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Japan: JALSG AML201; C000000157; 2001-2005 Ohtake, 2011 (51); Miyawaki, 2011 (86)	781 (1057) Age 15-64 y, de novo AML excluding FAB M3 or pre-diagnosed MDS	Consolidation (Induction) HDAC vs std chemo (MTZ, AraC, DNR, etoposide)	Induction (see Table 4-4): High-dose DNR + AraC vs std dose IDA + AraC Patients with CR (n=781) were randomized to 3 courses HDAC (2 g/m^2 q12h for 5 d) vs 4 courses std-dose chemotherapy with AraC at 100 mg/m^2/d CI [course 1: MTZ + AraC; course 2: DNR + AraC; course 3: ACR + AraC; course 4: AraC + etoposide + vindesine]	78%	5-y OS, 58% HDAC vs 56% std, p=0.954 overall; IDA induction: 58% vs 57%, p=0.79; DNR induction 58% vs 56%, p=0.71 Favourable cytogenetics 75% vs 66%, p=0.174 5-y DFS 43% vs 39%, p=0.724 overall; IDA induction: 42% vs 41%; DNR induction 44% vs 37% Favourable cytogenetics 57% vs 39%, p=0.050	Both regimens tolerated. More grade 3-4 infections in HDAC group (14.5% std vs 20.9% HDAC, p<0.001). More effect on WBC and requirement for GCSF in HDAC group.	ITT. <u>Post-remission:</u> 280 pts/group for 80% powered to demonstrate 10% superiority in 5-y DFS of HDAC (40% vs 30%)	No difference in survival between two consolidation arms. Benefit of HDAC only in favorable cytogenetic group.
Japan: JALSG AML92 Substudy; 1992-1994 Motoyoshi, 1997 (310) [Japanese]; Ohno, 1997 (311); see Miyawaki, 1999 (234) for induction details and results	182 (655) Age 15-70 y; AML in complete remission after 1-2 courses induction in the AML92 study	Consolidation (Induction) M-CSF (MTZ, AraC, DNR, BHAC in both)	Induction: DNR + BHAC + 6MP ± etoposide Consolidation plus [M-CSF vs placebo] M-CSF (human urinary macrophage colony-stimulating factor; mirimostim): 8×10^6 U/d by 2-h infusion, from 1 d after end of each consolidation chemotherapy for 14 d Consolidation according to AML92 protocol: 1st cycle: MTZ (7 mg/m^2/d by 30 min infusion, 3 d) + AraC (200 mg/m^2/d CI, 5 d). 2nd cycle: DNR (50 mg/m^2/d by 30 min infusion, 3 d) + etoposide (100 mg/m^2/d by 1-h infusion, 5 d) + BHAC (200 mg/m^2/d by 3-h infusion, 7 d) + 6MP (70 mg/m^2/d po, 7 d) 3rd cycle: BHAC (200 mg/m^2/d by 3-h infusion, 7 d) + ACR (14 mg/m^2/d by 30-min infusion, 7 d) Intrathecal methotrexate (15 mg), AraC (40 mg) and prednisolone (10 mg) given after each course	NR	DFS at median 42 m after start of consolidation: 41.3% M-CSF vs 30.8% placebo, ns DFS age 15-29: 65.6% vs 10.1%, p=0.013 DFS age 30-70: 37.0% vs 39.4%	Febrile neutropenia duration (p=0.00285) and incidence (p=0.02065) reduced; shorter recovery time for neutrophils (p=0.0348) and platelets (p=0.0364). Relapse rate 54.0% vs 70.8% overall; 34.4% vs 89.9% age 15-29, p=0.013	NR	

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Japan: JALSG GML200; UMIN-CTR (Japan): C000000220, C000000224; 2000-2005 Wakita, 2012 (185)	123 (245) Age 65-80 y, median 71 y, newly diagnosed AML, excluding FAB-M3 or pre-diagnosed MDS	Consolidation (Induction) Ubenimex (BHAC, MTZ, DNR, etoposide, ACR in both arms)	Induction (see Table 4-3): Fixed-schedule or response-oriented induction with DNR + BHAC All patients who had achieved CR were randomized to receive 3 courses of consolidation therapy with or without ubenimex (30 mg daily during consolidation + 3 more months) Consolidation: cycle 1 BHAC + MTZ; cycle 2 BHAC + DNR + etoposide; cycle 3 BHAC + ACR	62%	Pts with CR: 4-y OS 32.3% ubenimex vs 18.7% control, p=0.1 (median 752 d vs 489 d) Consolidation: 4-y RFS 16.4% ubenimex vs 10.1%, p=0.014 (median 384 d vs 229 d)	NR	ITT. Primary endpoint of 1st randomization was CR. 98 pts/group to have 70% power to demonstrate 10% non-inferiority in CR (60% vs 55%). Primary endpoint of 2nd randomization was RFS.	Ubenimex improved RFS, but effect on OS was not statistically significant
EORTC/GIMEMA AML-13; 1995-2001 Jehn, 2006 (313); see Amadori, 2005 (262) for induction results	346 (722) Age 61-80 y, median 68 y, newly diagnosed AML (including s-AML)	Consolidation (Induction GCSF) mini-ICE admin (iv vs oral) [IDA, AraC, etoposide]	Induction (see Table 4-11): 4 arms, 2×2 design: GCSF or not during induction (MICE), then GCSF or not after chemotherapy Pts with CR were randomized (n=346) to 1 course consolidation with either iv or oral mini-ICE. This was followed by a 2nd course or myeloablative chemotherapy with autoPBSC support in the younger cohort (<70 years of age) as chosen by the centre prior to the trial start date iv mini-ICE: IDA (8 mg/m^2/d iv, d 1, 3, 5), AraC, (100 mg/m^2/d CI, d 1-5), etoposide (100 mg/m^2 as 1-h infusion, d 1-3) Oral Mini-ICE: IDA (20 mg/m^2/d po, d 1, 3, 5), AraC (50 mg/m^2 q12h sc, d 1-5), etoposide (100 mg/m^2 q12h po, d 1-3)	54%	OS from 2nd randomization, median 4.4 y follow-up: median OS 17.8 m iv vs 15.7 m, p=0.19 3-y OS 30% vs 25%, p=0.35 At median 4.4 y follow=up: median DFS 10.4 m iv vs 9 m, p=0.15; 3-y DFS 21% vs 13%, p=0.15	Consolidation: instantaneous risk of death or relapse 17% higher in oral group, HR=1.18 (0.94-1.49) Non-infusional arm had more grade 3-4 vomiting (10% vs 2%, p=0.001), diarrhea (10% vs 4%, p=0.03) and shorter time to platelet recovery (median 19 vs 23 d, p=0.02) and hospitalization (mean 15 d vs 27 d, p<0.0001) 3-y cumulative incidence of relapse 67% iv vs 79%	ITT. Median DFS expected to be 10 m in iv arm and 2-y DFS 20%. A 10% loss or 12% increase in 2-y DFS would be clinically important and required 255 events with 80% power. HR of 1.43 or 0.7. 290 events reported.	No significant difference in anti-leukemic effect. Non-infusional required less hospitalization

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MRC AML15; ISRCTN17161961; 2002-2007 induction; 2002-2009 consolidation Burnett, 2011 (6); Burnett, 2013 (7); Pallis, 2011 (172) [p-glycoprotein]	1440 (3106). Effect of GO consolidation, n=948 Age >15 y, Predominantly <60 y, untreated AML (de novo or secondary), APL excluded. Children age 0-14 (n=87) allowed in some arms	Consolidation (Induction) MACE → MidAC vs AraC (dose); GO	Induction (see Tables 4-2, 4-8, 4-10): DA (DNR + AraC) ± GO vs FLAG-IDA (fludarabine + AraC + GCSF + IDA) ± GO vs ADE (AraC + DNR + etoposide) [± GO starting 2005] Consolidation if CR and transplant not scheduled: randomized for 2 cycles, 3 regimens ± GO (GO only in 1st consolidation cycle); plus randomization to additional cycle (5th cycle; AraC 1.5 g/m^2) or not (N=227) MACE ± GO → MidAC vs AraC (1.5 g/m^2) ± GO → AraC (1.5 g/m^2) vs AraC (3 g/m^2) ± GO → AraC (3 g/m^2) GO in all groups (when given) was 3 mg/m^2 d 1 MACE: AMSA (100 mg/m^2, d 1-5) + AraC (200 mg/m^2 CI, d 1-5) + etoposide (100 mg/m^2, d 1-5) MidAC: MTZ (10 mg/m^2/d slow iv, d 1-5) + AraC (1 g/m^2 by 2h iv infusion q12h, d 1-3) AraC 1.5: AraC (1.5 g/m^2 iv over 4 h, q12h, d 1, 3, 5) AraC 3.0: AraC (3.0 g/m^2 iv over 4h, q12h, d 1, 3, 5) Note: patients with more than 15% residual blasts in a marrow sample taken at least 18-21 d from the end of course 1 were defined as high risk irrespective of cytogenetics	85%	No OS difference with GO consolidation MACE vs AraC, OS 52% vs 52%, HR=0.92, p=0.3; censored 64% vs 60%, p=0.06 AraC 3 g vs 1.5 g, OS 53% vs 47%, HR=1.06, p=0.6 By cytogenetic risk groups, MACE better for adverse risk: OS 39% vs 0%, p=0.0004); no difference for favorable or intermediate risk groups No RFS difference with GO consolidation MACE/MidAC vs AraC: RFS 41% vs 40%, p=1.0; recurrence 49% vs 54%, p=0.3 AraC 3 g vs 1.5 g: RFS 42% vs 34%, p=0.1; relapse 51% vs 60%, p=0.06 5th Course AraC. No advantage	MACE/MidAC associated with more toxicity and myelosuppression, slower neutrophil and platelet recovery (p<0.001). Modest differences in hematologic toxicity for 3 vs 1.5 g/m^2 AraC, but more supportive care and hospitalization with 3 g/m^2. Deaths by cytogenetic group, AraC vs MACE: favourable OR=0.76 (0.48-1.20), intermediate OR=0.89 (0.74-1.08), adverse OR=3.17 (1.68-5.97) AraC 3g vs 1.5 g: favourable OR=0.68 (0.34-1.38), intermediate OR 1.24 (0.93-1.64), adverse OR=0.52 (0.23-1.19)	ITT Non-GO questions: 800 pts in consolidation to give 80% power to detect a 10% difference in OS	No benefit of GO during consolidation MACE/MidAC similar to AraC but superior in high-risk (unfavourable cytogenetics) pts

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MRC AML12; ISRCTN17833622; 1994-2002 Burnett, 2010 (153); Lowenberg, 2009, 2010 (45,46)	992 (2934) Age <60 y, median 41 y, de novo or s-AML / t-AML (n=239) and high-risk MDS; 16.7% were age 0-14 y (children) of which all but 2 pts were in the MAE vs ADE comparison; 2.9% age ≥60. Due to inclusion of children in MAE vs ADE, results cannot be directly compared with H-DAT/ S-DAT results	Consolidation (Induction) MACE then MidAC vs ICE/MidAC	Induction (see Tables 4-1, 4-5, 4-9): MAE (MTZ + AraC + etoposide) vs ADE (AraC + DNR + etoposide); subset randomized to GCSF or not *or* DNR + TG plus high (double) AraC vs standard AraC; ATRA vs none Pts with CR randomized to consolidation (n=992): MACE then randomize to 1 (MidAC) or 2 further courses (ICE then MidAC)	74%	OS, 2 courses consolidation 53% vs 52% one course, p=0.8 Relapse rate (%): 2 courses consolidation 49% vs one course 54%, p=0.1	NR	ITT. 800 pts in consolidation to give 80% power to detect 10% difference in OS	OS for 2-3 courses MAE vs 4-5 courses ADE ns, but OS 2-3 courses ADE worse than 2-3 courses MAE, p=0.003; OS worse with 2-3 courses ADE than 4-5 courses ADE, p=0.08
NCRI AML16; 2006-2012 Burnett, 2012 (58); Burnett, 2012 (67) [abstract]; Burnett, 2015 (151) [abstract]	573 (1880) Older pts suitable for intensive chemotherapy. Generally age >60 y, median 67 y (range 51-84 y); some younger pts if not suitable for trial for younger pts. Untreated de novo AML (77%), secondary AML (14%), or high-risk MDS (8%)	Consolidation; maintenance (Induction) DNR + AraC vs none. Maintenance: AZA vs none	Induction (see Tables 4-2, 4-10): DNR + AraC (DA arm) ± GO vs DNR + clofarabine (DClo arm) ± GO Post-induction, pts with CR were randomized to DNR (50 mg/m^2, d 1, 3) + AraC (100 mg/m^2 q12h, d 1-5) vs none [3 courses vs 2 courses in total including induction; n=573] Maintenance: Pts not planned for allograft were then randomized to AZA (75 mg/m^2/d for 5 d; repeat q6wx9) vs none (n=530)	59%	3rd course (consolidation): 3-y OS 34% vs 34%, p=0.4 3-y RFS 19% vs 21%, p=0.2 5-y OS 25% vs 22%, p=0.4 Maintenance 5-y OS 24% vs 20%, p=0.5; subgroup with consolidation: 26% vs 21%, p=0.7; subgroup without consolidation: 27% vs 18%, p=0.15	In patients who were MRD (minimal residual disease) negative, consolidation resulted in OS of 36% vs 26% without (p=0.09), while maintenance resulted in improved OS (40% vs 13%, p=0.003). In patients MRD+, consolidation resulted in worse OS (11% vs 27%, p=0.03, while maintenance had no effect (OS 20% vs 23%, p=0.9)	ITT. Primary outcome OS. Powered to detect difference of 10% in 2-y OS from 25% to 35% (equivalent to HR=0.76) with 90% power. 800 pts and 552 deaths required.	In pts with CR, no significant benefit for 3rd course (consolidation) Maintenance benefit not significant but appears higher in those without consolidation. Maintenance and consolidation may benefit pts more who are MRD- after 1 course of induction.

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
New Zealand AML-1; 1985-1988 Beard, 1991 (312)	56 (92) Age 13-65 y, de novo untreated AML	Consolidation DNR + AraC vs Etoposide + AMSA	Induction: AraC (100 mg/m^2 iv over 30 min q12h, d 1-7) + DNR (45 mg/m^2/d iv bolus, d 1, 2, 3) [1-2 courses] Pts randomized at diagnosis to receive (if in CR) 3 further courses AraC + DNR vs 3 courses etoposide (100 mg/m^2/d, 5 d) + AMSA (200 mg/m^2, 1 d) DNR (45 mg/m^2 iv bolus, d 1-2), AraC (100 mg/m^2 iv bolus q12h, 5 d), etoposide (100 mg/m^2 by 1-h infusion, 5 d), AMSA (200 mg/m^2 by 2-h infusion, d 1)	61%	Median survival from time of CR: 30 w vs 25 w, p=0.96	Relapse rate 83% vs 84% Etoposide/AMSA group had more frequent vomiting and longer duration severe neutropenia	NR	

6MP, 6-mercaptopurine (mercaptopurine); ADE, AraC + DNR + etoposide; A-HAM, ATRA + HAM = all-trans retinoic acid + high-dose cytarabine + mitoxantrone; A-ICE, ATRA + ICE; ACR, aclarubicin; AMSA, amsacrine; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; ATRA, all-trans retinoic acid; AZA, azacitidine; BHAC, N4-behenoyl-1-ß-D-arabinosylcytosine (widely used in Japan instead of AraC); CI, continuous iv infusion; CR, complete remission (complete response); CRi, complete remission with incomplete recovery; DA, DNR + AraC; DAT, DNR +AraC + 6-thioguanine (TG); DClo, DNR + clofarabine; DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; FLAG, fludarabine + high-dose AraC + GCSF; GCSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GO, gemtuzumab ozogamicin; HAM, high-dose cytarabine + mitoxantrone; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; ICE, idarubicin + cytarabine + etoposide; IDA, idarubicin; ITT, intention to treat; iv, intravenously; MACE, amsacrine + AraC + etoposide; MAE, MTZ + AraC + etoposide; MICE, MTZ + AraC + etoposide; MidAC, MTZ + AraC; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OR, odds ratio; OS, overall survival; PR, partial response/remission; po, oral administration (per os); RAEB-t, refractory anemia with excess of blasts in transformation; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; sc, subcutaneously; SCT, stem cell transplant; std, standard; t-AML, therapy-related AML following treatment of primary malignant disease; TG, 6-thioguanine; VCR, vincristine; WBC, white blood cell

Table 4-15. Consolidation and maintenance trials (or consolidation versus maintenance) Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Southeast Cancer Study Group (USA); 1981-1986 Vogler, 1995 (314)	184 (398) Age 15-50 y, newly diagnosed untreated AML; included M0 and M1 if failed to obtain 90% cytoreduction in marrow cellularity after 10-d trial of prednisone + VCR + methotrexate	Consolidation + maintenance AraC/DNR vs AraC/DNR → AMSA/AZA/TG vs TG/AraC/DNR/maintenance	Induction: DNR (45 mg/m^2 by rapid infusion, d 1-3) + AraC (200 mg/m^2/d CI, d 1-10; reduced to 100 mg/m^2/d due to 5 fatalities due to gastrointestinal toxicity in the first 29 pts) Pts with CR randomized to one of 3 arms: A: AraC (200 mg/m^2/d, 7 d) + DNR (45 mg/m^2/d, 3 d) for 3 courses B: One course as in arm A then AMSA (120 mg/m^2/d as 2-h infusion, 5 d) followed by AZA (150 mg/m^2/d CI, 7 d) + TG (100 mg/m^2 po q12h, 7 d) + DNR (45 mg/m^2/d, 3 d) C: 3 courses of TG (100 mg/m^2 q12h po, 5 d) + AraC (100 mg/m^2 iv push q12h, 5 d) + DNR (10 mg/m^2/d, 5 d) then 4 courses maintenance with AraC (100 mg/m^2/d CI, 5 d) + DNR (45 mg/m^2/d iv, d 1-2) every 13 w	55%	OS from onset of consolidation: median 22.7 m vs 14.6 m vs 22.7 m 5-y DFS 38% (arm A), 31% (arm B), 27% (arm C), ns	Remained in CR throughout consolidation: 67% arm A, 72% arm B, 80% arm C. Probability of remission at 5 y 0.384 (A) vs 0.309 B) vs 0.268 (C), ns. Infections during consolidation 55% vs 55% vs 17%	NR	
EORTC/GIMEMA AML8B; 1986-1993 Hengeveld, 2012 (319)	315 (603) Age 46-60 y, previously untreated AML. Some younger pts if centre did not perform stem cell transplants (n=72, 12%)	Consolidation + maintenance Intensive vs std consolidation + maintenance	Induction: DNR (45 mg/m^2, d 1-3) + AraC (200 mg/m^2, d 1-7); 1-2 courses Pts in CR: 2 courses intensive consolidation (AraC + AMSA or DNR) vs std consolidation and maintenance Intensive: AraC (500 mg/m^2 CI over 2 h q12h, d 1-6) + AMSA (120 mg/m^2 by 3-h infusion, d 5-7) → AraC (2 g/m^2 iv over 2 h q12h, d 1-4) + DNR (45 mg/m^2 push infusion, d 5-7) Standard: AraC (200 mg/m^2 CI, d 1-7) + DNR (45 mg/m^2 push infusion, d 1) then maintenance with 6 courses DNR (45 mg/m^2 push infusion, d 1) + AraC (100 mg/m^2 sc q12h, d 1-5) at 4-6 w intervals Italian centres used modification of standard treatment: 4 courses DNR (60 mg/m^2 iv, d 1) + AraC (60 mg/m^2 sc q8 h, d 1-5) + TG (70 mg/m^2 po q8h, d 1-5) every 4 w	61%	4-y OS from randomization: 32% intensive vs 34%, p=0.29 4-y RFS 24% vs 22%, p=0.49.	4-y relapse incidence 55% vs 75%, p=0.0003; treatment related mortality 22% vs 3%, p<0.0001. Stopped protocol for toxicity 31% vs 6%; for early relapse 4% vs 20%. Grade 3+ toxicity (cytopenias, infections, hemorrhages) more in intensive arm	ITT. RFS and OS. 300 pts randomized to observe 182 events and detect increase from 25% to 40% of pts alive without relapse at 3 y, HR=0.66	Intensive treatment lowered relapse but had higher toxicity and treatment-related deaths

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Japan: JALSG AML97; 1997-2001 Miyawaki, 2005 (315)	598 (789) Age 15-64 y, median 45 y, de novo AML, excluded prior MDS	Consolidation + maintenance Consolidation + maintenance vs different consolidation	Induction: AraC (100 mg/m^2 CI, d 1-7) + IDA (12 mg/m^2 as 30-min infusion, d 1-3); 2nd course if not CR Pts with CR randomized to 4 courses consolidation (arm A) or 3 courses consolidation + 6 courses maintenance (arm B). Note the first 3 courses are <u>not</u> the same in each arm. <u>Arm A</u>. Course 1: AraC (200 mg/m^2/d CI, d 1-5) + MTZ (7 mg/m^2/d as 30-min infusion, d 1-3); Course 2: AraC (200 mg/m^2/d, d 1-5) + DNR (50 mg/m^2/d as 30-min infusion, d 1-3); Course 3: AraC (200 mg/m^2/d, d 1-5) + ACR (20 mg/m^2/d as 30-min infusion, d 1-5); Course 4 (in arm A only): AraC (200 mg/m^2/d, d 1-5) + etoposide (100 mg/m^2/d as 30-min infusion, d 1-5) + VCR (0.8 mg/m^2 bolus injection, d 8) + vindesine (2 mg/m^2 bolus injection, d 10) <u>Arm B Consolidation</u>. Course 1: AraC (200 mg/m^2/d CI, d 1-5) + MTZ (7 mg/m^2/d as 30-min infusion, d 1-3); Course 2: BHAC (200 mg/m^2/d as 3-h infusion, d 1-7) + etoposide (100 mg/m^2/, d 1-5) + DNR (50 mg/m^2/d, d 1-3) + 6MP (70 mg/m^2/d po, d 1-7); Course 3: BHAC (200 mg/m^2/d, d 1-7) + ACR (14 mg/m^2/d, d 1-7) <u>Maintenance (arm B).</u> Course 1: BHAC (170 mg/m^2/d, d 1-5) + DNR (50 mg/m^2/d, d 1, 4) + 6MP (70 mg/m^2/d, d 1-7); Course 2. BHAC (170 mg/m^2/d, d 1-5) + MTZ (5 mg/m^2/d, d 1-3); Course 3: BHAC (170 mg/m^2/d, d 1-5) + etoposide (80 mg/m^2/d, d 1, 3, 5) + vindesine (2 mg/m^2/d, d 1, 8); Course 4: BHAC (170 mg/m^2/d, d 1-5) + ACR (14 mg/m^2/d, d 1-4) + 6MP (70 mg/m^2/d, d 1-7); Course 5: BHAC (170 mg/m^2/d, d 1-5) + DNR (50 mg/m^2/d, d 1, 4) + 6-mercaptopurine (70 mg/m^2/d, d 1-7); and Course 6: BHAC (70 mg/m^2/d, d 1-5) + etoposide (80 mg/m^2/d, d 1, 3, 5) + vindesine (2 mg/m^2/d, d 1, 8)	78.7%	5-y OS in pts with CR: 52.4% (arm A) vs 58.4%, p=0.599 5-y DFS in pts with CR: 35.8% vs 30.4%, p=0.543	NR	NR	Shorter treatment is as good as longer treatment including maintenance

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ALFA-9802; NCT00880243; 1999-2006 Thomas, 2011 (316); Cannas, 2012 (317)	237 (459) 15-50 y, de novo AML; excluded t(8;21) after Nov 2000	Consolidation + maintenance (Induction GM-CSF) HDAC + maintenance vs AMSA/EMA	Induction (see Table 4-11): DNR + AraC + MTZ ± GM-CSF priming (first 259 pts) (+ AMSA-AraC salvage if needed) Pts with CR randomized to consolidation; GM-CSF according to initial randomization 4 cycles HDAC → 4 cycles maintenance vs 1 cycle [AMSA + AraC] → 1 cycle EMA [etoposide + MTZ + AraC] [± GCSF as in induction for all stages] HDAC (3 g/m^2/12 h iv over 3 h, d 1, 3, 5) Maintenance: DNR (45 mg/m^2 iv, d 1) + AraC (100 mg/m^2/12 h sc, d 1-5) AMSA + AraC: AMSA (90 mg/m^2 iv, d 1), AraC (60 mg/m^2/12 h sc, d 1-5) MTZ + etoposide + AraC: MTZ (12 mg/m^2/d iv, d 1-3), etoposide (200 mg/m^2/d CI, d 8-10), AraC (500 mg/m^2/d CI, d 1-3 and d 8-10)	89%	OS median 62.9 m HDAC vs 55.6 m AMSA/EMA; 5-y OS 50% vs 48%, p=0.82 5-y EFS 42% vs 35%, p=0.24; intermediate cytogenetics 49% vs 29%, p=0.02; cytogenetically normal AML 48% vs 31%, p=0.04 No difference in cumulative incidence of relapse or treatment-related mortality	Median time to relapse 10.7 m vs 9.9 m. HDAC arm had more infections: event rate (# neutropenic fevers per patient-neutropenic days at risk) was 0.086 vs 0.043, p<0.0001 HDAC arm had less severe adverse effects: grade 3+ diarrhea 3% vs 24%; severe nausea/vomiting 5% vs 26%; mucositis 3% vs 26%; severe infections 19% vs 39%. HDAC group had faster platelet count recovery per cycle 24 d vs 47 d (however more transfusions overall with HDAC because of more cycles). Interaction with GM-CSF trial was not significant (similar effect for GM-CSF and no GM-CSF subgroups)	NR	Time-sequence chemotherapy (AMSA then etoposide/MTZ) did not produce benefit No GM-CSF interaction

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ALFA-9802; 1999-2003 Thomas, 2007, 2010 (276,277)	237 (459) Age 15-50 y, de novo AML; excluded s-AML or other active cancer; excluded t(8;21) after Nov 2000	Consolidation + maintenance (Induction GM-CSF) HDAC + maintenance vs AMSA/EMA ± GM-CSF	Induction (see Table 4-11): DNR + AraC + MTZ ± GM-CSF (first 259 pts) Post-remission (pts with CR); GM-CSF according to initial randomization 4 cycles HDAC → 4 cycles maintenance vs 1 cycle [AMSA + AraC] → 1 cycle EMA [etoposide + MTZ + AraC] [± GCSF as in induction for all stages] HDAC (3 g/m^2/12 h iv over 3 h, d 1, 3, 5) Maintenance: DNR (45 mg/m^2 iv, d 1) + AraC (100 mg/m^2/12 h sc, d 1-5) AMSA + AraC: AMSA (90 mg/m^2 iv, d 1), AraC (60 mg/m^2/12 h sc, d 1-5) MTZ + etoposide + AraC: MTZ (12 mg/m^2/d iv, d 1-3), etoposide (200 mg/m^2/d CI, d 8-10), AraC (500 mg/m^2/d CI, d 1-3 and d 8-10) Good risk group including favourable cytogenetics, constituted by core binding factor (CBF) leukemias and the good risk-2 subset (normal karyotypes with favourable genotypes) **3-y OS/DFS hazard ratios and significance compared with EMA without GM-CSF**	89%	3-y OS vs AMSA/EMA (no GM-CSF): EMA + GCSF HR=0.8, p=0.56; HDAC HR=1.04, p=0.9; HDAC + GM-CSF HR=0.82, p=0.62 OS, intermediate risk cytogenetics: EMA + GCSF HR=0.44, p=0.11; HDAC HR=0.38, p=0.06; HDAC + GM-CSF HR=0.26, p=0.01 3-y EFS vs AMSA/EMA (no GM-CSF): EMA + GCSF HR=0.77, p=0.44; HDAC HR=1.01, p=0.96; HDAC + GM-CSF HR=0.74, p=0.38 EFS, intermediate risk cytogenetics: EMA + GCSF HR=0.37, p=0.03; HDAC HR=0.41, p=0.04; HDAC + GM-CSF HR=0.29, p=0.008	The frequencies of severe adverse effects after consolidation therapy and the times to hematopoietic recovery after consolidation therapy did not differ significantly.	Planned accrual 344 pts; actual 262 pts due to interruption of GM-CSF	Overall no difference with GM-CSF, but improved survival for intermediate-risk group. Overall EMA and HDAC similar, but HDAC better in intermediate-risk group. No GM-CSF interaction
MRC AML11; 1990-1998 Goldstone, 2001 (69)	371 (1314) Initially accepted age 56+ y; age ≥60 y starting end of 1994, although younger pts allowed if not suitable for more intensive chemo in AML10/AML12. 2% of pts age <56 y. Any de novo or secondary AML	Consolidation; maintenance (Induction; consolidation) 1 vs 4 courses consolidation; maintenance: IFN-α vs none	Induction (see Tables 4-5, 4-8, 4-11): DAT vs ADE vs MAC (1:1:2 ratio); subset of pts (n=226) randomized to receive GCSF or placebo Pts in remission randomized to stop after a third course (DAT 2+7) or after 4 additional courses (DAT 2+7, COAP, DAT 2+5, COAP) Third randomization (n=362): IFN-α maintenance for 1 year vs none	55%	5-y OS, 3 vs 6 courses: 23% vs 22%, ns 5-y OS: 21% IFN vs 20% none 5-y DFS, 3 vs 6 courses: 16% vs 23%, ns 5-y DFS: 20% IFN vs 15% none	NR	ITT	

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ALFA-9803; NCT00363025; 1999-2006 Gardin, 2007 (53); Itzykson, 2011 (318)	164 (429) Age ≥65 y, median 72 y, previously untreated AML (de novo s-AML); 20% or more myeloid marrow blasts	Consolidation + maintenance (Induction) Intensive vs ongoing (Consolidation vs maintenance)	Induction (see Table 4-4): IDA + AraC vs DNR + AraC IDA (9 mg/m^2 d 1-4) vs DNR (45 mg/m^2 d 1-4) AraC 200 mg/m^2 iv, d 1-7 in both arms Consolidation if CR (2nd randomization): intensive (single course as for induction, in hospital) vs outpatient (ambulatory; 6 monthly cycles 45 mg/m^2 DNR iv, d 1 or 9 mg/m^2 IDA iv, d 1; plus 60 mg/m^2/12 h AraC sc, d 1-5)	57%	OS from CR: by ITT, 37% intensive vs 56% outpatient, p=0.03; by treatment rec'd HR=1.64, p=0.03 Subset age 65-70 (n=59): 2-y OS: 55% intensive vs 58% outpatient, ns 2-y DFS: ITT basis 17% intensive vs 28% outpatient, p=0.04; by treatment rec'd HR=1.62, p=0.025 Subset age 65-70: 2-y DFS 30% vs 28%, ns	Outpatient consolidation resulted in significantly shorter rehospitalization duration and lower red blood cell unit and platelet transfusion requirements	ITT. Primary endpoint 2-y OS	Outpatient consolidation better than intensive Subset age 65-70: difference compared with overall study may be due to small number in subgroup
MRC AML9; 1984-1990 Rees, 1996 (156)	212 (951) Age 1-79 y, median 53 y, age >55 y starting May 1988; de novo or secondary AML; randomization by minimization for age (6 groups), sex, previous randomization	Consolidation; maintenance (Induction) MAZE vs COAP; maintenance: AraC + TG then COAP vs none	Induction (see Tables 4-1, 4-3): DAT 1+5 vs DAT 3+10 Pts with CR were randomized (n=441) to 2 courses DAT 2+7 alternating with 2 courses either MAZE (m-AMSA, AZA, etoposide) or COAP (cyclophosphamide, VCR, AraC, prednisone) Those still in CR randomized (n=212) to either 1 y maintenance with 8 courses AraC + TG → 4 courses COAP or no further cytotoxic therapy	63%	5-y survival: 37% MAZE vs 31% COAP, p=0.3 Maintenance: 5-y OS 41% with vs 44% without maintenance	Post-remission relapses at 5 y: 66% MAZE vs 74% COAP, p=0.03; MAZE required more supportive care and resulted in more deaths (4.5% vs 0% following courses). 10-y cumulative risk of relapse 68% MAZE vs 76%, p<0.04	Aimed to recruit 1000 pts to be able to assess 10% difference in 5-y OS between induction treatments.	MAZE gives better control but more toxicity Low level maintenance conferred no advantage

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
German AMLCG 1992 1992-1999 Buchner, 2003 (320)	325 (832) Age 16-81 y (median 54 y), de novo AML	Maintenance vs intensive consolidation Maintenance vs s-HAM	Randomized to 2 arms prior to induction, but difference was only after 1st consolidation cycle for pts still in CR Both arms: induction with TAD + HAM, first consolidation cycle (if CR) with TAD TAD: AraC (100 mg/m^2 CI, d 1-2 and by 30-minute infusion q12h, d 3-8) + DNR (60 mg/m^2 by 30-min infusion, d 3-5) + TG (100 mg/m^2 po q12h, d 3-9) HAM: high-dose AraC (3 g/m^2 × 6; 1 g/m^2 age 60+) + MTZ (10 mg/m^2 × 3); HAM omitted in pts age >60 with CR Maintenance (monthly for 3 y) vs intensive consolidation (1 course S-HAM) Maintenance: AraC monthly (100 mg/m^2 sc q12h, 5 d) + DNR course 1 (45 mg/m^2 by 30 min infusion, d 3-4) + TG course 2 (100 mg/m^2 po q12h, d 1-5) + cyclophosphamide course 3 (1 g/m^2 iv, d 3) + TG course 4; repeat from course 1 until 3 y s-HAM: AraC (1 g/m^2 by 3-h infusion q12h, d 1, 2, 8, 9; reduced to 0.5 g/m^2 if age 60+) + MTZ (10 mg/m^2 by 30 min infusion, d 3, 4, 10, 11)	69.2%	OS median 17 m vs 14 m, 6-y OS 25% vs 22%, p=0.159 Age 16-60: median OS 22 m vs 18 m, 6-y OS 32% vs 28%, p=0.207 Age 60+: median OS 11 m vs 8 m; 6-y OS 11% vs 7%, p=0.242 5-y OS: good risk 45% vs 53%, p=0.231; poor risk 26% vs 21%, p=0.0612. Median RFS 19 m maintenance vs 12 m; 6-y RFS 31.4% vs 24.7%, p=0.0118 Age 16-60: median RFS 27 m vs 14 m, 6-y RFS 37% vs 31%, p=0.0232 Age ≥60 y: median RFS 11 m vs 10 m; 6-y RFS 18% vs 7%, p=0.1001 By treatment given (maintenance or s-HAM): median RFS 26 m vs 17 m, 3-y RFS 45% vs 37%, p=0.14, adjusted p=0.021	Outcome by good or poor-risk prognostic group. 5-y RFS: good risk 30% vs 47%, p=0.282; poor risk 24% vs 12%, p=0.0061. Freedom from relapse (5-y): good risk 39% vs 50%, p=0.664; poor risk 29% vs 17%, p=0.0092	Main outcome RFS. Expected 150 pts (100 CR) per year and median RFS of 16 m. With 6 y accrual and 2 y follow-up there would be 80% power to detect difference in median RFS of 5+ m	Maintenance had higher curative potential and improved prognosis; benefit was significant for poor-risk pts.

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
AMLSG AML HD98B (German); 1998-2001 Schlenk, 2004, 2009 (245,246)	61 (242) Age 61+ y, median 66.6 y with de novo AML, RAEB-t, s-AML, or t-AML	Consolidation (2nd) vs maintenance (Induction) Pathway then IDA + etoposide (iv) vs oral maintenance	Induction (see Table 4-9): ICE (std arm) vs A-ICE; if refractory then 2nd induction with A-HAE (AraC + etoposide + ATRA) If CR after 2 cycles induction then consolidation with HAM vs A-HAM (along initial randomization). Pts still in CR randomized to 2nd consolidation with IEiv [IDA (12 mg/m^2 iv, d 1 and 3), etoposide (100 mg/m^2 iv, d 1-5)] or 1 year oral IEpo [IDA (5 mg po, d 1, 4, 7, 10, 13); etoposide (100 mg po, d 1 and 13); repeat on d 29 for 12 courses]	32%	OS after 2nd randomization better for intensive consolidation, p<0.001	Cumulative incidence of relapse (CIR): 39% IEiv vs 80% IEpo, p=0.002	ITT. Sample size of 242 for induction based on CR. Stopped at interim analysis of 2nd randomization.	
ECOG EST 3483 1984-1988 Cassileth, 1988, 1992 (321,322)	221 (449) Age 15-65 y, median 44 y, de novo AML	Maintenance vs consolidation vs observation AraC + TG maintenance vs HDAC + AMSA consolidation vs none	Induction: DNR (60 mg/m^2/d iv push, d 1-3) + AraC (25 mg/m^2 iv push; then 200 mg/m^2/d, d 1-5) + TG (100 mg/m^2 po q12h, d 1-5) [1-2 courses] Pts with CR randomized to 2 y continuous maintenance with AraC + TG vs single course consolidation with HDAC + AMSA vs observation Maintenance: TG (40 mg/m^2 po q12h, d 1-4) + AraC (60 mg/m^2 sc, d 5), continued weekly for 2 y Consolidation: AraC (3 g/m^2 iv over 1h q12h, d 1-6) + AMSA (100 mg/m^2/d iv, d 7-9) Observation arm discontinued at interim analysis due to inferior remission duration compared with maintenance; 54 pts randomized to observation but 26 of these pts refused	68%	4-y OS 22% maintenance vs 33% consolidation, p=0.311; pts age <60: 27% vs 37%, p=0.195 OS median 12.7 m observation vs 16.1 maintenance, ns; OS at median 2-y follow-up 23% vs 45% 4-y EFS 16% maintenance vs 27% consolidation, p=0.068; pts age <60 15% vs 28%, p=0.047	Treatment-related mortality rate 0% maintenance vs 21% consolidation (57% in pts age 60+ and 13% in younger pts). Severe adverse effects more with consolidation, with life-threatening myelosuppression in virtually all pts <u>Observation</u> Median duration remission 4.1 m observation vs 8.1 m maintenance, p≤0.002; at median 2-y follow-up 0% vs 16% still in CR	ITT for remission duration and survival, (not including observation group).	Single course of consolidation gives better EFS than lengthy maintenance but toxicity is unacceptable especially in pts age >60 Maintenance is better than observation

6MP, 6-mercaptopurine (mercaptopurine); ACR, aclarubicin; ADE, AraC + DNR + etoposide; AMSA, amsacrine; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; AZA, azacitidine; BHAC, N^4-behenoyl-1-β-D-arabinosylcytosine (widely used in Japan instead of AraC since 1979); CI, continuous iv infusion; COAP, cyclophosphamide, VCR, AraC, prednisone; CR, complete remission (complete response); DAT, DNR +AraC + 6-thioguanine (TG); DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; EMA, etoposide + MTZ + AraC; GCSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GO, gemtuzumab ozogamicin; HAM, high-dose cytarabine + mitoxantrone; HDAC, high-dose cytarabine; IDA, idarubicin; IEiv, IDA + etoposide, iv; IEpo, IDA + etoposide, orally; IFN, interferon; ITT, intention to treat; iv, intravenously; MAC, MTZ + AraC; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OS, overall survival; po, oral administration (per os); RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; S-HAM, sequential high-dose cytosine arabinoside and mitoxantrone; sc, subcutaneously; std, standard; TAD, thioguanine + cytarabine + daunorubicin; TG, 6-thioguanine; VCR, vincristine

Table 4-16. Maintenance trials (including those with induction plus second randomization) Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
EORTC/HOVON AML-11; 1990-1994 Lowenberg, 1997 (199)	88 (318) Age 61+ y, median 68 y, untreated newly diagnosed AML	Maintenance (Induction GM-CSF + consolidation GM-CSF) AraC vs none	Induction (see Table 4-11): DNR + AraC ± GM-CSF induction DNR + AraC consolidation ± GM-CSF according to induction group Maintenance (if continuing CR): 2nd randomization to AraC (10 mg/m^2 sc q12h, 12 d; 8 cycles at 6 w intervals) or none	55%	OS: no difference, p=0.60 2-y DFS (from 2nd randomization): 20% vs 19%, p=0.45	NR	NR	
HOVON AML-9; 1986-1993 Lowenberg, 1998 (198)	147 (489) Age >60 y, median 68 y, AML	Maintenance (Induction + consolidation) AraC vs none	Induction (see Table 4-5): MTZ + AraC vs DNR + AraC Consolidation if CR using same agents but 1 d of DNR or MTZ 2nd randomization after consolidation for patients in CR: no further therapy (arm A) vs low-dose AraC (10 mg/m^2 sc q12h, d 1-12 at 42-d intervals for 8 cycles or until relapse) Insufficient pts in consolidation arms (208 planned vs 147 actual) so additional pts were randomized in the HOVON AML-11 trial (199) and a meta-analysis of the results of the two studies was performed. The AML-11 trial used higher AraC during induction (200 mg/m^2) but both trials used 10 mg/m^2 during maintenance. [note that the AML-11 is a trial of GCSF for induction]	42%	After 2nd randomization: OS median 62 w AraC vs 79 w, RR=0.83 (0.58-1.18); 5-y OS 18% vs 15%, p=0.29 AML-11 study, OS 36% vs 34%, p=0.600; combined analysis, 22% vs 23%, p=0.558 3-y DFS 20% AraC vs 7%, p=0.006; 5-y DFS 13% vs 7%, p=0.006; median DFS 51 w AraC vs 29 w none. AML-11 study, 3-y DFS 24% vs 20%, p=0.448; combined analysis, 16% vs 13%, p=0.007	NR	208 pts to detect 15% difference (10% vs 25%) in DFS at 3 y between maintenance groups with final analysis after 171 events	Low-dose AraC maintenance improved DFS but effect unclear in AML-11 trial with higher AraC during induction; no significant difference in OS
Memorial Sloan Kettering L-19; 1984-1989 Berman, 1991 (194); see Berman, 1997 for long-term data (192)	12 (130) Age 16-60 y (median 37 y), newly diagnosed AML; exclude pre-existing MDS, secondary leukemia or CML	Maintenance (Induction + consolidation) AraC vs none	Induction (see Table 4-4): IDA + AraC vs DNR + AraC If CR after 1 or 2 induction cycles then received 2 courses of consolidation therapy using same drugs as induction but lower dose Pts remaining in remission were randomized (n=12) to 1 y maintenance with low-dose AraC (5 mg/m^2 sc q12h for 14 d each month) or no further therapy	69%	OS median 54 m maintenance vs 23 m, p=0.37	NR	NR	Not enough pts to reach conclusions

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
SECSG; 1982-1985 Stein, 1990 (207)	76 (299) Age 51+ y, AML, FAB M1-M6; excluded pts with previous myelodysplasia in first 2 years of study	Maintenance (Induction) AraC + DNR vs none	Induction: AMSA + AraC vs DNR + AraC Patients with CR received consolidation (not randomized) then if still in remission were randomized (n=76) to maintenance phase: no further treatment vs AraC (100 mg/m^2/d CI, 5 d) + DNR (45 mg/m^2 iv, d 1-2), repeated every 13 weeks for 4 cycles	45%	OS median 12 m maintenance vs 40 m without, p=0.007 3-y RFS 21% maintenance vs 28% without, ns	Maintenance: median remission duration 8.5 m with vs 10.7 m without, ns. Pts with maintenance therapy: 91% had severe hematologic toxicity and 33% had serious infections	NR	Maintenance therapy had negative effect on survival
GIMEMA GSI 103 AMLE; 2001-2004 Latagliata, 2008 (208)	102 (301) Age >60 y, median age 68 y	Maintenance (Induction + consolidation) AraC + ATRA vs none	Induction + consolidation (see Table 4-6): DNX + AraC vs DNR + AraC After consolidation, pts with CR had 2nd randomization to [AraC (20 mg, twice a day, d 1-10) + ATRA (45 mg/m^2, d 1-10)] q28d × 12 vs none	50%	2nd randomization: HR=0.73, p=0.1664	NR	ITT	
German AMLCG 1981 (1982); 1981- about 1985 Buchner, 1985, 1990, 1992 (323-325); Buchner, 1997 (326) [abstract]	213 (503) Age 16+ y, median 47 y, AML	Maintenance AraC + DNR or cyclophosphamide vs none	Induction with TAD 9: AraC (100 mg/m^2/d CI, d 1-2; 100 mg/m^2 q12h by 30 min infusion, d 3-8) + DNR (60 mg/m^2/d iv, d 3-5) + TG (100 mg/m^2 q12h po, d 3-9); 2nd course if >5% residual blasts Pts in CR: randomized (n=145) to one course TAD 9 course for consolidation with or without subsequent monthly maintenance (until relapse, max 3 y) Consolidation as for induction Maintenance: AraC (100 mg/m^2 q12h sc, d 1-5) alternatingly combined with DNR (45 mg/m^2/d iv, d 3-4) (course 1), TG (100 mg/m^2 q12h po, d 1-5) (course 2 and 4), or cyclophosphamide (1000 mg/m^2 iv, d 3) (course 3); repeat after course 4. After total dose of 520 mg/m^2 DNR, DNR was replaced with TG as in courses 2 and 4. Courses applied at 28 –d intervals between starting days. Dose reductions made as required.	59% Age 60+: 41%	OS median 27 m maintenance vs 19 m without, p=0.02 Median remission duration 15 m vs 7 m, p=0.0001. 5-y DFS 23% vs 6%	Median survival after first relapse 7 m vs 8 m.	NR	Remission and survival improved with maintenance treatment

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Russian AML-06.06; 2006-2009 Parovichnikova, 2010 (176) [abstract and poster], (177) [Russian]; Sokolov, 2013 (327) [abstract]	143 (216) AML except M3 and s-AML	Maintenance AraC + 6MP vs none	Induction/consolidation: AraC + DNR; then HAM; then HAM (if not CR) or HDAC (if CR); then 2 cycles HDAC. AraC (100 mg/m^2 bid iv, d 1-7), DNR (45 mg/m^2, d 1-3), HAM (AraC 3 g/m^2 bid, d 1-3 + MTZ 10 mg/m^2 3-5 d), HDAC (AraC 3 g/m^2 bid, d 1, 3, 5) Randomized at start of treatment to maintenance with 5+2* AraC + 6MP (60 mg/m^2 bid) vs discontinuation of therapy *different publications indicate 5+2 and 7+3 d for maintenance	72%	OS NR Relapse probability 50% maintenance vs 83% without, p=0.0667.	Only 25% of pts completed treatment due to poor tolerability of 2 HAM and 2 HDAC consolidations	NR	Maintenance improves long-term results
SWOG S0106; NCT00085709; 2004-2009 Petersdorf, 2013 (63)	174 (595) Age 18-60 y, AML; excluded AML from prior hematological malignancy; 1 dose of prior intrathecal chemo for acute leukemia permitted. Post-consolidation stratified by age <35 y, 35+ y)	Maintenance (Induction) GO vs none	Induction (see Table 4-10): DNR + AraC + GO vs DNR + AraC Pts with CR received consolidation with AraC (3 g/m^2 by 3h CI q12h, d 1, 3, 5; administered monthly) Post-consolidation randomization (n=169) stratified by prior GO use: GO (5 mg/m^2, 3 doses at least 28 d apart) vs observation	70%	OS NR DFS not improved with post-consolidation GO, HR=1.48, p=0.97	GO maintenance: 4 pts with grade 4 infection, 50% had grade 3-4 thrombocytopenia	Primary outcome DFS for post-consolidation; 342 evaluable pts required to determine if true DFS HR=0.67 (GO vs observation) at 90% power.	GO in induction or post-consolidation failed to show improvement in CR, DFS, OS. GO withdrawn from US market based on this trial but other trials were ongoing.
Japan: JALSG AML87 (?); 1988-1991 Kobayashi, 1996 (328) [Japanese, English abstract]; see Ohno, 1993 (297) for study details other than ubenimex	50 AML	Maintenance (?) Ubenimex vs no immunotherapy	Pts in CR randomized to ubenimex (30 mg) vs no immunotherapy	NR	Survival longer in ubenimex group, p=0.012 Survival longer with ubenimex in pts age 50+ (p=0.005) but not <50 y	Remission duration longer in ubenimex group, p=0.015	NR	
Japan: JALSG AML89 1987-1991 Kobayashi, 1996 (168)	111 (326) Age 15+ y (15-82 y, median 48 y), newly diagnosed AML	Maintenance (Induction) Ubenimex vs none	Induction (see Table 4-1): Chemo + BHAC vs chemo + AraC After consolidation and maintenance pts with CR were randomized to immunotherapy with ubenimex or no drug	77%	OS NR 55-m DFS 53% ubenimex vs 52%, ns	NR	NR	Immunotherapy with ubenimex after maintenance did not improve DFS

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ECOG E2902; NCT00093470; 2004-2009 Luger, 2012 (329) [abstract] Note: Update results presented at ASH, Dec 2015. Luger, 2015 (330) [abstract]	144 Pts in CR after salvage therapy or pts age >60 y in first remission; median age 70 y (range 28-86 y)	Maintenance Tipifarnib vs none	Tipifarnib twice daily vs observation Tipifarnib (farnesyl transferase inhibitor, R115777): 400 mg bid (n=30) with dose reductions for toxicity; reduced to 300 mg bid (n=41) after first planned interim analysis; given on d 1-21. Courses repeated every 28 d in the absence of disease progression or unacceptable toxicity [https://clinicaltrials.gov/ct2/show/NCT00093470]	NR	12-m OS 59% vs 44%, p=0.07 At 110 events, relapse rate 60.3% vs 64.8%. Median DFS 9.3 m vs 5.8 m, p=0.21; DFS at 12 m: 39% vs 30%, p=0.26 Median DFS 8.87 m vs 5.26 m, p=0.058; DFS eligible pts only, 10.81 m vs 6.26 m, p=0.019	Non-hematologic toxicities minimal; significant hematologic toxicity (grade 3 + neutropenia or thrombocytopenia) at both doses of Tipifarnib and more frequent than on observation. No fatal toxicity.	Primary outcome DFS, secondary outcome OS; 5-y follow-up. 84% power to detect 76% relative increase in median DFS from 3.4 m to 6 m	
Sweden; 1992-1999 Lofgren, 2004 (275)	30 (110) Age 64+ y, median 77 y, untreated de novo AML, antecedent MDS excluded	Maintenance (Induction GM-CSF + consolidation GM-CSF) TG vs none	Induction (see Table 4-11): AraC + MTZ + etoposide ± GM-CSF Pts with CR received 2 cycles consolidation: 1st cycle AraC + MTZ + etoposide (as for induction except MTZ for 1 d); 2nd cycle AMSA (90 mg/m^2 as 1-h infusion, 4 d). GM-CSF given (or not) according to initial randomization Maintenance (n=30): 2nd randomization to low-dose TG (160 mg/wk) or none	64%	For pts randomized to maintenance: median OS 28 m TG vs 16.5 m none	For pts randomized to maintenance: median 18 m remission with TG vs 16 m none, ns	NR	No conclusions regarding maintenance due to low number of pts
ALFA-9801; NCT00931138; 1999-2006 Pautas, 2010 (181)	161 (468) Age 50-70 y; median 60 y, de novo AML	Maintenance (Induction + consolidation) IL-2 vs none	Induction and Consolidation (see Tables 4-3, 4-4). Induction: High dose DNR vs IDA × 4 vs IDA × 3 (std IDA); AraC for all pts Pts with resistant disease after 1 course could receive 2nd course with reduced HAM 2 courses consolidation if CR: AraC + either DNR or IDA (according to initial randomization Maintenance (n=161): 2nd randomization for pts in CR to recombinant IL-2 (rIL-2; 5×10^6 U/m^2 × 5 d each month) for 12 months vs none	77%	4-y OS 41% IL-2 vs 47%, (p=0.14 figure, p=0.34 text) 4-y EFS 28% vs 32%, p=0.88	NR	ITT, powered to show 15% difference between arms in second randomization	

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
CALGB 19808 post-remission; 2000-2006 Kolitz, 2014 (331)	214 (734) Age <60 y, previously untreated AML in first CR; s-AML, t-AML excluded	Maintenance IL-2 vs none	Induction: DNR, etoposide, AraC ± valspodar (PSC-833) Post-remission depended on cytogenetic risk (3 courses HDAC or HDAC + etoposide) After post-remission chemotherapy: Interleukin -2 or no further therapy Recombinant interleukin-2 (rIL-2): low-dose (1×10^6 U/m^2/d sc for 10-16 d, 6 courses) interspersed with high-dose (12-15 $\times10^6$ U/m^2 for 5 courses; with last dose extended to 16 d)	77%	5-y OS 63% vs 58% ITT; as treated 61% vs 60% DFS HR=0.75 (0.52-1.09, p=0.13); 5-y DFS 53% vs 42% ITT; as treated DFS 55% vs 43%, p=0.11	29% of IL-2 pts did not start treatment and 28% did not complete IL-2.	DFS primary endpoint; assumed 240 pts with CR randomized to IL-2; followed until 192 failures, giving 90% power to detect HR<0.625	No improvement but poor compliance with protocol
CALGB 9720; 1998-2002 Baer, 2008 (332); see Baer, 2002 (79) for induction	163 (669) Age 60+ y, median 68 y, de novo AML; s-AML, t-AML allowed	Maintenance (Induction) IL-2 vs none	Induction: ADE vs ADEP; ADEP discontinued after 120 pts and remaining pts received ADE Pts with CR after induction and consolidation randomly assigned to IL-2 or no further therapy IL-2 (rIL-2; aldesleukin, Chiron Therapeutics, Emeryville, CA): low-dose (0.9×10^6 U/m^2/d sc, d 1-14), high-dose (12×10^6 U/m^2/d sc bolus, d 15-17), then rest on d 18; repeat for total of 5 cycles with low-dose IL-2 shortened to 9 days	48%	From time of rIL-2 randomization, median 14.7 m combined, p=0.61 DFS from time of rIL-2 randomization, groups similar, median 6.1 m combined, p=0.47	NR	ITT	rIL-2 is not useful to prolong DFS in older pts
EORTC/GIMEMA AML-12; (EORTC 06991); 1999-2008 Willemze, 2014 (40); Willemze, 2011 (165) [abstract, IL-2 results]	528 (1942) AML, age 15-60 y, median 45 y	Maintenance (Induction) Il-2 vs none	Induction (see Table 4-1): HDAC vs std-dose AraC Pts in CR received consolidation with AraC (500 mg/m^2/12h, 6 d) + DNR (50 mg/m^2/d, 3 d). CR pts without suitable stem-cell donor were eligible for 2nd randomization to autologous SCT followed or not by low-dose IL-2 ($4-8\times10^6$ IU/d sc, 5 d/m during 1 y). 528 pts randomized but only 165/263 in IL-2 arm received IL-2 and 197/265 in observation arm were adequately documented	75%	5-y OS 52.2% IL-2 vs 50.9%, p=0.9 5-y DFS 44.2% IL-2 vs 40.4%, p=0.66	38% of IL-2 arm did not receive all injections in course 1 due to relapse (22%) or toxicity (16%). Grade 3-4 toxicity more frequent in IL-2 arm (hypersensitivity, fatigue, rigor/chills, arthralgia/ myalgia)	ITT. 577 pts required for IL-2 study to reach 255 events and allow detection of 11.5% increase in 3-y DFS from 50 to 61.5% (HR=0.70) at 80% power	IL-2 did not improve DFS or OS

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
MP-MA-0201; NCT00003991 1998-2000 Brune, 2006 (91); Brune, 2009 (92) [abstract]; Hellstrand, 2011 (93); Aurelius, 2012 (94)	320 Age 18+ y, median 57 y, de novo or secondary AML in first (n=261, CR1) or subsequent CR (n=59)	Maintenance IL-2 + histamine dihydrochloride vs none	Post-consolidation histamine dihydrochloride + IL-2 or no treatment (control) IL-2 (human recombinant IL-2, aldesleukin, Chiron Corp, Emeryville, CA): (16, 400 U/kg) + histamine dihydrochloride (0.5 mg), both given sc q12h for 10 cycles of 3 weeks; during cycles 1-3 was 3 w between cycles; between cycles 4-10 was 6 w between cycles		3-y OS from date of randomization: 48% vs 44%, p=0.21 Pts in 1st CR 55% vs 46%, p=0.16; pts in subsequent CR 19% vs 33%, p>0.5 OS at 6 y: HR=0.87, p=0.33; CR1 pts age 40-70 HR=0.67, p=0.07 3-y LFS improved by IL-2, 34% vs 24%, p=0.01; subgroup in 1st CR, 40% vs 26%, p=0.01; subgroup in subsequent CR, 10% vs 15%, p=0.40; subgroup M0, 1, 4-7 and age <60 HR=0.43, p=0.0089; M2, and age <60 HR=1.14, p=0.65	Side-effects typically mild to moderate; serious adverse events 17.8% vs 18.8% LFS at 6 y: 26% vs 21%, p=0.011; LFS at 6 y, CR1 pts: 30% vs 22%, p=0.015; age 40-70, HR=0.5, p=0.008; age <40, HR=0.77, p>0.5	Primary outcome LFS. Sample size based on improvement in median LFS of 50% in subjects in 1st CR, with 96 events needed per arm to give 80% power. In pts with subsequent CR, improvement of 75% required 51 events/ arm. Amended to analyze combined group.	IL-2 improved LFS; not significant effect on OS (but not powered to detect this)
German AMLCG/SAL; 1992-1995 Ganser, 2000 (333)	20 (110) Age 18-76 y, median 58 y, high-risk AML from MDS (s-AML, n=86) or t-AML (n=6); or RAEB-t (n=18)	Maintenance IL-2 dose	Induction: AraC (100 mg/m^2 CI, 7 d) + IDA (10 mg/m^2 iv bolus, d 1-3) + etoposide (100 mg/m^2 as 1-h infusion, d 3-7). Second course AraC (100 mg/m^2 CI, d 1-5) + IDA (10 mg/m^2 iv, d 1-2) + etoposide (100 mg/m^2 iv, d 1-5) 1 early consolidation course same as 2nd induction course; late consolidation course with AMSA (60 mg/m^2 iv bolus, d 1-5) + AraC (600 mg/m^2 as 2-h infusion q12h, d 1-5) GCSF after each course recommended After consolidation pts randomized to 4 cycles of either high or low-dose IL-2 IL-2: recombinant human interleukin-2, Hoffmann-LaRoche, Grenzach-Wyhlen, Germany), either 9×10^6 IU/m^2 or 0.9×10^6 IU/m^2 as 1-h infusion on d 1-5 and 8-12; repeated at 6-w intervals	45% 46% s-AML, 67% t-AML, 39% RAEB-t	Median survival 27 m vs 27 m, ns Median RFS 13 m high-dose vs19 m low-dose, p=0.8	IL-2 generally well tolerated, but had to be stopped in 2 pts due to cardiac arrhythmia. No difference in toxicity between treatment arms	NR	

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
SWOG S8124; 1982-1986 Hewlett, 1995 (334)	150 (524) AML pts with no prior therapy	Maintenance Vincristine + prednisone + TG + AraC vs none	Induction: DNR (70 mg/m^2, d 1-3) + AraC (100 mg/m^2 over 1 h q12h, 9 d) + TG (100 mg/m^2 po q12h, 9 d) + prednisone (40 mg/m^2 po or iv q12h, 9 d) + VCR (1 mg/m^2 iv, d 1, 9); for pts age 50-64 reduced DNR to 45 mg/m^2 iv for 3 d, AraC and TG for 7 d instead of 9 d; for pts over age 64 y further reduced DNR to 30 mg/m^2, d 1-3. 2nd course if persistent leukemia Pts with CR who did not undergo transplant received 2 courses consolidation with DNR (45 mg/m^2, 3 d; reduced to 30 mg/m^2 age >64 y) + AraC (7 d) + TG (7 d) Randomized to late intensification at 6 m from CR with same agents as consolidation and at 12 m with 3 cycles of POMP at 14 d intervals (VCR 2 mg/m^2 iv, prednisone 100 mg/m^2/d for 5 d, 6MP 500 mg/m^2 iv for 5 d and methotrexate 7.5 mg/m^2 iv for 5 d) ± monthly maintenance with VCR (1 mg/m^2 iv, d 1) + prednisone (40 mg/m^2 po, d 1-5) + TG (100 mg/m^2 po q12h, d 1-5) + AraC (20 mg/m^2 sc q6 h, d 1-5) until 24 m from CR	57%	7-y OS from time of randomization: 37% maintenance vs 31%, p=0.14, adjusted p=0.27 DFS at 7 –y from randomization: 29% maintenance vs 26% without; p=0.18, adjusted p=0.028	Relative risk of relapse or death 1.63 (1.07-2.56) without maintenance	NR	
Japan: JALSG AML87 1987-1989 Ohno, 1993 (297)	131 (265) Age 16+ y, (15-79 y, median 48 y) newly diagnosed AML, not previously diagnosed with MDS	Maintenance (Induction) 4 vs 12 courses maintenance	Induction (see Table 4-12): BDMP ± VCR, stratified by age (≤60 y, >60 y) and FAB class (M3 or non-M3) All received same consolidation, then re-randomized (n=131) to either 4 or 12 courses maintenance given every 6 weeks Course 1: BHAC (170 mg/m^2, d 1-6), DNR (30 mg/m^2, d 1, 4), 6MP (70 mg/m^2, d 1-6), and prednisolone (40 mg/m^2, d 1-4) Course 2: BHAC (1 70 mg/m^2, d 1-6), MTZ (5 mg/m^2, d 1 and 2), and prednisolone (40 mg/m^2, d 1-4) Course 3: BHAC (170 mg/m^2, d 1-6), ACR (14 mg/m^2, d 1-4), 6MP (70 mg/m^2, d 1-6), and prednisolone (40 mg/m^2, d 1-4) Course 4: BHAC (1 70 mg/m^2, d 1-6), etoposide (1 00 mg/m^2, d 1, 3, 5), vindesine (2 mg/m^2, d 1, 8), and prednisolone (40 mg/m^2, d 1-4). The 4 regimens were repeated thrice in the groups receiving 12 courses.	78%	OS NR Maintenance: DFS better with 12 courses, (48% vs 34%), p=0.0663	NR	Randomiza-tion stopped after interim analysis showed statistical difference in CR between groups	Intensive maintenance results in better DFS

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
South Africa; 1981-1985 Jacobs, 1990 (233)	32 (72) Age 12-71 y, median 36 y, untreated ANLL; excluded s-AML	Maintenance (Induction) 6 m vs 15 m; different regimens	Induction (see Table 4-8): (AraC + DNR + etoposide) vs DAT (AraC + DNR + TG); subset (n=29) randomized to receive *C. parvum* immunotherapy Pts in CR randomized to short (6 m) or extended (15 m) maintenance Short: cyclophosphamide (iv q1m, m 1-3) then (methotrexate + VCR + AraC, q1m, m 4-6) Extended: (AraC + etoposide + DNR) monthly × 9 then same as short course for 6 m	57%	NR	Median remission duration 24 w short course maintenance vs 35 w extended course, ns	NR	
GOELAM SA-2002 2002-2005 Pigneux, 2009 (335) [abstract]	330 Age 60+ y, median 70 y, de novo AML. Induction with 1 course IDA + AraC + lomustine	Maintenance Androgens (IDA + AraC ± androgen)	Induction: IDA (8 mg/m^2, d 1-5) + AraC (100 mg/m^2, d 1-7) + lomustine (200 mg/m^2, d 1) Pts in CR or PR received maintenance: 6 courses IDA (8 mg/m^2, d 1) + AraC (100 mg/m^2, d 1-5) once every 3 m, with a continuous regimen of methotrexate and 6MP in between. At diagnosis pts had been randomly assigned to norethandrolone (10 or 20 mg depending on body weight) or not starting after recovery from aplasia (d 20 to 30 after induction) and continued during 2 y maintenance therapy	NR	5-y OS 26% vs 19%, p=0.72; subgroup alive and in CR at 1 y: 60% vs 37%, p=0.034 5-y EFS 22% vs 16%, p=0.69; LFS 33% vs 23%, p=0.15 Subgroup alive in CR at 1 y: EFS 52% vs 32%, p=0.013; LFS 54% vs 37%, p=0.028	NR	ITT	Norethandrolone is beneficial, especially in pts in CR at least one year
Japan; 1980-1983 Ota, 1990 (336)	101 Age 15-65 y, ANLL (72% AML; 8% APL, 20% monocytic)	Maintenance Bestatin (maintenance ± bestatin)	Induction principally BHAC-DMP: BHAC (170 mg/m^2/d) + DNR (25 mg/m^2/d, d 1-2) + 6MP (70 mg/m^2/d) + prednisolone (20 mg/m^2/d, 10-15 d) or similar for 2-3 courses Pts with CR received 3 courses consolidation with BHAC-DMP (or similar) for 6 d and were then randomized to bestatin (ubenimex) or control Maintenance: alternating VEMP and BHAC-DMP every 5 weeks [or other combination chemotherapy with similar activity] + methotrexate (10 mg/m^2 injected twice intrathecally at time of consolidation chemotherapy and once every 4 m thereafter) ± bestatin VEMP: VCR (1.4 mg/m^2/w iv, d 1, 8, 15), cyclophosphamide (550 mg/m^2/w iv, d 1, 8, 15), 6MP (70 mg/m^2/d), prednisolone (20 mg/m^2/d) Bestatin (30 mg/d po, continued as long as possible, even after recurrence)	NR	OS, AML subgroup: 50% survival >55 m vs 18 m; 4-y OS 55.1% vs 24.4%, p=0.021 (Wilcoxon) or p=0.003 (Cox-Mantel)	AML subgroup: 50% remission duration 22 m vs 12 m; 4-y remission 39.5% vs 25.1%, p=0.158 (Wilcoxon) or p=0.072 (Cox-Mantel)	NR	Survival better with bestatin

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
SWOG 7823; 1978-1982 Morrison, 1992 (213); see Appelbaum 1997 (162) for long-term results	133 (642) Age >15 y, newly diagnosed AML. Induction stratified by age (<50 y, ≥50 y). Late intensification stratified by age and induction arm	Maintenance (Induction + consolidation) Continued maintenance vs late intensification; Levamisole late maintenance vs none	Induction + consolidation (see Table 4-7): ROAP (rubidazone/VCR/AraC/prednisone) vs ADOAP (the same combination using adriamycin [doxorubicin] in place of rubidazone) Pts on CR after 3 courses consolidation received monthly maintenance with VCR (1 mg iv, d 1), AraC (25 mg/m^2 sc q6h, 5 d), prednisone (100 mg po, 5 d) until CR for 9 m then randomized (n=133) to continued maintenance for 3 additional months or late intensification Late intensification: 3 courses POMP: 6MP (700 mg/m^2 iv, 5 d), VCR (2 mg iv, d 1), methotrexate (10.5 mg/m^2 iv, 5 d), prednisone (50 mg po q12h, 5 d); in the 2nd course increased 6MP (1000 mg/m^2) and methotrexate (15 mg/m^2); in the 3rd course increased 6MP (1200 mg/m^2) and methotrexate (18 mg/m^2); smaller doses for pts age >50 in courses 2 and 3. Late maintenance (randomized): pts in CR after 12 m (n=92) were randomized to levamisole for 6 months (100 mg/m^2 to the nearest 50 mg, po, 2 consecutive days each week) or no further treatment	54%	For late intensification vs continued maintenance: OS with median 9.3 y follow-up: median 34.5 m vs 19.3 m, p=0.027 DFS median 16.4 m vs 7.5 m, p=0.030; 8-y DFS 30% vs 19% Levamisole vs none: OS p=0.19 DFS, p=0.25	Late intensification vs continued maintenance: grade 4 toxicities 9% POMP vs 6%; severe or life-threatening toxicities 60% vs 21%, p<0.0001	NR	Late intensification with POMP better than continued maintenance Levamisole alone did not have significant survival effect
EORTC AML-6; 1983-1986 Jehn, 1990 (337)	248 (549) Age 11-65 y, median 47 y, newly diagnosed untreated AML; excluded s-AML	Maintenance Continued vs alternating treatment	Induction: DNR (45 mg/m^2 iv, d 1-3) + VCR (1 mg/m^2 iv, d 2) + AraC (200 mg/m^2, d 1-7, half by CI and half by iv push q12h, d 1-7 Pts with CR received 1 course consolidation same as induction except DNR only given on d 1 Pts still in CR randomized to arm 1 continued treatment) vs arm 2 alternating treatment; both given for 6 courses at 6 week intervals Arm 1: DNR (45 mg/m^2, d 1) + VCR (1 mg/m^2 iv, d 1) + AraC (100 mg/m^2 sc q12h, d 1-5) Arm 2: AMSA (150 mg/m^2 iv, d 1) + (in alternating courses) HDAC (3 g/m^2 infusion over 1 h q12h, d 1-2 for courses 1, 3, 5) or AZA (150 mg/m^2 iv, d 1-3 for courses 2, 4, 6)	67.4%	OS NR Median DFS 12 m in both groups, 23% alive at 4 y. Median survival from CR was 22 m; 34% alive at 4 y Survival from relapse Median 19 w HDAC/ AMSA vs 27 w, p=0.053	Alternating (HDAC) arm had higher hematological toxicity, twice as much septicemia (19.1% vs 9.1%), more hemorrhage (23.5% vs 18.2%), and longer hospital duration (2.5 w vs 1 w)		More toxicity with HDAC/AMSA
Germany; 1983-1987 Jehn, 1994 (340)	41 (66) Age 15-65 y, newly diagnosed AML, s-AML or t-AML allowed	Maintenance DNR + VCR + AraC vs HDAC/AZA + AMSA	Induction: DNR (45 mg/m^2/d iv bolus, 3 d) + VCR (1 mg/m^2, d 2) + AraC (200 mg/m^2/d, 7 d) [1-2 cycles] Pts with CR treated with 1 cycle early consolidation for 1 cycle, same as induction except DNR only on d 1. Pts then randomized to 9 m (6 cycles) of DNR (45 mg/m^2 iv, d 1) + VCR (1 mg/m^2, d 2) + AraC (100 mg/m^2 sc, d 1-5) vs HDAC (AraC 3 g/m^2 qd 12h, d 1-2) + AMSA (150 mg/m^2, d 1) alternating with AZA (150 mg/m^2, d 1-3) + AMSA (150 mg/m^2, d 1)	77%	OS same, p=0.41 DFS same, p=0.44			

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
GIMEMA LANL 8201; 1982-1987 Mandelli, 1992 (338)	156 (448) Age 15-55 y, median 38 y, previous untreated ANLL	Maintenance Conventional vs intensive vs none	Induction: DNR (45 mg/m^2 iv, d 1-3) + AraC (200 mg/m^2 CI, d 1-7); second course DNR (45 mg/m^2 iv, d 1-2) + AraC (200 mg/m^2 CI, d 1-5) Consolidation (4 courses): DNR (60 mg/m^2 iv, d 1) + TG (70 mg/m^2 po q8h, d 1-5) + AraC (60 mg/m^2 sc q8h, d 1-5; increased each cycle to 80 mg/m^2, 110 mg/m^2, then 150 mg/m^2) Those still in CR were randomized to no treatment (arm A), conventional maintenance for 18 courses with 5 d rest between each (arm B: AraC 100 mg/m^2 sc, d 5 + TG 100 mg/m^2 po, d 1-4), or intensive post-consolidation (arm C) Arm C consisted of 3 sequences of 2 courses each: etoposide (100 mg/m^2 iv, d 1-3) + AraC (150 mg/m^2 sc, d 1-3); AraC (150 mg/m^2 sc q8h, d 1-5) + TG (70 mg/m^2 po q8h, d 1-5); DNR (40 mg/m^2 iv, d 1) + AraC (300 mg/m^2/d CI, d 1-3)	68%	OS median 14 m, no difference Median DFS (from time of randomization) 15 m, 17 m, 19 m, ns	Severe myelosuppression in arm C; no substantial toxicities in arm B		If induction + consolidation is sufficiently intensive, additional therapy may offer no advantage
MD Anderson; Boumber, 2011 (339) [abstract]	45 Median age 57 y (24-77 y), non-favourable-risk AML in 1st or subsequent CR	Maintenance Decitabine vs conventional care	Induction + consolidation in all pts Pts in CR randomized to decitabine (20 mg/m^2/d iv, 5 d, every 4 to 8 weeks for 12 cycles) vs conventional care (low-dose sc AraC, prolonged intensive therapy, or observation) Pts in second or subsequent CR randomized after completion of salvage therapy		NR	At median 36.3 m follow-up, 45% vs 60% relapsed, p=0.7; of those with ≥1 y follow-up 45% vs 36% in continued CR	Primary endpoint was considered to be no relapse at 1 year	Decitabine well tolerated but study closed early due to higher relapse rate at 1 y. Larger study needed.
Finland; 1982-1985 Palva, 1991 (341)	45 (108) Age 15-59 y, median 44 y, de novo AML	Maintenance Interferon vs AraC + TG vs none	Induction with TAD: AraC (100 mg/m^2 q12h as 30 min infusion, d 1-7) + TG (100 mg/m^2 q12h po, d 1-7) + DNR (60 mg/m^2 iv, d 5-7) (1-2 courses) 6 m consolidation programs with courses given monthly: 1. AraC (d 1-5) + TG (d 1-5) + DNR (d 5) same doses as induction; omitted if 2 courses induction were given; 2. AraC (40 mg/m^2 iv q12h, d 1-5) + cyclophosphamide (500 mg/m^2 iv, d 3) + etoposide (60 mg/m^2 iv, d 3-7) + VCR (1.4 mg/m^2, d 1, 7); 3. Methotrexate (1g/m^2) with leucovorin rescue. Repeat courses 1 to 3. Pts still in CR randomized to alpha interferon vs AraC + TG given monthly vs none Interferon: human leukocyte interferon 3 MU sc daily during 1st month and thereafter every other day until relapse, or for 3 y AraC + TG: same doses as for induction given monthly for 5-d courses until relapse or for 3 y	79%	Median survival 33 m interferon vs 26 m chemo vs 20 m none; 5-y OS 22% vs 31% vs 31%, ns Median duration remission 15 m interferon vs 18 m chemo vs 15 m none, ns. Median RFS 15 m vs 16 m vs 15 m, ns	NR	NR	Maintenance was of no benefit after consolidation

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
BGM 84 1984-1986 Montastruc, 1990 (342)	47 (92) Age 50-70 y, mean 60.5 y, de novo AML	Maintenance Various	Induction: ACR (100 mg/m^2/d iv × 3) + AraC (100 mg/m^2/d CI, 7 d); 2nd course if not CR Consolidation: ACR (80-100 mg/m^2/d iv, 2 d) + AraC (100 mg/m^2/d sc, 5 d) Pts still in CR randomized to 4 monthly courses intensive sequential chemotherapy (8 drugs, Group A) vs ACR + AraC-based (Group B) Arm A: etoposide (50 mg/m^2/d iv, 5 d) + AMSA (40 mg/m^2/d iv, 5 d); ACR (100 mg/m^2/d iv, 2 d) + AraC (100 mg/m^2/d sc, 5 d); VCR (1.5 mg/m^2/d iv, 1 d) + 6MP (250 mg/m^2/d po, 5 d); methylprednisolone (100 mg/m^2/d po, 5 d) + methotrexate (7.5 mg/m^2/d iv, 5 d) Arm B: abbreviated induction regimen every 2 m AraC (100 mg/m^2/d sc, 5 d) + ACR (60 mg/m^2/d iv, 2 d) alternating with 6MP (70 mg/m^2/d po, 15 d) and methotrexate (15 mg/m^2 im twice a week during 15 d) every 2 m for 15 d with continuous daily androgen (stanazol 0.15 mg/kg/d) for 2 y	55%	OS NR 2-y DFS 33% arm B vs 13% arm A, p<0.05; median DFS 14 m arm B vs 10 m arm A Probability of being in remission at 2 y 46% arm B vs 16% arm A, p<0.04	NR	NR	Continuous maintenance chemotherapy may be useful

6MP, 6-mercaptopurine (mercaptopurine); ACR, aclarubicin; ADE, AraC + DNR + etoposide; ANLL, acute non-lymphoid leukemia; AMSA, amsacrine; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; ATRA, all-trans retinoic acid; AZA, azacitidine; BHAC, N^4-behenoyl-1-β-D-arabinosylcytosine (widely used in Japan instead of AraC since 1979); CI, continuous iv infusion; CR, complete remission (complete response); DAT, DNR +AraC + 6-thioguanine (TG); DFS, disease-free survival; DNR, daunorubicin; DNX, DaunoXome, a liposomal formulation of daunorubicin; EFS, event-free survival; GCSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GO, gemtuzumab ozogamicin; HAM, high-dose cytarabine + mitoxantrone; HDAC, high-dose cytarabine; IDA, idarubicin; IL-2, interleukin-2; ITT, intention to treat; iv, intravenously; LFS, leukemia-free survival; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OS, overall survival; po, oral administration (per os); PR, partial response/remission; RAEB-t, refractory anemia with excess of blasts in transformation; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; sc, subcutaneously; SCT, stem cell transplant; std, standard; t-AML, therapy-related AML following treatment of primary malignant disease; TAD, thioguanine + cytarabine + daunorubicin; TG, 6-thioguanine; VCR, vincristine

Table 4-17. Ongoing post-remission trials Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
NCRI AML17; ISRCTN55675535; 2011-2013 Burnett, 2015 (47,152)	508 (1206) Median 53 y (range 16-72 y), AML or high-risk MDS. 84% de novo AML, 10% s-AML (including t-AML), 6% high-risk MDS	Consolidation (Induction)	90 mg/m^2 DNR + AraC vs 60 mg/m^2 DNR + AraC [± GO ± etoposide] 90 or 60 mg/m^2 DNR: (90 or 60 mg/m^2, d 1, 3, 5; Course 2: 50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-10) After course 1, pts were defined by risk of relapse; pts designated favourable or intermediate risk received 2nd course with DNR (50 mg/m^2, d 1, 3, 5) + AraC (100 mg/m^2 q12h, d 1-8) along with treatment depending on molecular group • FLT3 mutation (n=130) randomized to Lestaurtinib (CEP-701: 40-80 mg bd from 2 d post chemo to 2 d before next course, up to max 28 d) vs placebo • CBF received GO (3 mg/m^2 on d 1 of course 2) • Non CBF, non-FLT3, and not poor risk (n=118) randomized to Everolimus (5-10 mg/d, from 2 d post chemo to 2 d before next course, max 28 d) or not Of the pts eligible for Lestaurtinib or Everolimus, 371 randomized to addition 1 or 2 course of the treatment plus AraC (3 g/m^2 q12h, d 1, 3, 5) High (poor) risk (Group A: CR but adverse features; Group B: no CR; Group C: relapse): 393 pts were randomized (2:1) to DNR + clofarabine or FLAG + IDA DNR (50 mg/m^2, d 1, 3, 5) + clofarabine (20 mg/m^2, d 1-5) FLAG-IDA: fludarabine (30 mg/m^2, d 2-6) + AraC (2 g/m^2, 4 h post fludarabine, d 2-6) + GCSF (263 µg sc, d 1-7) + IDA (8 mg/m^2, d 4-6)	74%	High risk after induction Group A, median 25.8 m follow-up, 4-y OS 30% DNR-Clo vs 48%FLAG-IDA, p=0.10; 4-y RFS 34% DNR-Clo vs 46% FLAG-IDA, p=0.2	NR	ITT. 1700 pts to give 90% power to detect HR=0.80 in 5-y DFS improved from 45% to 53%; closed by monitoring committee after 1206 pts due to early mortality with DNR 90 mg/m^2	Results of 2nd or 3rd randomizations will be reported separately but did not impact DNR dose comparison
ALFA/GOELAMS EFFIKIR; NCT01687387 2012- (ongoing); Vey, 2013 (343) [abstract]	150 planned Age 60-80 y, AML pts in first CR	Maintenance	Standard induction and consolidation then randomized to placebo or Iirilumab Iirilumab anti-KIR monoclonal antibody (IPH2102/BMS986015): either 0.1 mg/kg q12w or 1 mg/kg q4w) for up to 2 y	NR	NR	NR	Primary endpoint LFS; 50 pts/arm to detect improvement in LFS with HR=0.60 and 80% power	
Italy; QOLESS AZA-AMLE; ongoing Oliva, 2014 (344) [abstract]	28 (88) Age >60 y, newly diagnosed AML, de novo or s-AML from MDS	Maintenance AZA vs supportive care	Induction: 2 course 3+7: DNR (40 mg/m^2/d, d 1-3) + AraC (100 mg/m^2/d CI, d 1-7) Pts with CR: consolidation with AraC (800 mg/m^2 by 3-h infusion bid, d 1-3); if still in CR randomized to AZA or best supportive care (BSC) AZA (50 mg/m^2 sc or iv, d 1-5, 8-9) every 28 d, increasing dose to 75 mg/m^2 if tolerated for cycles 2-6, then cycles every 56 d for 4.5 y post-remission	NR	OS median 2 y after randomization: >2 y vs 57 w, p=0.219 Median DFS >2 y vs 14 w, p=0.008	NR	Primary endpoints DFS at 2 and 5 y. Target 54 randomized pts.	AZA prolongs DFS, trial ongoing

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Japan; 1988-1990 Urabe, 1993 (345)	168 Age 15-65 y, untreated ANLL (M1-M5)	Maintenance Ubenimex vs control	Induction (1-2 courses): DNR (25 mg/m^2/d iv, d 1-2; d 5, 6, 9 if required) + BHAC (170 mg/m^2/d iv, 10-15 d) + 6MP (70 mg/m^2/d po, 10-15 d) + prednisolone (20 mg/m^2/d po, 10-15 d) 2 courses consolidation: DNR (25 mg/m^2/d iv, d 1, 4) + BHAC (170 mg/m^2/d iv, d 1-6) + 6MP (70 mg/m^2/d, d 1-6) + prednisolone (20 mg/m^2/d po, d 1-6) Pts registered and randomized at beginning of maintenance therapy Maintenance every 5 w for >2 y: chemotherapy ± Ubenimex (30 mg/d po as long as possible) Maintenance: VEMP + BHAC-DMP alternately. VEMP: VCR (1.4 mg/m^2/w iv, 3 w), cyclophosphamide (550 mg/m^2/w iv, 3 w), 6MP (70 mg/m^2/d, 15 d), prednisolone (20 mg/m^2/d oral, 15 d); BHAC-DMP as in induction Methotrexate (10 mg/m^2) administered intrathecally twice during consolidation and at least every 4 months thereafter	NR	50% survival >1381 d vs 928 d, ns, follow-up ongoing	Remission duration better with ubenimex, p=0.0338; 50% remission duration 508 d vs 386 d. No difference in side effects and abnormal laboratory findings	NR	Ubenimex prolonged duration of remission. Observation and analysis is ongoing.
QUAZAR AML-001 NCT01757535 2013 –(2018) https://clinicaltrials.gov/ct2/show/NCT01757535 Roboz, 2015 (346) [abstract]	460 planned, 168 as of Jan 2015. First CR with induction ± consolidation, age ≥55 years	Maintenance Oral AZA	oral AZA [CC-486] (14 d of each 28 d cycle) vs placebo	NR	NR	NR	≥ 90% power to detect a statistically significant treatment effect on OS (n = 330 deaths; expected duration 60 months)	NR

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison post-remission	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ALFA-0702/CLARA NCT00932412 2009-2013 Note: Results presented at ASH, Dec 2015. Thomas, 2015 (347) [abstract]	221 (468) De novo AML, excluded CBF-AML, age 18-60 y, median 48 y. Patients with non-favourable in first remission	Consolidation	3 cycles consolidation: Clofarabine + AraC vs HDAC Clofarabine (30 mg/m^2, d 2-6) , AraC (1 g/m^2/12 h, d 1-5), HDAC (3 g/m^2/12 h, d 1,3,5) GCSF priming in all pts Timed sequence induction with DNR (60 mg/m2, d 1-3, d 8-9) + AraC (500 mg/m2 CI, d 1-3; and 1 g/m2/12 h bolus, d 8-10) and GCSF priming; first salvage with IDA and HDAC could be proposed if no CR/CRp after 1 course induction. Pts in CR/CRp after 1 course with non-favorable AML or CR/CRp after salvage were eligible for transplant or randomized consolidation.	NR	Median follow-up of 37.4 m. Data censored for SCT. 2-y RFS 52.1% vs 30.5%, HR=0.62, p=0.023 2-y OS 68.1% vs 49.8%, p=0.18 CID 3.9% vs 1.9%, p=0.60 CIR 44.0% vs 67.7%, p=0.023.	Clofarabine arm had higher hematologic toxicity, infections, and liver toxicities. No difference in post-SCT outcome according to randomization arm.	Primary endpoint RFS. Secondary endpoint CIR, death in first CR/CRp (CID)	Clofarabine improved RFS in pts not undergoing SCT

6MP, 6-mercaptopurine (mercaptopurine); ANLL, acute non-lymphoid leukemia; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; AZA, azacitidine; BHAC, N^4-behenoyl-1-β-D-arabinosylcytosine (widely used in Japan instead of AraC since 1979); CI, continuous iv infusion; CID, cumulative incidence of death in relapse; CIR, cumulative incidence of relapse; CR, complete remission (complete response); DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; FLAG, fludarabine + high-dose AraC + GCSF; GCSF, granulocyte-colony stimulating factor; GO, gemtuzumab ozogamicin; IDA, idarubicin; ITT, intention to treat; iv, intravenously; LFS, leukemia-free survival; MDS, myelodysplastic syndromes; NR, not reported; OS, overall survival; po, oral administration (per os); RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; sc, subcutaneously; t-AML, therapy-related AML following treatment of primary malignant disease; VCR, vincristine

Table 4-18. Relapsed or refractory AML Back to Recommendations Back to Results Back to Discussion

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
German AMLCG; 1987-1992 Kern, 1998 (98)	186 Age 18+ y, median 50 y, relapsed or refractory AML (from AMLCG trials). TAD-TAD or TAD-HAM induction (age <60 y); TAD age >60 y	Reinduction AraC dose (MTZ in both arms)	MTZ plus high vs intermediate-dose AraC MTZ (10 mg/m^2/d as 30 min infusion, d 3-4, 10-11) AraC by 3-h infusion q12h, d 1-2, 8-9 • Pts age <60 (n=138): AraC 3 g/m^2 vs 1 g/m^2 • Pts age >60 (n=48): AraC 1 g/m^2 vs 0.5 g/m^2	Age <60: 52% (3 g) vs 45% (1 g), p=0.01 Age >60: 44% (1 g) vs 43% (0.5 g), ns Age <60 refractory (including early relapse): 46% vs 26%, p=0.045	OS, age <60: median 4.2 m vs 5.3 m, p=0.78 DFS, age <60: median 5.3 m vs 3.3 m, p=0.35	Early deaths •age <60: 32% (3 g) vs 17% (1g) [mostly due to infections, 27% vs 11%, p=0.01] •age <60 refractory: 31% vs 13%, p=0.045 •age >60: 36% (1 g) vs 26% (0.5g) Non-response • age <60: 12% vs 31%, p=0.01 • age <60 refractory: 19% vs 52%, p=0.045 • age >60: 16% vs 26% More non-hematological adverse effects in age <60 y with 3 g vs 1 g AraC: infections 78% vs 63%, p=0.04 (severe 59% vs 49%, ns); stomatitis 47% vs 28%, p=0.02 (severe 12% vs 9%, ns); severe nausea/vomiting, 26% vs 17%; diarrhea (21% vs 12%); disturbance of consciousness (10% vs 0%, p=0.01)	Primary endpoint CR and DFS. Assuming improvement of 20% in CR rate, required 76 pts per arm.	Higher dose gives lower non-response rate but more early deaths, primarily due to uncontrolled infections; improved supportive care and infection control is required with HDAC. HDAC benefit greater in pts with refractory AML or short remission duration

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Germany; OSHO + SAL; EudraCT #2014-000083-18; 1999-2006 Thiel, 2015 (148)	252 Median age 59 y; relapsed or refractory AML	Bolus vs CI administration of Mito-FLAG	All pts had received AraC-based pretreatment (previous induction) with anthracycline (38%) or MTX (38%) or both (23%) Mito-FLAG + (AraC bolus) vs Mito-FLAG + (AraC CI) AraC bolus (B): AraC (1 g/m^2 over 1 h, q12 h, 5 d) + MTZ (7 mg/m^2/d, d 1,3,5) + fludarabine (15 mg/m^2, 4 h before AraC) + GCSF AraC CI: AraC (150 mg/m^2 CI, 5 d) + MTZ (7 mg/m^2, d 2, 4, 6) + fludarabine (15 mg/m^2 q12h, total of 11 times) + GCSF GCSF same in both arms: 5 µg/kg/d sc or iv, from d 0 until neutrophil recovery to 0.5×10^9/L on 3 consecutive days or until successful stem-cell apheresis Pts with CR or good partial remission received second identical cycle	54% vs 43%, p=0.1 Age ≤60 y: 47% vs 44%, p=0.8 Age) 60 y: 63% vs 41%, p=0.03	OS median 7.1 m vs 6.6 m, p=0.53; 2-y OS 29% vs 24%; 5-y 23% vs 19%, ns Median DFS 7.8 m vs 67.1 m, p=0.53, HR=1.15 EFS HR=087, p=0.3	No difference in grade 3-4 neutropenia, thrombocytopenia, mucositis, renal and liver toxicity. More infections with mito-FLAG bolus (84% vs 69%, p=0.01). Early deaths (within 42 d): 12% vs 13%, p=0.9	Primary endpoint CR, ITT. Sample size to reveal difference of 15% in CR (60% bolus vs 75% CI) with power of 80%. Required 266 pts. Stopped at 256 pts for administrative reasons	Non-significant trend in CR for bolus, no difference in survival outcomes
NCRI AML17; ISRCTN55675535; 2011-2013 Burnett, 2015 (47,152)	1206 (3215) High risk after induction: Group A, 393 pts (311 adverse features, median age 55 y; Group B/C, 82 relapse/ refractory, median age 47 y)	Induction; consolidation DNR dose: 90 vs 60 mg (GO, etoposide)	Induction DNR + AraC ± GO ± etoposide After course 1, high risk patients: Group A: CR but adverse features Group B: no CR (refractory) Group C: relapse: Randomized (2:1) to DNR + clofarabine or FLAG + IDA DNR (50 mg/m^2, d 1, 3, 5) + clofarabine (20 mg/m^2, d 1-5) FLAG-IDA: fludarabine (30 mg/m^2, d 2-6) + AraC (2 g/m^2, 4 h post fludarabine, d 2-6) + GCSF (263 µg sc, d 1-7) + IDA (8 mg/m^2, d 4-6)	74%	High risk after induction Group A, median 25.8 m follow-up, 4-y OS 30% DNR-Clo vs 48%FLAG-IDA, p=0.10; 4-y RFS 34% DNR-Clo vs 46% FLAG-IDA, p=0.2 Group B/C median 12.7 m follow-up: 3-y OS 11% vs 35%, p=0.4 (18 m OS censored for transplant 30% vs 38%) Group A/B/C: HR=1.29 favouring FLAG-IDA, p=0.07	FLAG-IDA resulted in slower count recovery and more supportive care	NR	

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NCT00074737; ELP1001 Cortes, 2012 (348)	53 Age 18+ y; 1st salvage AML pts who had either failed to respond to induction or had relapsed within 12 m	Reinduction AraC dose: (Cenersen + IDA in all arms)	Bayesian design Cenersen + IDA plus either AraC 100 mg, AraC 1 g, or none (n=21, n=19, n=13) Cenersen (2.4 mg/kg, d 1-4), IDA (12 mg/m^2, d 2-4); AraC (100 mg/m^2, d 2-8) or AraC (1 g/m^2, d 2-5; d 2-4 if age 60+) Cenersen is a p53 antisense oligonucleotide 2nd course if not CR; up to 4 additional course if response to first 2 cycles	ITT: 14% vs 21% vs 8% Per protocol: 23% vs 36% vs 13%	NR	Diarrhea, constipation, abdominal pain, febrile neutropenia, rash, headache, dizziness, vomiting increased with AraC dose	Primary outcome CR.	Additional studies of Cenersen required
Classic I; 2006-2009 Faderl, 2012 (102)	320 Age 55+ y, refractory or relapsed AML; no previous clofarabine; no intermediate- or high-dose AraC unless CR was >6 m	Reinduction Clofarabine	Clofarabine (40 mg/m^2) vs placebo Both followed by AraC (1 g/m^2, 5 d) Clofarabine or placebo as 1 hr iv infusion; AraC 1 g/m^2 as 2-h infusion starting 3 h after clofarabine/placebo Optional consolidation (1 cycle) if CR 2nd cycle if improvement but not CR, followed by optional consolidation (1 cycle)	35.2% vs 17.8%, p<0.01 Overall response (CR + CRi): 46.9% vs 22.9%, p<0.01	OS median 6.6 m vs 6.3 m, p=1.00 4-m EFS 37.7% vs 16.6%, p<0.01	Similar frequencies of grade 3-4 adverse events (77% vs 74%); serious adverse events 60% vs 49% (infections 38% vs 22%; deaths 14.3% vs 5.2%) 30-d mortality 16% vs 5%, p<0.01	Primary endpoint OS. Follow-up until 260 deaths to achieve 90% power to detect improvement in median OS from 5.5 m to 8.25 m	Clofarabine improved response rate and EFS but not OS
German AMLCG Fiegl, 2014 (104)	326 (281 analyzed) Age 16+ y, Relapsed or refractory AML	Reinduction Fludarabine (AraC + IDA in both arms)	AraC + IDA ± fludarabine AraC (1 g/m^2 as 3-h infusion q12h, d 1-2, 8-9; 3 g/m^2 age <60 y with refractory AML or 2+ relapse) IDA (10 mg/m^2 daily, d 3–4 and 10–11) Fludarabine (15 mg/m^2, 4 h before AraC) GCSF given to all pts Pts without CR or CRi removed from trial; rest received post-remission therapy, preferably allogeneic SCT, otherwise autologous SCT	44% vs 35%, ns CR+CRi: 54% vs 42%, p=0.056	OS median 6.7 m vs 5.8 m, p=0.48 RFS median 5.8 m vs 3.9 m, p=0.31	Median time to treatment failure 3.38 m vs 2.04 m, p<0.05. Early death 20% vs 20% Non-response: 26% vs 37%, p=0.054; younger pts (60 y) 24.2% vs 39.5%, p<0.05 Higher grade 3-4 toxicities with fludarabine: bleeding 9% vs 6%, p<0.05; nausea and vomiting 21% vs 11%, p<0.01; pulmonary effects 17% vs 8%, p<0.05.	Per protocol analysis. Time to treatment failure (TTF), required 127 evaluable pts per arm with predicted improvement of 15%.	Fludarabine has beneficial but moderate impact

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MD Anderson; 2011-2012 Mathisen, 2012 (105) [abstract]	50 Median age 56 y, relapsed AML	Reinduction + consolidation Clofarabine vs fludarabine (IDA + AraC in both arms)	IDA + AraC plus either clofarabine or fludarabine IDA (10 mg/m^2/d, 3 d), AraC (1 g/m^2/d, 5 d), clofarabine (15 mg/m^2/d, 5 d), fludarabine (30 mg/m^2/d, 5 d) 1 cycle induction + up to 6 cycles consolidation using same drugs with attenuated schedule	43% vs 30%, ns	NR	Atypical infections 10% vs 0%, p=0.2; radiographic evidence of atypical pneumonia 10% vs 0%, p=0.2; bloodstream infections 47% vs 35%, p=0.59; viral infections 7% vs 15%	Primary outcome Infections	
MD Anderson; ≈2011- ongoing (continues to accrue) Mathisen, 2012 (106) [abstract]	49 Median age 57 y, relapsed or refractory AML	Reinduction + consolidation Clofarabine vs fludarabine (IDA + AraC in both arms)	IDA + AraC plus either clofarabine or fludarabine IDA (10 mg/m^2/d, 3 d), AraC (1 g/m^2/d, 5 d), clofarabine (15 mg/m^2/d, 5 d), fludarabine (30 mg/m^2/d, 5 d) 1 cycle induction + up to 6 cycles consolidation using same drugs with attenuated schedule	32% vs 25% CR + CRp + CRi: 44% vs 38%	OS median 4 m vs 5 m	4-w mortality 16% vs 4% Difference in grade 3-4 toxicities: transaminitis 5% vs 11%; mucositis 0% vs 11%	Primary outcome overall response rate (CR + CRp + CRi)	Both effective, better outcome with clofarabine
Leukemia Intergroup; 1982-1987 Larson, 1992 (349)	36 (164) Age 16-85 y, median 55 y, AML in first relapse; <80% reduction in abnormal cells with HDAC	Reinduction AMSA (pretreated with HDAC)	Pts were treated with HDAC (3 g/m^2/12 h, 6 d; reduced to 2 g/m^2 for pts age 70+); those with <80% (<40% in text) reduction in abnormal cells were randomized to AMSA (100 mg/m^2 as 1-h infusion, d 7-9; max 2 courses) or not Pts with CR who subsequently relapsed were treated with HDAC + AMSA Prior treatment included AraC + anthracycline, some received HDAC consolidation	60% vs 19%, p=0.01 After 1 course: 53% vs 14%	OS median 6 m vs 2 m, p=0.08	Severe toxicities (cardiac, gastrointestinal, hepatic) greater with AMSA	NR	
EORTC LCG 06893; 1991-1995 Willemze, 1997 (350)	63 Age 14-70 y, relapsed acute leukemia: AML (n=57), acute lymphocytic leukemia (n=5, CML BC (n=1))	Reinduction AMSA vs IDA (decitabine in both arms)	Decitabine + either AMSA or IDA Decitabine (5-aza-2'deoxyctidine; Pharmachemie, Haarlem, The Netherlands): 125 mg/m^2 as 6-h infusion q12h, 6 d AMSA (120 mg/m^2 as 1-h infusion, d 6-7), IDA (12 mg/m^2 as 15 min infusion, d 5-7)	26.7% AMSA vs 45.5% IDA	OS NR No difference in DFS	IDA group had more grade 3-4 toxicity (nausea/ vomiting, diarrhea, infections)	NR	No conclusions regarding AMSA vs IDA due to small number of pts
Belgium; 1985-1989 Martiat, 1990 (97)	52 Relapsed AML (n=34) or refractory AML (n=18); excluded s-AML	Reinduction AMSA vs MTZ (AraC in both arms)	AraC (3 g/m^2/d iv over 2 h, 5 d) followed by either AMSA or MTZ MTZ: 7 mg/m^2/d (5 mg/m^2/d if older than 60 y) AMSA: 120 mg/m^2/d (90 mg/m^2/d if older than 60 y) Pts with CR given maintenance or transplant Initial induction: conventional dose AraC + DNR	46% AMSA vs 58% MTZ, p=0.415	Median survival 8 m AMSA vs 12 m MTZ, p=0.326	Severe (grade 3-4) gastrointestinal toxicity was more frequent in AMSA group (27% vs 4%, p=0.021). Treatment-related death 4 pts AMSA vs 2 pts MTZ, p=0.097	NR	Neither AMSA nor MTZ were superior for CR and survival, while MTZ was better tolerated

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China; 2009-2011 Chen, 2014 (351) [Chinese, English abstract]	56 Age 16-60 y, relapsed or refractory AML	Reinduction Pirarubicin vs MTZ (etoposide + AraC in both arms)	Pirarubicin + AraC + etoposide vs MTZ + AraC + etoposide Pirarubicin (25 mg/m^2/d iv, d 1-3), AraC (100 mg/m^2 iv, d 1-7), etoposide 60 mg/m^2/d iv, d 1-3), MTZ (8 mg/m^2/d iv, d 1-3)	79.0% vs 55.6%, p=0.035 CR + PR: 86.8% vs 88.9%, ns	OS, no significant difference No significant difference in RFS	Hematologic and non-hematologic toxicity were similar except lower dosage of GCSF, red blood cells and platelet transfusion with pirarubicin	NR	Pirarubicin regimen might be effective salvage
France; 1992-1995 Belhabri, 1999 (352)	53 Age >18 y, median 66 y, high risk newly diagnosed AML not eligible for other protocols or s-AML or t-AML (n=5); or relapsed or resistant AML (n=48)	Reinduction + maintenance IDA vs MTZ (carboplatin in both arms)	Carboplatin plus either IDA or MTZ Carboplatin (200 mg/m^2/d CI, d 3-7), IDA or MTZ (12 mg/m^2/d iv bolus, d 1-3) Pts with PR after 1 course eligible for 2nd course but none received a 2nd course Pts with CR received maintenance therapy with 6 monthly courses carboplatin (200 mg/m^2/d CI, d 1-3) plus either IDA or MTZ (12 mg/m^2/d iv bolus, d 1)	29% IDA vs 28% MTZ, p=0.79	OS median 2 m vs 2.5 m, p=0.49 Median DFS 2 m vs 2.5 m, p=0.81	Toxicity-related deaths 18% IDA vs 28% MTZ, ns. No significant differences between arms regarding toxicity	Primary endpoints CR, DFS, OS	
SWOG 8326; 1985-1992 Karanes, 1999 (353)	162 Age 14-76 y, relapsed or refractory AML; excluded those with previous HDAC treatment	Reinduction + consolidation MTZ (AMSA) (HDAC in all arms)	HDAC ± MTZ AraC (3 g/m^2 iv over 2h q12h, d 1-6; 2 g/m^2 for pts age >50 y), MTZ (10 mg/m^2/d iv, d 7-9 2nd course if d 14 bone marrow was hypocellular or normocellular with blasts 10-25% 48 of 62 pts with CR continued on the same drugs (but different schedule) for 3 courses consolidation (n=48): HDAC (d 1-3), MTZ (d 1) Third arm HDAC + AMSA closed in June 1988 by Data Monitoring Committee due to excessive toxicity. With 55-63 pts per arm, fatal toxicity during induction was 29% HDAC + AMSA vs 11% HDAC + MTZ vs 7% HDAC	44% vs 32%, p=0.15; adjusted p=0.013	OS median 6 m vs 8 m, p=0.58 (abstract) or p=0.94 (text) After consolidation: median OS 11 m vs 11 m RFS median 5 m vs 9 m, p=0.30 After consolidation: median DFS 11 m vs 8 m, p=0.60	Induction deaths 17% vs 12%, p=0.65 in abstract; 16% vs 10%, 0.25 in text. Grade 3+ toxicity: neurologic 3% vs 7%, p=0.28, mucositis 6% vs 0%, p=0.028 Consolidation treatment-related deaths, n=2 vs n=1. 29% vs 0% stopped consolidation early due to toxicity	For two arms (HDAC ± MTZ), accrual of 172 pts to give 89% power to detect difference between CR rates of 40% and 75% (HR=1.67) and HR =2.0 for RFS. Closed early at interim analysis due to no significant difference	Trend to higher CR with MTZ; survival conclusions limited by small number of pts.

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UK MRC AML-R; 1992-1997 Liu Yin, 2001 (100)	235 Median age 48 y (4-75 y), relapsed (n=175) or refractory AML (n=60)	Reinduction ADE admin (AraC + DNR + etoposide); CsA	Sequential vs std ADE (AraC + DNR + etoposide) (n=170) Both arms with or without CsA, n=213) CsA (5 mg/kg/d for first 47 pts, increased to 10 mg/kg/d in latter part of trial) Seq ADE (2 courses): AraC (2 g/m^2/d CI, d 1-3; for pts age >55 reduced to 0.67 mg/m^2/d) + DNR (50 mg/m^2/d iv, d 1-3) + etoposide (200 mg/m^2/d CI, d 8-10) Std ADE (3 courses): AraC (100 mg/m^2 iv 12-hourly, d 1-10) + DNR (50 mg/m^2 iv, d 1, 3,5) + etoposide (100 mg/m^2/d iv, d 1-5); 2nd and 3rd cycles same except AraC given only d 1-8	Seq ADE vs std ADE: 33% vs 54%, p=0.01 overall; 38% vs 57% age <60; 25% vs 48% age 60+ CsA vs none: 41% vs 45%, p=0.6 overall; 46% vs 42% age <60; 25% vs 57% age 60+	3-y OS 6% seq ADE vs 12% std ADE, p=0.03 7% CsA vs 8% none, p=0.5 overall; age 60+ worse with CsA, p=0.0003; age <60 8% vs 8%, p=0.5 3-y DFS 14% seq ADE vs 22% std, p=0.2 14% CsA vs 13% none, p=0.9	No difference in hematological toxicity or non-hematologic toxicity, except more hepatic toxicity with Seq ADE/CsA (p=0.003) Induction deaths 24% std ADE vs 16% std ADE; 20% CsA vs 17% none	ITT. Primary outcomes CR and OS. 200 and 600 pts to detect 20% and 10% absolute differences in survival within each randomized comparison with 80% power	Std ADE superior to Seq ADE No benefit of CsA; detrimental to pts age >60
AEG35156 Schimmer, 2011 (354)	40 Age >18 y, median 62.5 y, AML refractory to initial induction. 12 pts had history of myelodysplasia or myeloproliferative neoplasms	Reinduction AEG35156 (HDAC + IDA in both arms)	HDAC + IDA + AEG35156 vs HDAC + IDA 27 pts AEG35156, 13 pts none AEG35156 (antisense oligonucleotide to human XIAP): 650 mg iv over 2 h, d 1-3, 8 HDAC: AraC (1.5 g/m^2 CI, d 4-7 if age <65 or d 4-6 if age >65 y) IDA: 12 mg/m^2 iv over 30 min, d 4-6 Initial induction: AraC (100-200 mg/m^2 CI, 5-7 d) + either DNR (45-90 mg/m^2, 3 d) or IDA (12 mg/m^2, 3 d)	18% vs 46% CR + CRp: 41% vs 69%, p=0.18	NR	Induction deaths 11% vs 0%; deaths deemed not related to AEG35156. Serious adverse events 44% vs 31%; hematologic toxicity similar.	Designed to enroll 60 pts (40 AEG35156), assuming CR/CRp of 50% in control and 70% in experimental arm. Terminated after 40 pts due to apparent lack of benefit.	AEG35156 did not improve remission
NCT00512083 Rizzieri, 2010 (355) [abstract]	71 Relapsed (≤3 previous lines of therapy) or refractory AML	Reinduction AS1411 (HDAC in both arms)	Cohort 1: HDAC (1.5 g/m^2 bid, d 4-7) ± AS1411 (10 mg/kg/d CI, d 1-7) Cohort 2: HDAC (as above) ± AS1411 (40 mg/kg/d) AS1411 is an advanced aptamer targeting nucleolin	21% AS1411-10, 19% AS1411-40, 5% control	NR	Grade 3-4 toxicity similar for all groups. Deaths within 28 d of treatment: 5% for AS1411- 10, 8% for AS1411-40 and 14% for controls	NR	AS1411 may enhance anti-leukemic activity.

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NCT01034410 Stuart, 2010 (356) [abstract]	90 planned Age 18-70 y, Primary refractory AML or AML in first relapse; excludes APL, s-AML	Reinduction AS1411 dose (HDAC in all arms)	AS1411 (40 mg/kg/d CI, d 1-7) + AraC (4 g/m^2/d bid iv, d 4-7) vs AS1411 (80 mg/kg/d) + AraC (4 g/m^2/d) vs AraC (4 g/m^2/d)	NR	NR	NR	NR	The study was terminated. See https://clinicaltrials.gov/ct2/show/NCT01034410
France; 1995-1998 Belhabri, 2002 (357)	95 Age >18 y, median 58 y, relapsed or refractory AML (n=86); or high-risk AML not eligible for other protocols or t-AML or s-AML (n=9)	Reinduction ATRA (IDA + AraC in both arms)	IDA (12 mg/m^2/d iv bolus, d 1-3) + AraC (1 g/m^2/12 h iv bolus, d 1-6) ± ATRA (45 mg/m^2/d oral, d 1 to hematological recovery, CR or d 28) Pts in CR received maintenance therapy with 6 monthly courses IDA (10 mg/m^2/d iv, d 1) + AraC (100 mg/m^2/d sc, d 1-5)	55% vs 58%, ns	OS median 5.5 m vs 8 m, ns Median DFS 3.4 m vs 5.2 m, ns	No significant differences in toxicity	Primary endpoint CR, DFS, OS.	ATRA can be administered safely but has no advantage
NCT00822094; 2009-2011 Cortes, 2015 (358) https://clinicaltrials.gov/ct2/show/NCT00822094	125 Age 18-65 y, first relapse AML	Reinduction CPX-351	CPX-351 vs investigator's choice of salvage therapy; 2:1 randomization CPX-351: 100 units/m^2 by 90 min infusion, d 1, 3, 5 (1st infusion) or d 1, 3 (2nd infusion, consolidation) (1 unit = 1 mg AraC + 0.44 mg DNR) Salvage: generally AraC + anthracycline, often with 1 or more additional agents	37% vs 31.8% Poor risk: 28.6% vs 20.7%	OS median 8.5 m vs 6.3 m, HR=0.75, p=0.19; poor-risk subgroup 6.6 m vs 4.2 m, HR=0.55, p=0.02 Survival at 1 y: 36% vs 27%, p=0.33; poor-risk subgroup 28% vs 9% EFS median 4.0 m vs 1.4 m, HR=0.66, p=0.08; poor-risk subgroup median 1.9 m vs 1.2 m, HR=0.63, p=0.08	60-d mortality: 14.8% vs 15.9%; poor-risk subgroup 16.1% vs 24.1% 90-d mortality 21.4% vs 37.9%	Main endpoint 1-y OS. 83.6% power to detect absolute increase of 23% (from 27% to 50%) in 1-y survival	Possible improvement with CPX-351, especially for poor-risk pts

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HOVON; 1995-2000 Daenen, 2004 (359)	80 Age 18+ y, refractory or relapsing AML; excluded pts who had received induction with MTZ + etoposide within 6 m	Reinduction CsA (MTZ + etoposide in both arms)	MTZ + etoposide ± CsA MTZ (10 mg/m^2/d, 5 d), etoposide (100 mg/m^2/d as 1-h infusion, 5 d), CsA (5 mg/kg bolus 2h before first dose of MTZ/etoposide, then 12.5 mg/kg/d CI until 12 h after last MTZ/etoposide dose) 2nd and 3rd cycle if CR or PR Any previous chemotherapy allowed, although most pts had previously received IDA + AraC then AMSA + AraC, plus MTZ/etoposide consolidation	53% vs 43%, p=0.37	OS median 9 m vs 8 m, ns 12 m OS 37% vs 37%, 36 m OS 12% vs 20%, 60 m OS 7% vs 11% DFS median 8 m vs 9 m, ns; 12 m DFS 38% vs 35%, 36 m DFS 14% vs 29%, 60 m DFS 10% vs 20%	Pts discontinued protocol due to severe toxicity, refusal of treatment, or intercurrent death: 40% vs 15%, p=0.02. Grade 2-4 non-hematological effects 90% vs 66%, p=0.03: hemorrhage, liver function, mucositis, nausea/ vomiting, neurotoxicity higher with CsA (all p<0.05) More infections with CsA, 90% vs 72%, p=0.05	ITT. Primary endpoints CR, toxicity. Required 25 pts per arm to estimate CR rate within 10%. Detection of 20% improvement would require 170 pts	CsA did not improve treatment outcome
SWOG 9126; 1993-1998 List, 2001 (75)	226 Age 18-70 y, median 53 y, relapse or refractory AML (78%); or previous untreated s-AML or t-AML (17%); or RAEB-t (5%)	Reinduction + consolidation CsA (AraC + DNR in both arms)	AraC + DNR ± CsA AraC (3 g/m^2/d by 3h infusion, d 1-5), DNR (45 mg/m^2/d CI, d 6-8), CsA (2h iv loading of 6 mg/kg + 6-h infusion of 4 mg/kg on d 6; then 16 mg/kg/d CI, 72h concurrently with DNR) Pts with persistent leukemia and >50% reduction in blasts received 2nd course Pts with remission received 1 course consolidation (n=57) with DNR ± CsA according to induction assignment, but at shorter schedule: AraC (d 1-3), DNR ± CsA (d 4-6)	39% vs 33%, p=0.14 One course: 38% vs 26%, p=0.032 Pgp + subgroup: 46% vs 26%; Pgp- subgroup: 39% vs 34%	2-y OS 22% vs 12%, p=0.046 overall; 21% vs 14% relapsed or refractory; 26% vs 5% previously untreated Moderate or bright Pgp expression: median 12 m vs 4 m Absent or low Pgp expression: median 6 m vs 6 m 2-y RFS 34% vs 9%, p=0.031overall; 28% vs 10% relapsed or refractory; 60% vs 5% previously untreated Pgp + median RFS 17 m vs 7 m; Pgp- median 7 m vs 5 m	Induction deaths 15% vs 18% Resistant disease 31% vs 47%, p=0.0077 Grade 3 nausea 11% vs 3%, p=0.016; difference in other toxicities not significant except hyper-bilirubinemia (31% vs 4%, p<0.0001) Survival and induction response improved with increasing DNR serum concentrations in CsA pts but not controls	ITT. 220 pts to give 82% power to detect 50% increase in CR from 35% to 53% and 90% power to detect mortality HR=0.67	CsA reduces resistance to DNR and improves survival

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CALGB 8722; 1987-1990 Lee, 1998 (360)	167 Age 19-77 y, median 55 y, relapsed or refractory AML; 123 pts in 1st relapse, 22 in 2nd relapse, 22 refractory	Reinduction Diaziquone, etoposide, mitoxantrone combinations	Diaziquone + etoposide vs diaziquone + MTZ vs MTZ + etoposide Diaziquone (28 mg/m^2/d CI, 5 d), etoposide (150 mg/m^2/d CI, 5 d), MTZ (12 mg/m^2/d, 3 d); 2nd course permitted at d 14 or later if bone marrow showed significant residual leukemia Initial induction could not include >450 mg/m^2 DNR	30% diaziquone + MTZ vs 23% MTZ + etoposide vs 23% diaziquone + etoposide, ns	NR	Grade 3+ stomatitis 24% on diaziquone arms and 43% on MTZ + etoposide	NR	
NCT01147939; 2010-2012 Roboz, 2014 (361)	381 Age 18+ y, median 62 y, relapsed or refractory AML: age 18+ y and refractory or relapsed after 2-3 previous induction/ reinductions; or age 65+ y with adverse cytogenetics and relapsed disease after 1-3 previous induction/ reinductions	Reinduction Elacytarabine	Elacytarabine vs investigator choice of 1 of 7 common salvage regimens Elacytarabine 2 g/m^2/d, d 1-5; q3w at the discretion of the investigator Salvage regimens: • AraC (1-6 g/m^2/d, up to 6 d); • MTZ + etoposide + AraC; • Fludarabine + AraC + GCSF ± IDA • AraC (max 40 mg/d) • Decitabine or AZA • Hydroxyurea • Supportive care	15% vs 12% CR + CRi: 23% vs 21%, ns	OS median 3.5 m vs 3.3 m, p=0.96 OS median age 65+: 2.9 m vs 4.1 m, p=0.32 RFS median 5.1 m vs 3.7 m, ns. Median DFS 90 d vs 118 d	Early mortality: 17% vs 15% at 30 d, 34% vs 30% at 60 d More adverse events with elacytarabine, mainly hematologic No significant differences in OS among any of the investigator choice regimens	Primary endpoint OS. Designed to detect HR=0.70 with 87% power, required 300 events. Based on historical 1-y OS of 10%, planned 380 pts.	No clinically meaningful benefit of elacytarabine or other salvage regimens

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
China; 2004-2006 Zhang, 2013 (95)	228 Age 18+ y, median 43.3 y, refractory or relapsed AML	Reinduction Etoposide (AraC + ACR + GSCF in both arms)	Low dose CAG ± etoposide CAG: AraC (10 mg/m^2 q12h sc, d 1-14); ACR (14 mg/m^2, either d 5-8 with etoposide or d 1-4 without), rhG-CSF (200 µg/m^2, d 0-14) Etoposide (30 mg/m^2, d 1-4) 4 additional cycles given to pts with CR/PR if no suitable donor for allo-HSCT, then pts randomized to high-dose chemotherapy or maintenance Refractory disease defined as not achieving CR after 2 courses of standard DNR (45 mg/m^2) + AraC (100-200 mg/m^2) or equivalent regimen	71.1% vs 50.9%, p=0.0002 Age <60: 77.2% vs 56.8%, p=0.004 Age >60: 50.0% vs 30.8%, p=0.158 Unfavourable risk: 60.3% vs 37.3%, p=0.009; Std risk: 81.1% vs 64.7%, p=0.119; favourable-risk: 92.9% vs 84.6%, p=0.496	5-y OS 27.2% vs 24.4%, p=0.650 Pts with CR/PR: 30.1% vs 34.6%, p=0.519	Similar grade 3-4 adverse effects. Pts with CR who had allo-HSCT had better 5-y OS (73.8% vs 10.8%, p<0.001)	ITT. Primary endpoints CRT and OS. Power of 92% to show increase of 20% in CR (from 50% to 70%)	
SECSG; 1984-1986 Vogler, 1994 (96)	131 Age 16+ y, 1st or 2nd relapsed or refractory AML	Reinduction Etoposide (HDAC in both arms)	HDAC ± etoposide AraC (3 g/m^2 over 90 min q12h, 6 d), etoposide (100 mg/m^2, d 7-9) 2nd course for consolidation in pts with PR or CR	38% vs 31%, ns CR + PR: 39% vs 40%	OS age <50 p=0.036 5-y DFS 8% vs 6%	Median duration remission 25 m vs 11.9 m Trend but not statistically significant increase in gastrointestinal, cerebellar, hepatic toxicity with etoposide	NR	Etoposide had marginal effect but increased toxicity
Japan; AML-92 or AML-89 1990-1992 Ohno, 1994 (362)	58 Relapsed or refractory AML (n=50) or AML from MDS (n=8)	Reinduction GCSF (MTZ + etoposide + BHAC in both arms)	GCSF vs Placebo MTZ (7 mg/m^2 by 30 min iv, 3 d), etoposide (100 mg/m^2 by 1 h iv, 5 d), BHAC (200 mg/m^2, 2-h infusion, 7 d) GCSF (recombinant human GCSF, Filgrastim, Kirin/Sankyo, Tokyo, japan; 200 µg/m^2 from 2 d before induction until 35 d after	50% vs 37%, p=0.306 AML: 54% vs 42%	OS NR No difference in EFS (p=0.3642) or DFS (p=0.5449)	NR	NR	
EMA91 (France) Thomas, 1999 (99)	192 Age <65 y, previously treated AML (refractory or in first relapse after at least 6 m CR)	Reinduction GM-CSF (MTZ + etoposide + AraC in both arms)	MTZ + etoposide + AraC plus either GM-CSF or placebo MTZ (12 mg/m^2/d iv, d 1-3), AraC (500 mg/m^2/d CI, d 1-3, 8-10), etoposide (200 mg/m^2/d CI, d 8-10) GM-CSF (*E coli*-derived GM-CSF, Novartis/Schering Plough, Basel, Switzerland): 5 µg/kg/d CI with max 400 µg total daily dose, d 4-8 6 monthly courses maintenance if CR: MTZ (12 mg/m^2 iv, d 1) + etoposide (200 mg/m^2 iv, d 1) + AraC (80 mg/m^2/d sc, d 1-5)	65% vs 59%, p=0.35 Refractory: 51% vs 46% Relapse: 89% vs 81%	OS median 303 d vs 254 d; no difference in OS at 18 m, p=0.32 Median DFS 251 d vs 240 d; no difference in DFS at 18 m, p=0.45	Median time to progression 154 d vs 115 d; PFS at 18 m: 33% vs 19%, p=0.08 Severe hematologic toxicity in all pts, no difference between groups	Primary endpoint CR and PFS at 18 m. Sized to detect difference of 25% in CR or 20% in PFS with 90% power	GM-CSF might marginally increase efficacy

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
Japan; 1988-1989 Ohno, 1990 (363)	108 Relapsed or refractory acute leukemia (AML, n=67; ALL, n=30); included s-AML (n=2). Age 13-69 y, median 49 y	Reinduction GCSF (MTZ + etoposide + BHAC in both arms)	GCSF vs control MTZ (5 mg/m^2/d in 30 min infusion, d 1-3), etoposide (80 mg/m^2/d in 1-h infusion, d 1-5), BHAC (170 mg/m^2/d in 2-h infusion, d 8-12) Additional MTZ on d 8, 10, 12 if bone marrow not severely hypoplastic; etoposide, d 8, 10, or 12 in some highly refractory cases GCSF (KRN8601, Kirin and Sankyo, Tokyo; 200 µg/m^2/d in 30 min infusion, from 2 d after chemotherapy until neutrophil count rose above 1500/µL, then the dose reduced to 100 µg then 50 µg and discontinued if counts stayed above 1500/µL	50% vs 36%, p=0.162 AML: 57% vs 39%	NR	Deaths due to infection or bleeding: n=4 vs n=7 Rate of relapse not different, p=0.899	NR	
UK MRC AML-HR; 1998-2003 Milligan, 2006 (101)	405 High-risk pretreated AML: relapsed from 1st CR; resistant disease; refractory disease after 2 courses; poor-risk cytogenetics and 1 course chemo	Reinduction Fludarabine + HDAC vs DNR + AraC + etoposide; GCSF; ATRA	2×2×2 factorial design, pts could undergo any or all of the randomizations: HDAC + fludarabine (FLA) vs AraC + DNR + etoposide (ADE) (n=250) ATRA or not (n=362) GCSF or not (n=356) FLA: fludarabine (30 mg/m^2/d by 30-min infusion, d 1-5) + AraC (2 g/m^2/d iv over 4 h, d 1-5; reduced to 1 g/m^2/d for pts age 60+) ADE: AraC (100 mg/m^2 q12h iv push, d 1-10), DNR (50 mg/m^2/d slow iv, d 1, 3, 5), etoposide (100 mg/m^2/d by 1-h infusion, d 1-5); 2nd cycle same except AraC on d 1-8 only GCSF: 5 µg/kg/d sc or iv, starting on d 1 of each course until neutrophil count >0.5×10^9/L for 2 consecutive d up to max 28 d ATRA: 45 mg/m^2/d po, starting d 1 of course 1 and continuing daily for 90 d	FLA vs ADE, 61% vs 63%, p=0.8 ATRA vs none, 60% vs 63%, p=0.6 GCSF vs none, 58% vs 61%, p=0.7	<u>4-y OS</u> FLA vs ADE 16% vs 27%, p=0.05 ATRA vs none, 21% vs 24%, p=0.09 GCSF vs none, 22% vs 22%, p=0.8 <u>4-y DFS</u> FLA vs ADE, 23% vs 29%, p=0.2 ATRA vs none, 29% vs 29%, p=0.5 GCSF vs none, 31% vs 28%, p=0.5 <u>4-y relapse rate</u> FLA vs ADE, 65% vs 67%, p=0.6 ATRA vs none, 59% vs 59%, p=0.5 GCSF vs none, 58% vs 66%, p=0.4	<u>Toxicity:</u> Similar toxicity except ADE arm had more diarrhea (p<0.001; not significant for grade 3+), nausea and vomiting (p=0.04), hospitalization time (p=0.002); while GCSF arm had faster neutrophil recovery (p=0.002), more platelet support (course 2, p=0.01) and blood support (course 1, p=0.04), and worse cardiac function (course 2), p=0.009	400 pts per comparison (200/arm) to give 90% power to detect 10% improvement in 2-y OS from 10% to 20% in the absence of interactions among the 3 comparisons	FLA may be inferior. ATRA or GCSF do not improve outcomes

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
NCT00112554; 2005-2007 Giles, 2009 (364)	263 Age 18+ y, median age 59 y, first relapse AML after CR with duration of 3-24 m	Reinduction Laromustine (HDAC in both arms)	HDAC plus laromustine or placebo AraC (1.5 g/m^2/d CI, d 1-3), laromustine (600 mg/m^2 iv over 30-60 min, d 2) Pts without at least a CRp but without disease progression could receive 2nd induction Pts with CR or CRp received consolidation as per initial randomization but with laromustine reduced to 400 mg/m^2	20% vs 16% Age <60 y and CR <12 m: 11% vs 15% Age <60 y and CR 12+ m: 22% vs 44% Age ≥60 y and CR <12 m: 28% vs 4% Age ≥60 y and CR 12+ m: 24% vs 11% CR + CRp: 35% vs 19%, p=0.005	OS median 128 vs 176 d, p=0.087 In pts with response, median OS 264 d vs 451 d, p=0.572 PFS median 54 d vs 34 d, p=0.002	30-d mortality 11% vs 2%, p=0.016 Better response with laromustine did not result in better OS due to excess of early deaths More serious adverse events with laromustine, 74% vs 51%, p<0.001; infections, 45% vs 27%, p=0.005; respiratory 21% vs 7%, p=0.004, pulmonary 34% vs 17%, p=0.006	Analysis on as-treated basis. Initially designed to include 420 pts randomized 2:1. Stopped enrolment after interim analysis at 210 pts due to treatment-related mortality	Explore alternative doses or schedules of laromustine to reduce toxicity
Cephalon 204; NCT00079482; 2004-2008 Levis, 2011 (365)	220 Age 18+ y, FMS-like tyrosine kinase-3 (FLT3) mutant AML in first relapse	Reinduction Lestaurtinib	Chemotherapy ± lestaurtinib Lestaurtinib (an FLT3 inhibitor): 80 mg q12h po, d 7 and following; bone marrow biopsy performed on d 15-17 and lestaurtinib continued if cellularity ≤5% Chemotherapy depended on duration of remission: 1-6 m received MTZ (8 mg/m^2/d iv, d 1-5) + etoposide (100 mg/m^2 iv, d 1-5) + AraC (1 g/m^2/d iv, d 1-5); 6-24 m received AraC (1.5 g/m^2/d, d 1-5) 2nd course: upon recover of peripheral blood counts or d 42 the bone marrow was assessed; if d 15 cellularity ≥20% and ≥50% reduction in blasts then given a 2nd course If d 15 marrow showed persistent leukemia then removed from protocol Lestaurtinib continued up to d 112 in responding pts; if judged of ongoing clinical benefit could continue on an extension protocol Control pts eligible for crossover if partial response as revealed by d 42 assessment (n=7 during trial; 30 additional pts later during extension protocol)	17% vs 12%, p=0.25 CR+CRp: 26% vs 21%, p=0.35	No difference Pts with lestaurtinib plasma levels >20 µM had worse OS compared with controls (median 92 d vs 139 d, p=0.01) or to pts <20 µM (median 92 d vs 169 d)p=0.002)	Discontinued therapy due to disease progression or lack of response: 41% vs 67%, p<0.001 Mean time to response 43 d vs 41 d Early deaths (30 d): 12% vs 6%, p=0.24 Grade 3-4 adverse events 94% vs 93%, p=0.8; severe infection 32% vs 21%.	Outcomes of CR and OS. Planned sample size of 220 pts to yield 80% power based on odds ratio of 2.44 for CR/CRp. Study powered for OS. Analyzed cross-over pts according to control arm	Lestaurtinib added to salvage therapy gave no additional benefit

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ECOG E2995 Greenberg, 2004 (18)	129 Age 15-70 y, median 58 y, relapsed or refractory AML (n=89); or high-risk MDS (RAEB-t) or s-AML (n=40)	Reinduction PSC-833 (valspodar) (MTZ + etoposide + AraC in both arms)	MTZ + etoposide + AraC ± PSC-833 PSC-833 (valspodar; a multidrug resistance gene-1 modulator) arm: PSC-833 (2 mg/kg iv loading dose then 10 mg/kg/d for 5 d) + MTZ (4 mg/m^2/d iv push, d 1-5) + etoposide (40 mg/m^2/d iv over 30-60 min, d 1-5) + AraC (1 g/m^2/d over 1 h iv, d 1-5) Different doses in control arm due to pharmacokinetic interactions of PSC-833, MTZ, and etoposide Control: MTZ (8 mg/m^2/d, d 1-5) + etoposide (100 mg/m^2/d, d 1-5) + AraC (1 g/m^2/d, d 1-5) Maximum 2 induction cycles; pts with CR received additional cycle as consolidation within 4-6 w of CR	17% vs 25%, p=0.28 Age <50: 15% vs 39%, p=0.14 Age 50+: 17% vs 20%, ns	OS median 4.6 m vs 5.4 m, p=0.18 Median DFS 10 m vs 9.3 m, p=0.68	No significant differences in grade 3+ non-hematologic toxicity, except liver toxicity in PSC-833 (60% vs 38%, p=0.01)	Designed to detect improvement in CR from 20% to 40%. Early closure at 40% accrual because of lack of superiority of PSC-833	PSC-833 did not improve CR or OS
ECOG E1906; 2008-2013 Litzow, 2014 (368) [abstract]	91 Age 18-70 y prior diagnosis of AML, relapse <1 y after initial CR or refractory to initial induction (<2 courses) or 1 course reinduction. Upper limit changed to 65 y due to deaths	Reinduction Various	Carboplatin + topotecan vs FLAM vs sirolimus-MEC Arm A: carboplatin (150 mg/m^2/d CI, d 1-5) + topotecan (1.6 mg/m^2/d CI, d 1-5) Arm B (FLAM): flavopiridol (30 mg/m^2 in ½ h then 60 mg/m^2 over 4 h iv, 3 d) + AraC (667 mg/m^2 CI, d 6-8) + MTZ (40 mg/m^2 iv over 1-2 h, d 9) Arm C: sirolimus (12 mg po, d 1 then 4 mg po, d 2-9) + MTZ (8 mg/m^2/d over 15 min iv, d 4-8) + etoposide (100 mg/m^2/d over 1 h iv, d 4-8) + AraC (1 g/m^2/d over 3 h iv, d 4-8) Arm C discontinued after first stage evaluation at n=18 pts per group due to lower response	6% vs 17% vs 10% CR+CRi: 14% vs 28% vs 15%, ns	NR	NR	Primary outcome CR or CRi.	FLAM excessively toxic in elderly but suitable for younger pts
GOELAM; 1992-1995 Solary, 1996 (366)	140 Age 14-66 y, relapsed AML (n=108) or refractory AML (n=32)	Reinduction Quinine (MTZ + AraC in both arms)	MTZ + AraC ± quinine MTZ (12 mg/m^2/d, d 2-5), AraC (1 g/m^2/12 h, d 1-5), quinine (30 mg/kg/d CI starting 24 h before MTZ, d 1-5)	60% vs 53% Refractory: 47% vs 27%, ns Relapsed 64% vs 60%, ns	NR	Quinine group had more nausea, vomiting, mucositis, and cardiotoxicity. Quinine group had longer time to platelet count recovery (mean 36 d vs 29 d, p=0.037 for relapsed AML)	NR	

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
USA (lintuzumab); 1999-2001 Feldman, 2005 (17)	191 Age 18+ y, relapsed (within 1 y of 1st remission) or primary resistant AML. Excluded resistant AML pts with cumulative AraC dose of ≥3 g/m^2	Reinduction + consolidation Lintuzumab (MTZ + etoposide + AraC in both arms)	[MTZ + etoposide + AraC (MEC)] ± lintuzumab MTZ (8 mg/m^2/d, 6 d), etoposide (80 mg/m^2/d, 6 d), AraC (1 g/m^2/d, 6 d), Lintuzumab (12 mg/m^2 iv, for 4 d after completion of chemotherapy and 2nd cycle 10-12 d later; pts without CR allowed up to 10 additional cycles lintuzumab until progression or start of other therapy Pts with CR received 1 cycle consolidation with attenuated MEC: MTZ (2 d; or none if signs of cardiotoxicity) + etoposide (4 d) + AraC (4 d); pts received 2 cycles lintuzumab or none according to initial randomization Pts in lintuzumab group remaining in CR could receive monthly lintuzumab maintenance up to 8 more cycles	29% vs 23% CR + CRp: 36% vs 28%, p=0.28	OS median 156 d, no difference between arms	No differences in adverse effects, other than mild antibody infusion-related toxicities (fever, chills, hypotension) in 6% of lintuzumab pts.	Primary endpoint overall response (CR + CRp).	Lintuzumab was safe but did not statistically improve response or survival
VALOR; NCT01191801; 2010-2013 Ravandi, 2014, 2015 (369,370) [abstracts]; Smith, 2015 (371) [presentation]	711 AML, refractory disease or first relapse. 63% age ≥60 y	Reinduction Vosaroxin (AraC in both arms)	AraC plus vosaroxin or placebo AraC (1 g/m^2 iv over 2 h, d 1-5), vosaroxin (90 mg/m^2 iv over 10 min, d 1, 4; 70 mg/m^2 in subsequent cycles) Pts with CR or CRp received 1-2 cycles consolidation Previous induction with at least 1 cycle AraC plus anthracycline or anthracenedione	30.1% vs 16.3%, p=0.00001 Age ≥60: 31.9% vs 13.8%, p<0.0001	OS median 7.5 m vs 6.1 m, p=0.06, adjusted p=0.02 overall Censored for ASCT: 6.7 m vs 5.3 m, p=0.03 Pts age 60+: 7.1 m vs 5.0 m, p=0.003 Pts age <60: 9.1 m vs 7.9 m, p=0.6 Early relapse (CR duration 90 d to 12 m) 6.7 m vs 5.2 m, p=0.04 Refractory 6.7 m vs 5 m, p=0.23 Late relapse 14.1 m vs 12.3 m, p=0.96 EFS 2.1 m vs 1.3 m, p<0.0001 Median LFS age ≥60: 10.3 m vs 6.5 m, p=0.20	30-d mortality 7.9% vs 6.6%; 60-d mortality 19.7% vs 19.4%; age ≥60: 30-d mortality 10.2% vs 9l.0%, 60-d mortality 20.4% vs 22.6% Adverse effects: febrile neutropenia 11.3% vs 7.4%; sepsis 8.7% vs 4.3%; pneumonia 7.6% vs 4.9%; bacteremia 8.5% vs 2.9%; stomatitis 3.4% vs 1.4% In pts age ≥60: serious adverse effects 57% vs 33%	Primary outcome OS, short-term mortality. Per adaptive design, sample size was increased by 225 pts after interim analysis. Designed for 90% power for OS with HR=0.71 with 450 pts; HR=0.77 with 732 pts	Improved CR and OS with vosaroxin, especially in pts age 60+ or with early relapse

Trial name(s) or location, enrolment, source	Number of patients and characteristics	Phase randomized; major comparison	Arms or comparison	CR	OS; other survival outcomes (EFS, DFS, RFS)	Other outcomes	Statistical power and analysis	Conclusion
ECOG; NTC00005962; 2000-2002 Litzow, 2010 (367)	82 Primary refractory AML, first relapse after remission <1 y, or 2nd or greater relapse	Reinduction Various	AraC + GO vs AraC + liposomal DNR vs AraC + cyclophosphamide + topotecan + mesna Arm A: AraC (1 g/m^2/d iv, d 1-4) + GO (6 mg/m^2 iv, d 5) Arm B: AraC (1 g/m^2/d iv, d 1-4) + liposomal DNR (135 mg/m^2/d iv, d 1-3) Arm C: cyclophosphamide (300 mg/m^2 q12h iv, d 1-3) + AraC (1 g/m^2/d iv, d 2-6) + topotecan (1.5 mg/m^2/d CI, d 2-6) mesna (600 mg/m^2/d CI, d 1-3) Pts with CR allowed transplant or consolidation with one additional course of the same treatment, except arm B in which liposomal DNR was reduced to 100 mg/m^2/d	8% vs 7% vs 4% CR + CRp: 12% vs 7% vs 4%	OS median 3.7 m vs 2.4 m vs 3.8 m, p=0.7	No difference in grade 3+ non-hematological toxicity Treatment related deaths: 0% vs 14% vs 4%	Primary outcome CR or CRp	None of the regimens was effective enough to study further
ECOG E5483 1984-1988 Robles, 2000 (372)	86 (356) Age 18-75 y, median 47 y, relapsed or refractory AML; no previous HDAC or AMSA; not t-AML	Maintenance AraC maintenance	HDAC + AMSA; pts with CR randomized to low-dose AraC maintenance or observation HDAC (3 g/m^2 over 1 h iv q12h, d 1-6), AMSA (100 mg/m^2 as 1-h infusion, d 7-9) AraC (10 mg/m^2 sc q12h for 21 d every 2 m until relapse; starting 1-3 w after documented CR)	42%	OS from randomization: median 10.9 m vs 7.0 m, p=0.615 Median DFS 7.4 m vs 3.3 m, p=0.084	ITT basis: LFS 7.9 m vs 3.7 m, p=0.084. As treated: LFS 7.7 m vs 3.1 m, p=0.027	90 pts with CR to give at least 90% power to detect 100% increase in LFS. Required 405 pts assuming 22% CR to induction	Low-dose AraC maintenance can increase DFS. Due to high toxicity (28% mortality), HDAC + AMSA is not recommended for induction
GIMEMA; 1992-1996 Meloni, 1997 (373)	32 (264) Relapsed or refractory AML in second or subsequent CR	Maintenance Interleukin-2 (rIL-2)	Reinduction with MTZ + etoposide + AraC followed by consolidation Pts still in CR and not undergoing bone marrow transplant were randomized (n=32) to Interleukin-2 or not Interleukin-2 (rIL-2): 2 cycles at 8-18×10^6 IU/m^2/d CI then monthly 5-d courses at 4-8×10^6 IU/m^2/d; due to toxicity the first 2 cycles were reduced in 1994 to 8×10^6 IU/m^2/d	55%	OS NR For pts in 2nd CR (n=25): RFS 17% vs 0%; median time to relapse (5 m) similar in both groups DFS at 1 y: 42% vs 15%	NR	NR	Accrual goal not reached. Number of pts too low for statistically meaningful comparison. Further RCTs are needed.

ACR, aclarubicin; ADE, AraC + DNR + etoposide; AMSA, amsacrine; AraC, cytarabine = arabinofuranosyl cytidine = cytosine arabinoside; ATRA, all-trans retinoic acid; AZA, azacitidine; CI, continuous iv infusion; BHAC, N^4-behenoyl-1-β-D-arabinosylcytosine (widely used in Japan instead of AraC since 1979); CsA, cyclosporin A (cyclosporine); CPX-351, a liposomal formulation of cytarabine and daunorubicin (5:1 molar ratio); CR, complete remission (complete response); CRi, complete remission with incomplete recovery; CRp, complete remission without full platelet recovery; DFS, disease-free survival; DNR, daunorubicin; EFS, event-free survival; FLAM, flavopiridol + AraC + MTZ; GCSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GO, gemtuzumab ozogamicin; HAM, high-dose cytarabine + mitoxantrone; HDAC, high-dose cytarabine; HSCT, hematopoietic blood stem cell transplantation; IDA, idarubicin; IL-2, interleukin-2; ITT, intention to treat; iv, intravenously; LFS, leukemia-free survival; MDS, myelodysplastic syndromes; MTZ, mitoxantrone; NR, not reported; OS, overall survival; po, oral administration (per os); Pgp, P-glycoprotein; PR, partial response/remission; RAEB-t, refractory anemia with excess of blasts in transformation; RFS, recurrence-free survival; s-AML, secondary AML arising from MDS or myeloproliferative disease; sc, subcutaneously; SCT, stem cell transplant; std, standard; t-AML, therapy-related AML following treatment of primary malignant disease; TAD, thioguanine + cytarabine + daunorubicin

Back to Recommendations Back to Results Back to Discussion

Systemic Treatment of Acute Myeloid Leukemia (AML)

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the Program in Evidence-Based Care (PEBC) Report Approval Panel (RAP) and the Guideline Development Group (GDG) Expert Panel (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in September 2015. The RAP approved the document on September 18, 2015. They considered it a comprehensive, high-quality, and technical document. The other main comments from the RAP and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from RAP

Comments	Responses
Directions on where to look for guidance on the role of stem cell transplant and treatment of acute promyelocytic leukemia (APL) would be helpful. Why is transplant outside scope, and is it being addressed by another group?	Transplant citations were already included in the discussion, and have been added to the background of Section 2. Citations to APL guidelines have been added. The scope was determined so as not to overlap other recent guidelines and to allow this guideline to be completed in a reasonable amount of time with the resources available.
It would be a benefit if absolute improvements and risks could be articulated in the key evidence section or justification section.	Additional data have been added to the key evidence for some of the recommendations.
If the objective is to only consider conventional-dose systemic therapy, then that probably should be mentioned here.	The target population and Question 1 specify that it applies to patients who can tolerate intensive treatment. Conventional and high-dose treatments are included in the document, but not low-dose (which would apply to patients not suitable for intensive treatment).
Consider whether there is a strategy to visually represent these recommendations (e.g. flow chart, care plan). It is realized this may not be possible and may be assessable as is for the target readers.	This would be extremely complex, and care varies by treatment centre. The authors considered the document useful as is to the key readers.
The search period of 25 years appears very long. Should the search have been refined to a more recent time period? Have there been changes during that time period (drugs, patient factors, management issues, etc.) that may influence influenced survival rates and effects on disease and make interpretation of the data more difficult?	Current practice was established over 30 years ago, and since then many trials have tried to improve response or survival with limited success. It was deemed necessary to include trials back to that time period. A paragraph has been added to the methods in the systematic review (Section 4) The introduction/background to the recommendations indicates that improvement in

Perhaps this should be addressed and discussed. Would transplant, which evolved over these years, influence the studies, patients, results and outcomes in the various studies as to possibly effect the final recommendations of the group?	management of infection and other aspects of supportive care probably accounts for the lower treatment-related mortality and better survival in more recent studies, even when comparing the same chemotherapy regimens. In specific recommendations, as well as in the literature review, it is noted there are differences between results of earlier and more recent trials for some treatments such as high-does cytarabine. While the role of transplant has evolved and continues to be refined, the authors considered these recommendations to be appropriate as written.
It is unclear whether consideration of health benefits, side effects, and risks have been considered in formulating recommendations.	This is covered in the background/introduction to the recommendations in Section 3.
Recommendation 1 Evidence supporting recommendation of daunorubicin (DNR) for induction is weak in view of meta-analytic evidence that mitoxantrone (MTZ) is superior. It would be preferred the authors' buttress their opinion that the daunorubicin dose was too low in these randomized controlled trials with some empiric evidence that a higher dose of DNR provides equivalent efficacy to MTZ.	This should be read in conjunction with the statement in Key Evidence that DNR is the most studied and commonly used anthracycline for AML induction. Additional comments have been added to the interpretation of evidence to stress that MTZ was compared with doses of DNR lower than that in the recommendation or current use. Both MTZ and DNR_{60} are preferred over DNR_{45}. There is no direct evidence comparing MTZ and DNR_{60} (the recommended dose), and the Working Group believes the evidence insufficient to state a preference.
Recommendation 1 What is the definition of a young patient, old patient, and poor-risk factors?	Risk factors based on the European LeukemiaNet guideline (2) and a sentence on age have been added to the background and preamble and cross-referenced in the recommendation.
Recommendation 3 I am less convinced that there is not a role for cladribine. Is this because the context (Polish studies) does not translate well the Canadian scene? Cladribine, compared with fludarabine and clofarabine, seemed more promising and consistent in your key evidence section.	The authors are aware of some concerns with the Polish trial. Confirmatory trials are ongoing; however, the results so far appear not to support the level of benefit of cladribine found. The interpretation of evidence section has been revised to discuss this.
Recommendation 8 Is this the same definition of age as in Recommendation 1 of Question 1? Do prior different treatments make a difference on effectiveness?	Age definition is the same. Prior treatment may make a difference and this is indicated in the qualifying statements.
Recommendation 10 Is refractory and relapse the same definition in all studies over the 25 years used in the search?	It is likely there exist differences in the definitions of refractory and relapse among studies and over the 25-year time; however, the authors believe these differences do not alter the conclusions.

Expert Panel Review and Approval

Of the 23 members of the GDG Expert Panel, 16 members cast votes and 2 abstained, for a total of 78% response in September-October 2015. Of those that cast votes, all approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from the Expert Panel

Comments	Responses
Recommendation 1 Consider a stronger recommendation in favour of idarubicin (IDA) as the anthracycline of choice for upfront treatment. Evidence suggests complete remission and overall survival are better with IDA so I would be favouring that one over DNR and MTZ.	IDA and DNR were considered equivalent. There was lack of consensus on whether or not IDA is better than higher dose DNR. The evidence is stronger for IDA compared with DNR_{45}; survival effects were not different for IDA compared with higher dose DNR. Further details have been added to interpretation of evidence.
Isn't bullet point 3 in Recommendation 1 covered by bullet point 1? (I appreciate the evidence base is different but it seems repetitive)	The bulleted points in Recommendation 1 have been reorganized.
For recommendation 10, was there any discussion or role of inserting a statement about taking these relapsed/refractory patients to stem cell transplantation should they attain a response? (I appreciate this is not a focus of the document…but might be important in even deciding whether a patient should be treated with an aggressive re-induction or not).	While the intent in the treatment of relapsed and refractory AML is generally that responding patients go to allogenic transplant, the final decision about who is a transplant candidate is discussed in other guidelines (12)
Recommendation 10, I would not include the outcome rates, found it a bit confusing as to what it was referring (presumably the etoposide), I would think best to put those data in the key evidence.	This has been moved to key evidence.

EXTERNAL REVIEW BY ONTARIO CLINICIANS AND OTHER EXPERTS

Targeted Peer Review

Five targeted peer reviewers from Quebec, Alberta, and British Columbia who are considered to be clinical experts on the topic were identified by the Working Group. All agreed to be the reviewers and submitted responses. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=5)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				3	2
2. Rate the guideline presentation.			2	2	1
3. Rate the guideline recommendations.			2	2	1
4. Rate the completeness of reporting.		1	1	1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	3	1
6. Rate the overall quality of the guideline report.			1	2	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			2	2	1
8. I would recommend this guideline for use in practice.			2	2	1
9. What are the barriers or enablers to the implementation of this guideline report?	Gemtuzumab ozogamicin (GO) is not approved/available in Canada. Availability of midostaurin. Chemotherapy not "yet" approved in Canada may be acceptable in a compassionate use if demonstrated beneficial in particular cases such as a bridge to transplant in refractory AML Rapid availability of diagnostics-cytogenetics, FLT3 mutation testing				

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	Responses
Clarify objective to be "recommendations regarding the most effective *intensive* systemic treatment of AML"	"Intensive" has been added.
The guideline is oriented toward chemotherapy. Transplant needs to be mentioned more. One of the major decisions is whether to consolidate with chemotherapy or transplant. I would consider transplant systemic therapy. Otherwise perhaps rename the guideline "chemotherapy options for treatment of AML"	This guideline was worded based on the understanding that while transplantation is systemic, systemic therapy as a term is generally used to refer to chemotherapy and biologic or targeted therapy. We believe this is clear in the questions, in which transplant is specifically excluded. This is more fully addressed in the background in Section 2 and the preamble to recommendations for Question 2, as well the methods and exclusion criteria for the systematic review in Section 4.
Better define the target population. Consider defining not fit for "standard"	The assumption was that standard induction therapy is intensive treatment, and that those unable to tolerate these

induction chemotherapy instead of deemed suitable for intensive treatment as all will be users of chemotherapy agents somehow.	may receive palliative care including supportive care alone, or less intensive chemotherapy such as low-dose cytarabine (AraC). This is explained in the background portion of Section 2.
Consider a section on AML cases that are not fit for standard induction chemotherapy, including a discussion of azacitidine.	These patients were specifically excluded. Readers are referred to other guidelines
Need to comment on role of azacitidine (see AZA-AML-001trial)	The AZA-AML-01 trial is included in Table 4-12 and consideration of it has been added to the results portion of the systematic review (other induction agents). Numbers in the arms comparing standard induction to azacytidine were not large enough to determine whether or not the therapies were equally effective. Most places did not enrol patients in this trial who were fit enough for intensive induction. Other trials using AZA in addition to standard therapy found no additional benefit. While AZA may be an alternative for those unable or unwilling to receive standard intensive therapy, evidence is insufficient to recommend it otherwise.
Meta-analysis suggests benefit, albeit small, to idarubicin (IDA) versus DNR 60 mg/m^2/day	While there appears to be a small additional benefit of IDA compared with DNR, the difference was small enough that we considered both to be acceptable choices.
When referring to stem cell transplant, in addition to referring to other Cancer Care Ontario documents, also recommend early referral to a transplant centre for all patients that may be stem cell transplant candidates	This has been added to Section 2 background, as well as the preamble to recommendations for Questions 2 and 3.
For certain agents, notable AraC, precise use of dosing information should be used consistently (e.g., 3 g/m^2 q12 h instead of just 3 g/m^2)	Time period (generally q12 h or /day) has been added in the text where it was missing.
The role of cytogenetic risk stratification may determine which intensive induction chemotherapy or post-remission approach to use. This is alluded to but there is no mention of combination therapy with targeted FLT3 inhibitors. Readers need to know the current opinion of these agents such as sorafenib.	As indicated in the background of Section 2, some chemotherapy regimens may also work better for specific subtypes of AML, and this is considered in recommendations for HDAC. Most trials (with a few exceptions) were neither designed nor powered to distinguish treatment effectiveness for specific molecular subgroups. Evidence for sorafenib and other targeted agents is discussed in the literature review (Section 4) but our interpretation is that trials did not provide sufficient evidence for their use and therefore no recommendations were made. Some trials are ongoing.
Recommendation 2 Surprised by inclusion of GO in induction. Recommendation of GO seems inappropriate when the drug was withdrawn from the market in 2010 and not commercially available in Canada. I do not agree entirely with the GO recommendation – there is no evidence supporting its use in patients with adverse risk cytogenetics in any study. I	Our interpretation of the evidence is that GO at 3 mg/m^2 is of benefit and therefore merits a recommendation for its administration. In Table 4-10, notes for the SWOG S0100 trial indicate GO was withdrawn from the US market based on this trial even though other trials were ongoing. This trial used GO at 6 mg/m^2, which we have stated is not recommended; later trials investigating GO at 3 mg/m^2 found benefit. Upcoming information suggests GO may be soon approved. This is a difference in interpretation. As indicated, the authors believe the evidence is insufficient to exclude specific subgroups.

do agree that it should be recommended for other patients.	
Not sure whether there are not data to support four rounds of consolidation	There are no data to support four rounds consolidation.
Recommendation 10 High-dose etoposide and cyclophosphamide have been widely used in relapsed/refractory AML over the last 25 years, based on the [case-series] study by Brown et al (388)	A targeted literature search indicates that, based on the trial by Brown et al (388), a case-series study (n=42) was conducted in Vancouver, BC (23) mainly in patients with poor response to high dose AraC (1.5 g/m^2 q12 h for six days) + DNR (45 mg/m^2/day for three days) and found 54% CR. Both this study and the previous one by Brown et al suggested benefit in patients with resistance to HDAC. Another small consecutive case-series in 34 patients with refractory AML (initial induction with standard 7+3 AraC + DNR) or relapsed AML (389) found benefit in the relapsed pts (48% complete remission) but not refractory patients (8% complete remission). The authors suggested possible benefit for patients with underlying cardiac or neurologic disease unable to tolerate additional anthracyclines or HDAC. No comparative trials appear to have been published. The Leukemia/Bone Marrow Transplant Program of BC's current treatment guideline (390) indicates that patients without complete response to conventional 7+3 chemotherapy (AraC 100 mg/m^2/d + DNR 60 mg/m^2) be treated with high-dose etoposide (2.4 g/m^2 CI over 34 h) plus cyclophosphamide (2 g/m^2/day, days 3 to 5). This appears to be an internal unpublished guideline. No rationale is given for the change in initial induction from HDAC in their trial (23) to conventional dose AraC in the guideline. Based on the above, the authors consider evidence on high-dose etoposide and cyclophosphamide very limited after HDAC regimens and not available after conventional 7+3 regimens. A trial comparing HDAC + anthracycline ± etoposide versus high-dose etoposide + cyclophosphamide appears warranted. Until that time, we are unable to recommend high-dose etoposide + HDAC as general practice, but acknowledge its use in those resistant to or unable to tolerate HDAC and/or anthracycline.
Add definition for relapsed/refractory AML. Relapse after a long period of remission may be approached in a manner similar to new leukemia. The role of blast marrow assessment day 14 of first induction to justify reinduction prior to day 28 and does this meet the definition of refractory?	As indicated in Recommendation 10, there is a difference in opinion as to whether relapse after a long period is a new disease, and this may be resolved in the future by molecular testing. Day 14 marrow blast assessment is used for historical reasons in Leukemia Intergroup trials, but is not current practice otherwise. There is no good rational and has never been explicitly shown to be of benefit in aiding decisions about retreatment.
Consider including a flow chart decision algorithm approach to summarize the recommendations.	This would be extremely complex, and care varies by treatment centre. The authors considered the document useful as is to the key readers.

There appears to be some inconsistency in discussion of Section 4 and recommendations regarding fludarabine-based regimens. Consistent results of FLAG-IDA in relapsed/refractory AML are not emphasized throughout the guideline	Strong consistent results have not been reported. Limitations to studies have been given in key evidence and qualifying statements. The authors believe stronger recommendations are not warranted.
Add statement in summary of recommendations about not being any recommendations for Question 4 as it just seems they are missing.	This has been added.
Section 4 (literature review) lacks summary statements and associated levels of evidence, although this is rephrased in Section 2. Sections 2 and 4 could be merged.	The structure of our work is to complete a systematic review of the evidence first, and then to develop recommendations separately. In order to avoid too much repetition, the reader is referred to the recommendations (Section 2) instead of including detailed conclusions in the systematic review.
The recommendations regarding maintenance therapy include dated studies that are now over 20 years old. No one uses maintenance therapy. I think Recommendation #9 should be reworded to state that the evidence does not support the use of maintenance therapy in patients who have received consolidation therapy.	We did not consider there to be sufficient evidence to make a recommendation at this time. The effect of this is that current practice will continue until such time as more evidence becomes available. Based on past experience there is no evidence maintenance is useful as it currently exists; however, there are ongoing studies examining this issue (e.g., trials in Table 4-17). Ongoing trials with new drugs with different mechanisms of action and targeted therapy may find a benefit. The qualifying statement has been reworded to reflect this.
The report needs to include new data to be presented at American Society of Hematology (ASH) conference this year on Midostaurin. This study demonstrates a clear survival benefit of adding the FLT3 inhibitor Midostaurin to induction chemotherapy for patients with FLT3 mutations. Consideration should be given to recommending this as frontline therapy in these patients.	This has been added in Ongoing studies (Table 4-13) and a footnote in the results section as the data were not available at the time of the literature review. Our policy is not to make recommendations based only on non-published data or abstracts. A comment has been added in the background regarding new agents.
Recommendation 10 should include FLAG-IDA, for which there are several published reports demonstrating efficacy in the relapsed setting. Should also include FLAG for patients who are unable to tolerate anthracyclines.	Wording similar to recommendation 3 for induction has been added to the qualifying statements.
Recommendation 10: For the second and third regimens listed, why is only AraC 500 mg/m^2 CI or 100 mg/m^2 q12h considered? What about MEC (MTZ + etoposide + AraC [1 g/m^2 q24h]), or NOVE-HiDAC (MTZ + etoposide + AraC [1.5 g/m^2 q12h]? These are widely used. I think it would be better to either remove any reference to AraC dosing, or include all the published options.	Mention of other doses has been added to the qualifying statements.
There is no specific reference to how to treat primary induction failures to 3+7.	We use refractory to mean refractory to the first line induction treatment, whatever that may be.

This is not necessarily the same as refractory disease. The latter term should be defined – refractory to what? 3+7 or HiDAC?	
The recommendations on consolidation therapy should also state that two to three consolidations are not required for patients who are to undergo allogeneic hematopoietic stem cell transplantation. There is ample evidence that those patients can go to transplant right after induction or 1 consolidation, and this does not compromise outcomes.	A sentence has been added to the preamble to the recommendation to indicate this.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. Professionals in the PEBC database with a valid email address and who were categorized as having hematological or leukemia interest, or with a profession of hematologist or hematopathologist were informed of the guideline and asked if they would participate in the consultation.

One hundred seventeen people (99 in Ontario and 8 elsewhere) were contacted and 20 (17%) responses were received. Thirteen stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from seven people are summarized in Table 5-5. Four reviewers indicated it was a thorough and comprehensive summary of the evidence. The other major comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				4 (71%)	3 (43%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1 (14%)	2 (29%)	4 (57%)
3. I would recommend this guideline for use in practice.		2 (29%)		2 (29%)	3 (43%)
4. What are the barriers or enablers to the implementation of this guideline report?	Drug availability, e.g., gemtuzumab ozogamicin Delays in obtaining cytogenetic information Regional practices may differ; standard protocols involve nursing staff, pharmacy, etc. Current practice, toxicities, relatively minor differences in outcome Disease Registry to track and trace patients in clinical trials worldwide would be (is) beneficial				

Table 5-6. Modifications/actions taken/responses regarding main written comments from professional consultation.

Comments	Responses
We address molecular profiling of the disease but we need to address personalized profiling of the patient who has the disease and then address the treatment protocol accordingly. Simply, leukemia treatment in the future should be like antibiotic sensitivity we have to choose the right drug for the right disease in the right patient. These new concepts are being introduced through Personalized Medicine and Personalized Cancer Medicine.	We agree that this is important and will find more application in the future. The importance of molecular profiling is noted in the background of Section 2.
Some areas as still somewhat ambiguous including optimal consolidation and treatment of relapsed/refractory disease but hopefully newer agents and/or studies will help to clarify best treatment practices.	As noted, this is a limitation of the current data.
The Canadian Leukemia Studies Group (CLSG) trial was excluded. I suggest including it in your analysis. Day 14 marrow and its prognostic significance is excluded and should be part of the guideline (see CLSG trial). In patients age >60 years, addition of MTZ + etoposide at day 14 or upon recovery for those not responding or in remission is excluded.	No publications of randomized controlled trials from the CLSG were located in the literature search. The pilot phase II study was not a randomized trial (391). Detailed searches as a result of this suggestion found two abstracts from 2005 and 2006 (392,393). Lack of full publication with longer follow-up despite the 10 years since preliminary results limits our use of the results.

Conclusions

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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APPENDICES

APPENDIX 1. MEMBERS OF THE WORKING GROUP AND EXPERT PANEL

Name	Profession	Institution/Location	Role
Andre Schuh	Hematologist	Princess Margaret Cancer Centre/University of Toronto, Toronto	Working Group chair
Brian Leber	Hematologist	McMaster University/Juravinski Cancer Centre, Hamilton	Working Group
Mitchell Sabloff	Hematologist	Ottawa General Hospital/University of Ottawa, Ottawa	Working Group
Glenn G. Fletcher	Health Research Methodologist	Program in Evidence-Based Care, Hamilton	Working Group
Chris Bredeson	Hematologist	The Ottawa Hospital, Ottawa	Expert Panel
Rena Buckstein	Hematologist	Odette Cancer Centre at Sunnybrook Health Sciences Centre, Toronto	Expert Panel
Matthew Cheung	Hematologist	Odette Cancer Centre at Sunnybrook Health Sciences Centre, Toronto	Expert Panel
Patricia Disperati	Hematologist	Toronto East General Hospital, Toronto	Expert Panel
Jill Dudebout	Hematologist	Cancer Centre of Southeastern Ontario at Kingston General Hospital / Queen's University, Kingston	Expert Panel
Lisa Hicks	Hematologist	St. Michael's Hospital, Toronto	Expert Panel
David Hodgson*	Radiation oncologist	Princess Margaret Hospital, Toronto	Expert Panel
Sindu Kanjeekal	Hematologist	Windsor Regional Cancer Centre at Windsor Regional Hospital, Windsor	Expert Panel
C. Tom Kouroukis	Hematologist	Juravinski Cancer Centre, Hamilton	Expert Panel
Nicole Laferriere	Hematologist	Northwestern Ontario Regional Cancer Centre at Thunder Bay Regional Health Sciences Centre, Thunder Bay	Expert Panel
Leonard Minuk	Hematologist	London Health Sciences Centre, London	Expert Panel
Anca Prica	Hematologist	Odette Cancer Centre at Sunnybrook Health Sciences Centre, Toronto	Expert Panel
David Robinson	Patient Representative, Economist	Department of Economics, Laurentian University, Sudbury	Expert Panel
Robert (Bob) Stevens	Hematologist	Grand River Regional Cancer Centre, Kitchener	Expert Panel
Jonathan Sussman	Radiation oncologist	Juravinski Cancer Centre / McMaster University, Hamilton	Expert Panel
Ivan Tyono *	Pharmacist	Odette Cancer Centre at Sunnybrook Health Sciences Centre, Toronto	Expert Panel
Anthony Woods	Hematologist	Durham Regional Cancer Centre, Oshawa	Expert Panel
Yael Zaretsky	Hematologist	Credit Valley Hospital, Toronto	Expert Panel

*Abstained from voting on whether to approve the document.

APPENDIX 2. CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Hematology Disease Site Group members, and internal and external reviewers were asked to disclose potential conflicts of interest.

One author declared no conflicts. MS reported consulting fees of >$5000 from Celgene Advisory Board; research grants from Celgene, Roche, and Lundbeck; was principle investigator of a trial of azacitidine versus conventional care in older subjects with AML; and was involved with advisory boards for Lundbeck and Amgen. ACS declared being a shareholder in Aurora Interactive Inc, research support from Celgene, and was principle investigator of trials of lenalidomide maintenance in AML and of azacitidine in elderly AML patients (AZA-AML-001). BL declared consulting fees from the Medial Advisory Boards and Speakers Bureau, Celgene Canada and Novartis Canada.

For the Expert Panel, 18 members declared they had no conflicts of interest, and 5 declared conflicts. CB declared research support and support of the fellowship program from Otsuka, Sanofi, and Celgene, was principal investigator on a trial of busulfan compared with total body irradiation in hematopoietic cell transplantation. CB is President of the CBMTG and President Elect of the ASBMT; both organizations received support from several commercial entities. LH declared grants as co-investigator from Gilead Sciences. PD declared travel support from Novartis. RB declared a grant from Celgene for the National Registry and is principle investigator for a trial on lenalidomide in myelodysplastic syndromes (MDS) and a trial on azacitidine.

Members of the RAP declared they had no conflicts of interest.

The targeted peer reviewers declared the following potential conflicts of interest. TN received financial support (research grants, advisory boards, honoraria for talks) from Celgene, Novartis, Alexion, and Jansen; advisory board and research support from Celgene; and was principle investigator of a trial of gemtuzumab ozogamicin in younger patients with AML. JB received clinical trial research grants from Merck, Novartis, Boehringer-Ingelheim, Pfizer, Celgene, Astex, and Ambit. MLS received consulting funds from Novartis, Pfizer, Bristol-Myers Squibb (BMS), Jazz, Celgene, and Lindrech; Research support from Celgene, was principal investigator for clinical trials (NCIC ALC.3, LAC.4, MDC.1; Phase I and II KPT (Karyopharm); Pfizer MDS Study, and was an author or the Alberta Provincial Guideline for AML. JS received travel support and consulting fees as a member of the Advisory Boards from Celegene and Novartis; was principle investigator of studies of volasertib (Boeringer Ingelheim), azacitidine (Celgene) and Tosedostat (Opal study, Chroma Therapeutics); and provided input to a review of Quebec pharmaceutical practices and outcomes of 5-azacitidine in MDS and AML.

Several of the coauthors and reviewers (JB, JK, BL, TN, MS, ACS, JS) were involved in a Canadian consensus guideline on treatment of older patients with AML.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy.

To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca

APPENDIX 3. LITERATURE SEARCH STRATEGY

Search Date: October 17, 2014

Embase 1988 to 2014 Week 41, Ovid MEDLINE(R) without Revisions 1996 to October Week 2 2014, Ovid MEDLINE(R) 1988 to 1995, Ovid MEDLINE(R) Daily Update October 16, 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 16, 2014

#	Searches
1	exp phase 3 clinical trial/ or exp "phase 3 clinical trial (topic)"/ or exp clinical trial, phase iii/ or exp clinical trials, phase iii as topic/ or exp phase 4 clinical trial/ or exp "phase 4 clinical trial (topic)"/ or exp clinical trial, phase iv/ or exp clinical trials, phase iv as topic/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or exp controlled clinical trial/ or exp randomized controlled trials as topic/ or exp randomization/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/ or exp placebos/ or exp placebo/ or ((exp phase 2 clinical trial/ or exp "phase 2 clinical trial (topic)"/ or exp clinical trial, phase ii/ or exp clinical trials, phase ii as topic/ or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/) and random$.tw.) or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or ((singl$ or double$ or treple$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw. or placebo?.tw. or (allocat: adj2 random:).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.
2	exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw.
3	exp evidence based practice/ or exp practice guideline/ or guideline.pt. or practice parameter$.tw. or practice guideline$.mp. or (guideline: or recommend: or consensus or standards).ti. or (guideline: or recommend: or consensus or standards).kw.
4	2 not 1
5	3 not (1 or 2)
6	limit 1 to yr=1990-current
7	limit 4 to yr=1990-current
8	limit 5 to yr=2009-current
9	(exp Acute granulocytic leukemia/ or exp acute megakaryocytic leukemia/ or exp acute monocytic leukemia/ or exp acute myeloblastic leukemia/ or exp acute myelomonocytic

leukemia/ or exp Leukemia, Myeloid, Acute/ or (Acute adj2 leuk?emia$ adj2 (granulocytic or megakaryocytic or monocytic or myeloblastic or myelomonocytic or myeloid or myelocytic or myelogenous or nonlymphoblastic or non-lymphoblastic or nonlymphocytic or non-lymphocytic or erythroid or monoblastic or basophilic or erythroid or monoblastic or nonlymphoid or non-lymphoid)).tw. or (acute panmyelosis with myelofibrosis or pure erythroid leuk?emia$ or erythroleuk?emia$ or myeloid sarcoma or myeloid leuk?emia$ associated with Down syndrome or myeloid proliferations related to Down syndrome or transient abnormal myelopoiesis or blastic plasmacytoid dendritic cell neoplasm or therapy-related myeloid neoplasms).tw. or ANLL.mp. or (AML not (angiomyol: or amylose or amlodipine)).mp.) not ((comment or letter or editorial or case reports or historical article or note).pt. or exp case report/ or exp case study/)

10 (exp Myelodysplastic syndrome/ or exp Myelodysplastic syndromes/ or ((dysmyelopoietic or myelodysplastic) adj1 syndrome?).mp. or (Myelodysplasia? adj hematopoetic).mp. or (bone marrow dysplasia or myelodysplasia or 5q-syndrome or 5q syndromeor mixed myelodysplastic myeloproliferative disease or refractory anemia or refractory cytopenia with multilineage dysplasia or refractory cytopenia with multilineage dysplasia).mp.) not ((comment or letter or editorial or case reports or historical article or note).pt. or exp case report/ or exp case study/)

11 10 not 9

12 6 and 9

13 7 and 9

14 8 and 9

15 6 and 11

16 7 and 11

17 8 and 11

18 remove duplicates from 12

19 remove duplicates from 13

20 remove duplicates from 14

21 remove duplicates from 15

22 remove duplicates from 16

23 remove duplicates from 17

24 18 or 19 or 20

25 21 or 22 or 23

26 (5 and 9) not 8

27 (5 and 11) not 8

28 remove duplicates from 26

29 remove duplicates from 27

October 23, 2014 reran search [see lines 26 to 29 above] to include older (pre-2009) guidelines as review of results indicated that "guidelines" search also found non-guideline articles that may be of interest.

Section 6: Document Assessment and Review

*C. Bredeson, K. Yee, L.D. Durocher-Allen, and Members of the **Acute Leukemia Advisory Committee***

February 28, 2019

The 2016 guideline recommendations

REQUIRE UPDATING

This means that the guidance document needs updating to ensure that the recommendations reflect current evidence and practice. The existing recommendations remain relevant and it is still appropriate for this document to be available while the updating process unfolds.

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care on February 2, 2016.

In December 2017, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (LDA) conducted an updated search of the literature. Two clinical experts (CB and KY) reviewed and interpreted the new eligible evidence and proposed the existing recommendations should be updated. Members of the Acute Leukemia Advisory Committee (See Appendix 1 for membership) discussed the guideline on February 28, 2019 and determined that the guideline requires updating.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. What is the most effective systemic induction treatment for adults with previously untreated acute myeloid leukemia (AML) who can tolerate intensive treatment?

2. What is the most effective systemic post-remission treatment (consolidation and/or maintenance, excluding stem cell transplant) for adults with previously untreated AML?

3. What is the most effective systemic treatment (reinduction, consolidation, maintenance; not including stem cell transplant) for adults with relapsed or refractory AML who can tolerate intensive treatment?

4. Which patient characteristics are most important when making treatment decisions?

Target Population:

The target population is adult patients with AML (excluding acute promyelocytic leukemia [APL]) who are deemed suitable for intensive treatment.

Study Selection Criteria:

Inclusion Criteria:

• Adult patients with AML randomized to systemic treatment versus other systemic treatment (including different schedule/dose) or placebo

• For induction therapy, at least one arm consisted of systemic therapy including a combination of a cytarabine and an anthracycline (or derivative such as the anthracenedione mitoxantrone)

• RCTs could include a mixture of leukemias/myelodysplastic syndromes (MDS) as long as at least 50% of patients had AML or outcomes of AML patients were reported separately.

• Reported outcomes related to disease control (complete remission rate) and/or survival.

Exclusion Criteria:

• Studies focused on stem cell transplantation, supportive care (e.g., transfusions, prevention or treatment of infections or iron overload). Granulocyte colonystimulating factor (GCSF) or related agents were not excluded when it appeared use was being evaluated as part of the systemic therapy to treat AML (instead of complications/side effects).

• RCTs of systemic treatment compared with transplantation.

• Retrospective studies, prospective cohort studies, case control studies, case series studies.

• Studies focused on patients with APL, acute lymphoblastic leukemia, non-acute leukemias, or MDS.

Original Search Details:

- Clinical practice guideline providers: National Guideline Clearinghouse, SAGE, CMA, NICE, SIGN, ASCO, NCCN, National Health and Medical Research Council, and the New Zealand Guidelines Group.
- 2006 to August 18, 2015 (MEDLINE and EMBASE)
- Conference abstracts: American Society for Clinical Oncology (ASCO), American Society for Hematology (ASH), and European Hematology Association (EHA) - 2009 to 2015
- ClinicalTrials.gov

Summary of New Evidence:

The search covered the time period from August 2015 to March 2018. The search strategy is shown in Appendix 2. A total of 2673 hits from MEDLINE, EMBASE, and clinical practice guideline providers were retrieved. Sixty one were identified as relevant publications: 5 guidelines, 3 systematic reviews, and 53 publications of primary studies and abstracts. Four ongoing trials were identified. The Clinical Experts noted that the most important and compelling evidence concerned midostaurin and CPX-351. Therefore, the evidence pertaining to these agents was collated into one table: 3 guidelines, 1 systematic review, and 8 primary

studies (Table 1). The evidence not pertaining to midostaurin and CPX-351 was categorized by guideline literature (Table 2), systematic reviews (Table 3), and primary studies (Table 4). Ongoing studies are shown in Table 5.

Impact on the Guideline and its Recommendation

The landscape of AML treatment is changing rapidly; it focuses on clinical and genomic features to guide treatment (i.e. selects specific patient populations). Cytogentic and molecular characterization of AML at diagnoses (and relapse) is important for new and emerging therapies that can help guide individualized treatment. With the recent approval of midostaurin in combination with duanorudicin (idarubicin) + cytarabine for patients with untreated FLT3 mutated AML and anticipated approval of CPX-351 (Vyxeos) for the treatment of adults with two types of AML: newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC), and Gemtuzumab ozogamicin (Mylotarg)for the treatment of adults with newly diagnosed AML whose tumors express the CD33 antigen (CD33-positive AML), the current guidelines require an update.

Clinical Expert Interest Declaration:

Dr Bredeson reported that he has received research funding from Otsuka Celgene Sanofi.

Dr Yee reported being a principal investigator for a phase 1 multicenter, open-label dose escalation and dose-expansion study of MEDI7247; a phase 3 trial of guadecitabine versus treatment choice in adults with previously treated AML; a phase 1b trial with MK-8628; a phase 1 study evaluating safety, tolerability, pharmacokinetics of escalating doses of AGS67E; a phase 1b/2 multi arm study with venetoclax in combination with cobimetinib and venetoclax in combination with idasanutlin; a phase 3 study of SGI-11- vs treatment choice; a phase 1 study of dose escalation to investigate the safety, pharmacokinetics, pharmacodynamics of GSK2879552; a phase 1 dose finding study of bromodomain inhibitor OTX015; a phase 1 study dose escalation study of RO6839921; a multi-center extensions study of R05045337; a multicenter open label phase 1/1b study of R05503781; a phase III multicenter randomized trial of CPX-351 vs cytarabine and daunorubicin in pts 60-75 yrs; a phase I study of the safety and efficacy of vismodegib in relapsed/refractory AML and MDS pts; a phase III study of volasertib in combination with subcutaneous low dose cytarabine vs placebo + low dose cytarabine in pts >= 65 yrs.

Ontario
Cancer Care Ontario
Action Cancer Ontario

Document Review Tool

Number and Title of Document under Review	12-9 Systemic Treatment of Acute Myeloid Leukemia (AML)
Current Report Date	February 2, 2016
Date Assessed (by DSG or Clinical Program Chairs)	December 6, 2017
Health Research Methodologist	Lisa Durocher-Allen
Clinical Expert	Dr. Christopher Bredeson and Dr. Karen Yee
Approval Date and Review Outcome (once completed)	February 28, 2019 UPDATE

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No
2. Does the newly identified evidence support the existing recommendations?	No
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	No

Review Outcome as recommended by the Clinical Expert	UPDATE
If the outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	
DSG/GDG Commentary	

Table 1. Summary of evidence pertaining Midostaurin or CPX-351

Citation (ref)	Search dates	Recommendations
Guidelines		
Brandwein 2017; Canadian Cib [1]	Consensus process; no lit search details	• Intensive induction therapy should be considered for all pts below age 80, except for those with high co-morbidity score, and those with adverse risk cytogenetics who are not potential candidates for HSCT in CR. However, there is no consensus as to what degree of comorbidity constitutes an absolute contraindication to such therapy. • In the case of pts with adverse risk cytogenetics, induction therapy should generally be restricted to pts that are potential candidates for HSCT in CR. • Although co-morbidity indices are helpful, geriatric assessment tools for physical function and cognition can aid in decision-making regarding suitability for intensive chemotherapy. However they should not replace clinical judgement. • Older pts with de novo AML and intermediate or favourable risk cytogenetics, who are deemed suitable candidates, should receive induction treatment consisting of anthracycline or anthracenedione for 3 days plus cytarabine (100-200 mg/$m^{2)}$ for 7 days (3+7). Acceptable anthracyclines/anthacenediones include: Daunorubicin 60 mg/m^2 daily x 3 days; Idarubicin 12 mg/m^2 daily x 3; Mitozantron 12 mg/m^2 daily x 3. • For pts with contraindications to antrhacyclines (e.g. impaired left ventricular function or extensive prior anthracycline exposure), the FLAG regimen (fludarabine, cytarabine and filgrastim) would be a suitable option, in addition to those in the initial recommendations. • For older pts who are candidates for intensive chemotherapy, FLT ITD and TKD mutations testing results should be provided within one week. For pts up to age 70 with a FLT3 ITD or TKD mutation, midostaurin, if available, should be added to induction and consolidation, and continued as maintenance therapy if not transplanted, in the scheduled used in the RATIFY and German AMLSG studies. • For non-FLT3 mutated patients up to age 70 with de novo AML and favourable or intermediate risk cytogenetics, gemtuzumab ozogamicin, if available, should be added to induction and consolidation therapy, in the scheduled used in the ALFA study. • For pts with de novo AML and adverse risk cytogenetics, induction chemotherapy (either in a standard format or in the context of a clinical trial) should be used for transplant candidates. Non-transplant candidates should be enrolled in a clinical trial or should receive hypomethylating agent. • For AML arising from prior MDS or CMML or therapy related AML, CPX-351, if available should be used as induction and post-remission therapy in pts age 60-75 who are eligible for intensive therapy. • If CPX-351 is not available, standard induction chemotherapy should be used for HSCT candidates. For non-HSCT candidates otherwise medically fit for intensive therapy and with intermediate/favourable risk cytogenetics, induction chemotherapy or hypomethylating agents are both reasonable options. • For pts not medically fit for intensive therapy, or with adverse risk cytogenetics and not a candidate for alloHSCT, enrolment in a clinical trial or a hypomethylating agent (if not previously utilized) should be considered. **Author comment: Recommendation which have not been specifically revised from the original paper are still felt to apply and were not repeated in paper.*
Dohner et al.; European LeukemiaNet [2]	Consensus process; no lit search details	Patients eligible for intensive chemotherapy: Induction therapy (all ages) ("7+3"): 3 d of an IV anthracycline: daunorubicin at least 60 mg/m2; idarubicin 12 mg/m2 or mitoxantrone 12 mg/m2, and 7 d of continuous infusion cytarabine (100-200 mg/m2) Consolidation therapy- Younger patients (18-60/65 y)* Favorable risk genetics: 2-4 cycles of IDAC (1000-1500 mg/m2 IV over 3 h q12h, d1-3; or 1000-1500 mg/m2 IV over 3 h d1-5 or 6) Intermediate-risk genetics: Allogeneic HCT from matched-related or unrelated donor; 2-4 cycles of IDAC (1000-1500 mg/m2 IV over 3

		h q12h, d1-3; or 1000-1500 mg/m2 IV over 3 h d1-5 or 6), or High-dose therapy and autologous HCT Adverse-risk genetics: Allogeneic HCT from matched-related or unrelated donor Consolidation therapy- Older patients (60/65 y) Favorable-risk genetics: 2-3 cycles of IDAC (500-1000 mg/m2 IV over 3 h q12h, d1-3; or 500-1000 mg/m2 IV over 3 h d1-5 or 6) Intermediate/adverse-risk genetics: No established value of intensive consolidation therapy; consider allogeneic HCT in patients with low HCT-Comorbidity Index, or investigational therapy * Patients, at least those aged 18 to 60 y, with newly diagnosed AML and activating FLT3 mutations may be considered to receive additional therapy with midostaurin (administered after the chemotherapy); Results from assessment of MRD should be taken into account for selecting the appropriate consolidation therapy. Patients considered not candidates for intensive chemotherapy: Azacitidine: 75 mg/m2, SC, d1-7, q4 wk, until progression (Approved by FDA and EMA for adult patients who are not eligible for HCT with AML with 20% to 30% blasts and multilineage dysplasia; in addition, approved by EMA for patients who are not eligible for allogeneic HCT with AML with >30% marrow blasts.) Decitabine: 20 mg/m2, IV, d1-5, q4 wk, until progression. (Approved by EMA (not by FDA) for patients with newly diagnosed de novo or secondary AML, who are not candidates for standard induction chemotherapy.) Low-dose cytarabine: Low-dose cytarabine (20 mg q12h, SC, d1-10, q4 wk; until progression); not recommended in patients with adverse-risk genetics Best supportive care: Including hydroxyurea; for pts who cannot tolerate any antileukemic therapy, or who do not wish any therapy Common salvage regimens in patients not responding to a first induction cycle or with relapsed disease who are candidates for intensive therapy IDAC (with or without anthracycline): IDAC (1000-1500 mg/m2 IV over 3 h q12 h, d1-3 [500-1000 mg/m2 in patients .60 y]; or 1000-1500 mg/m2 IV over 3 h d1-5 or 6 [500-1000 mg/m2 in patients .60 y]); with or without daunorubicin 45-60 mg/m2, IV, d1-3; idarubicin 8-10 mg/m2, IV, d3-5, or mitoxantrone 8-10 mg/m2, IV, d1-3. Evidence from pharmacologic studies and clinical trials in first-line treatment indicate that doses higher than 1500 mg/m2 are above the plateau of the maximal therapeutic effect; single-agent IDAC should not be used in patients relapsing within 6 mo following consolidation with higher doses of cytarabine. FLAG-IDA: Fludarabine 30 mg/m2 IV, d2-6; cytarabine 1500-2000 mg/m2 IV over 3 h, starting 4 h after fludarabine infusion, d2-6; idarubicin 10 mg/m2 IV, d2-4; G-CSF 5 mg/kg, SC, d1-5; additional G-CSF may be administered starting 7 d after end of chemotherapy until WBC count .500/uL. Consider dose reduction in patients >60 y: fludarabine 20 mg/m2; cytarabine 500-1000 mg/m2; idarubicin 8 mg/m2 MEC: Mitoxantrone 8 mg/m2, d1-5; etoposide 100 mg/m2, d1-5; cytarabine 1000 mg/m2, d1-5. Idarubicin may be replaced by mitoxantrone 10 mg/m2, IV, days 2 to 4 (FLAG-MITO); or by amsacrine 100 mg/m2, days 2 to 4 (FLAG-AMSA). Allogeneic HCT: Consider transplantation for patients with primary refractory disease, for patients in second CR or with major cytoreduction but still active disease following salvage therapy. Consider second transplantation under certain conditions (see "Salvage treatment"). Perform early HLA typing
National Comprehensive Cancer Network O'Donnell 2017 [3]	Consensus Process; no lit search details	**Age <60 yrs:** ***Induction*:** Clinical Trial or Standard-dose cytarabine 100–200 mg/m2 continuous infusion x 7 days with idarubicin 12 mg/m2 or daunorubicin 60–90 mg/m2 x 3 days (category 1) or Standard-dose cytarabine 200 mg/m2 continuous infusion x 7 days with daunorubicin 60 mg/m2 x 3 days and cladribine 5 mg/m2 x 5 days (category 2A) or High-dose cytarabine (HiDAC) 2 g/m2 every 12 hours x 6 days or 3 g/m2 every 12 h x 4 days with idarubicin 12 mg/m2 or daunorubicin 60 mg/m2 x 3 days (1 cycle) (category 1 for patients 45 y, category 2B for other age groups) or Standard dose cytarabine 200 mg/m2 continuous infusion x 7 days with daunorubicin 60 mg/m2 x 3 days and oral midostaurin 50 mg every 12 hours, days 8-21 (FLT3-mutated AML) or Fludarabine 30 mg/m2

		IV days 2–6, HiDAC 2 g/m2 over 4 hours starting 4 hours after fl udarabine on days 2–6, idarubicin 8 mg/m2 IV days 4–6, and G-CSF SC daily days 1–7 (category 2B) **After induction:** I*f significant residual disease without a hypocellular marrow:* Cytarabine 1.5–3 g/m2 every 12 hours x 6 days or Standard-dose cytarabine with idarubicin or daunorubicin or Standard-dose cytarabine with daunorubicin and midostaurin. *If significant cytoreduction with low % residual blast:* Standard-dose cytarabine with idarubicin or daunorubicin or Standard-dose cytarabine with daunorubicin and midostaurin **Post remission therapy:** *Pts with Core binding factor cytogenetic translocations without KIT mutation or favorable-risk molecular abnormalities*: Clinical trial or HiDAC 3 g/m2 over 3 h every 12 h on days 1, 3, 5 x 3–4 cycles. *Pts with intermediate-risk cytogenetics and/or molecular abnormalities:* Clinical trial or Matched sibling or alternative donor HCT or HiDAC 2–3 g/m2 over 3 h every 12 h on days 1, 3, 5 x 3–4 cycles or HiDAC 3 g/m2 over 3 h every 12 h on days 1, 3 and 5 with oral midostaurin 50 mg every 12 hours on days 8-21 *Treatment related disease or poor-risk cytogenetics and/or molecular abnormalities:* Clinical trial Matched sibling or alternative donor HCT or HiDAC 3 g/m2 over 3 h every 12 h on days 1, 3 and 5 with oral midostaurin 50 mg every 12 hours on days 8-21 or Consolidation therapy if cytogenetic remission **Age >=60 yrs:** ***Induction:*** *De novo AML without unfavorable cytogenetics*: Clinical trial or Standard-dose cytarabine (100–200 mg/m2 continuous infusion x 7 days) with idarubicin 12 mg/m2 or daunorubicin 60–90 mg/m2 x 3 days or mitoxantrone 12 mg/m2 x 3 days *Unfavorable cytogenetics:* Clinical trial or Lower-intensity therapy (5-azacytidine, decitabine) or Standard-dose cytarabine (100–200 mg/m2 continuous infusion x 7 days) with idarubicinqqq 12 mg/m2 or daunorubicin 60–90 mg/m2 x 3 days or mitoxantrone 12 mg/m2 x 3 days or Standard dose cytarabine 200 mg/m2 continuous infusion x 7 days with daunorubicin 60 mg/m2 x 3 days and oral midostaurin 50 mg every 12 hours, days 8-21 (FLT3-mutated AML) or Clofarabine ± standard-dose cytarabine (category 3) **After standard dose cytarabine:** *If residual disease on follow up bone marrow:* Clinical trial or additional standard-dose cytarabine with anthracycline (idarubicin or daunorubicinrrr) or mitoxantrone or Standard-dose cytarabine with daunorubicin and midostaurin or Intermediate-dose cytarabine (1–<2 g/m2) containing regimens or Reduced-intensity allogeneic HCT or Await recovery or Best supportive care **Post Remission Therapy** *Complete Response:* Reduced-intensity HCT or Clinical trial or Standard-dose cytarabine (100–200 mg/m2/d x 5–7 d x 1–2 cycles) ± anthracycline (idarubicin or daunorubicin) or Consider intermediate-dose cytarabine 1–1.5 g/m2/d x 4–6 doses x 1–2 cycles for patients with good performance status, normal renal function, better-risk or normal karyotype with favorable molecular markers or Intermediate-dose cytarabine 1–1.5 g/m2 over 3 h every 12 h on days 1, 3 and 5 with oral midostaurin 50 mg every 12 hours on days 8-21 or Maintenance therapy with hypomethylating regimens (5-azacytidine, decitabine) every 4–6 weeks until progression (if patient received hypomethylating agents in induction) or Observation *Induction failure*: Clinical trial or Allogeneic HCT (preferably in clinical trial) or Best supportive care

Citation (ref)	Search details	Inclusion criteria	Intervention/comparison	Results	Included studies
Systematic Review					

Stansfield 2017 [4] Systematic Review	PubMed database (January 1990– January 2016) using the primary search terms PKC412, FLT3, midostaurin, and AML. ClinicalTrials.gov database was also searched for ongoing trials.	Phase I, II, and III trials reported in English evaluating the safety and efficacy of midostaurin in patients with AML or MDS were included. Midostaurin as monotherapy was also looked at but outside the scope of this	Midostaurin + Hypomethylating agents (decitabine or azacitidine in R/R AML) Midostaurin + cytotoxic chemotherapy	Various schedules and doses of midostaurin have been studied, given on days 8–21 or on a continuous basis at 25–75 mg orally twice/day. CR rates were low, ranging from 2–18%. In the study with bortezomib and MEC chemotherapy, CR and CRi attainment measured 57% and 26%, respectively, and 12 of the 19 patients who achieved a CR or CRi went on to receive an allogeneic transplantation. CLAG plus ATRA study, the CR measured 22% 7+3 chemo + midostaurin (phase 1 study) = (50 mg twice/day given for 14 days; days 1–7 and 15– 21 if given concomitantly or on days 8–21 if given sequentially); CR = 74% and 92% of FLT3-WT andFLT3-mutant patients In a phase 3 study (RATIFY), median OS was shown to be significantly superior in the midostaurin arm compared with the placebo arm (74.7 mo vs 25.6 mo, HR 0.78, 95% CI 0.63– 0.96, p=0.009). Subgroup analysis showed that the OS benefit of midostaurin compared with placebo persisted regardless of allelic burden or the TKD mutation. Median event-free survival was also shown to be significantly superior in the midostaurin arm compared with the placebo arm (8.2 mo vs 3.0 mo, HR 0.78, 95% CI 0.66– 0.93, p=0.002). No significant difference in CR was noted between arms (59% for midostaurin vs 54% for placebo, p=0.15)	Williams et al. 2013; Cooper et al. 2015; Strati et al. 2015; Stone et al. 2017

Primary Studies					
Trial Name Citations (ref)	**Population**	**Arms / Dose (n)**	**Outcomes**	**Follow-up**	**Results**
Cancer and Leukemia Group B (CALGB) 10603 (RATIFY) trial NCT00651261 May 2008-October 2011 Stone 2017 (results as of March 7 2016); Stone 2017 abstract [5]	Newly diagnosed AML patients with FLT3 mutations (age 18-59; n=717) met the following other eligibility criteria: a diagnosis of AML (excluding APL) that was not therapy-related, a bilirubin level of less than 2.5 times the upper limit of the normal range, and the absence of other major coexisting illnesses.	Standard chemotherapy (daunorubicin 60mg/m2/d IV D1,2,3 and cytarabine 200mg/m2 IV D1-7) Midostaurin (n=360) or placebo (n=357) was administered at a dose of 50 mg orally twice daily on days 8 through 21 If CR was achieved after induction: 4 cycles of high-dose cytarabine (at a dose of 3000 mg2, administered over a period of 3 hours every 12 hours D1, 3, 5). Midostaurin or placebo was administered at a dose of 50 mg orally twice daily on days 8 through 21 Patients who remained in remission after completion of consolidation therapy entered a maintenance phase in which they received midostaurin or placebo, administered at a dose of 50 mg orally twice daily, for twelve 28-day cycles.	OS; EFS; DFS	59 months (n=359 pts)	Median OS (M vs P) = 74.7 mths (95%CI 31.5 to not reached) vs 25.6 (95% CI 18.6-42.9), p=0.009 (one sided stratified log rank test) **author notes: difference between groups in median overall survival may be large because of the inflection points on the Kaplan–Meier curves* HR for death Overall= 0.78 (95% CI, 0.63 to 0.96; one-sided P = 0.009 by stratified score test) ITD high HR=0.80 (0.57-1.12), p=0.19 (two sided) ITD low HR=0.81 (0.60-1.11), p =0.19 (two sided) TKD HR= 0.65 (0.39-1.08), p =0.10 (two sided) Median EFS (M vs P)= 8.2 months (95% CI, 5.4 to 10.7) vs 3.0 months (95% CI, 1.9 to 5.9), p = 0.002 one sided stratified log rank test. HR 0.78, 95% CI 0.66-0.93), p =0.002 (one sided stratified score test 4 yr EFS = 28.2% vs 20.6% The benefit of midostaurin with respect to event-free survival was consistent across the FLT3 subtypes. Median DFS (M vs P) : 26.7 months (95% CI, 19.4 to not reached) vs 15.5 months (95% CI, 11.3 to 23.5), p= 0.01 (stratified log rank test. CR 60 days M vs P: 59% vs 54%, p = 0.15 CR during induction M vs P: 65% vs 58%: p=0.053
Dohner 2017 Post hoc analysis of pts treated within RATIFY trial	428 of 717 pts gave informed consent for biomarker analyses and who could be categorized to one of the 4 ELN NPM1wt/ FLT3 -ITDhigh subgroups: NPM1mut/ FLT3 -ITDlow (n=85)			59 months (range, 42 to 81 mo)	Rates of CR positively correlated with NPM1 status, but not with FLT3 -ITD allelic ratio (p=.016) OS was significantly different among the 4 groups (p=.001): NPM1mut/ FLT3 –ITDlow (not reached); NPM1mut/ FLT3 –ITDhigh (27 mths); NPM1wt/ FLT3 -ITDlow (20 mths); NPM1wt/ FLT3 –ITDhigh (17 mths). non-censored EFS significantly differed among the 4 groups (p=.001); median EFS times were NPM1mut/ FLT3 –ITDlow 16 mo, NPM1mut/ FLT3 –ITDhigh 8 mo, NPM1wt/ FLT3 -ITDlow 4 mo, and NPM1wt/ FLT3 –

	NPM1mut/ FLT3 -ITDhigh (n=159) NPM1wt/ FLT3 -ITDlow (n=75) NPM1wt/ FLT3 -ITDhigh (n=109) (allelic ratio: high, >=0.5; low, <0.5)				ITDhigh 4 mo Multivariate analysis revealed NPM1/FLT3 -ITD genotypes, treatment arm with M in favor to PBO, WBC, and alloHCT as independent prognostic factors for OS.
Larson 2017 [6] abstract	untreated AML pts (exclusive of APL) age 18-60 years	Induction consisted of daunorubicin and cytarabine plus Midostaurin (M) or Placebo (50 mg orally twice daily, d8-21). Re-treatment with a second course was allowed if residual AML was noted on a d21 marrow exam. Pts achieving CR received 4 cycles of high-dose cytarabine plus M or placebo (d8-21) followed by 12 4-week cycles (336 days) of maintenance with M or placebo (50 mg orally twice daily)	CR	Median f/u 59 mths	CR was achieved within the protocol-specified 60 days by 403 pts (CR60; 56%); no significant difference between arms (212/360 (59%; 95% CI, 54-64%) on the M arm and 191/357 (54%; 48-59%) on Placebo) (Fisher's p=0.15) 174 of the 403 CR60 pts began maintenance still in CR1. DFS at end of maintenance between the 2 arms (HR=1.4 [95% CI, 0.63-3.3]; p=0.38)
NCT01696084 Lancet 2016 [7] (abstract); 2017 [8] (abstract) Medeiros 2016 [9] (abstract) Uy 2017 (abstract) [10]	Patients 60-75 years of age with untreated AML with a history of prior cytotoxic treatment, antecedent MDS or CMML (+/- prior hypomethylator treatment), or AML with WHO-defined MDS-related cytogenetic abnormalities from Dec 2012 to Nov 2014 at 39 US and Canadian sites (n=309)	CPX-351 (100 units/m2/d days 1, 3, 5) n=153 7+3 (cytarabine 100 mg/m2/day x 7 days, daunorubicin 60 mg/m2/d days 1, 2, 3) n=156 Pts with CR) or CR with incomplete platelet or neutrophil recovery (CRi) could receive up to 2 cycles of consolidation therapy	OS, EFS, 60 day mortality, CR+CRi	13.7 mths	CPX-351 treatment resulted in superior for: OS: HR=0.69; P=0.005; median OS 9.56 vs. 5.95 months EFS: HR=0.74; P=0.021 CR+CRi response : 47.7% vs. 33.3%; P=0.016 60-day mortality favored CPX-351 (13.7% vs. 21.2%) Subgroup analysis CPX-351 vs 7+3: 60-69yrs CR+CRi 50.0% vs 36.3, OR 1.76 (95%CI 1.00-3.10) Median OS: 9.63 vs 6.87, HR 0.68 (95%CI, 0.49-0.95) 70-79yrs CR+CRi 43.9% vs 27.8% OR 2.03 (95% CI, 0.9204.49) Median OS: 8.87 vs 5.62, HR 0.55 (95% CI 0.36-0.84) Pts with tAML: Median OS= 12.17mo vs 6.64mo, HR =0.49 (95% CI 0.27,0.88) Median EFS= 2.50 mo vs 1.64 mo, HR= 0.66 (0.38,1.17)

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>Remission duration= 10,87 mo vs 6.11 mo, HR =0.50 (0.17,1.50)</td></tr>
<tr><td>NCT01696084

Kolitz 2017 (abstract) Induction results presented above in Lancet 2016</td><td>Pts aged 60-75 yrs with newly diagnosed, high risk AML</td><td>Pts were randomized 1:1 to 1-2 induction cycles of CPX-351 or 7+3. Pts with CR or CR with incomplete platelet or neutrophil recovery (CRi) could receive up to 2 consolidation cycles (CPX-351: 65 u/m2 [C 65 mg/m2 + D 28.6 mg/m2] on Days 1 and 3; 7+3: C 100 mg/m2/day x 5 days + D 60 mg/m2 on Days 1 and 2). Site of administration was not protocol defined.</td><td>OS</td><td>NR</td><td>Few pts received induction as outpatient therapy (CPX-351 n = 3/153 and 7+3 n = 1/151 in each cycle). 49/153 CPX-351 pts and 32/151 7+3 pts received consolidation, with a substantial proportion of pts receiving CPX-351 as outpatients (consolidation 1: 51%; consolidation 2: 61%)
<table>
<tr><td></td><td colspan="2">Inpatient</td><td colspan="2">outpatient</td></tr>
<tr><td></td><td>Cpx-351</td><td>7+3</td><td>Cpx-351</td><td>7+3</td></tr>
<tr><td>Consolidation 1 (n/N)</td><td>(24/49)</td><td>30/32)</td><td>(25/49)</td><td>(2/32)</td></tr>
<tr><td>Median OS (mo)</td><td>14.72</td><td>9.26</td><td>25.43</td><td>6.87</td></tr>
<tr><td>HR (95% CI)</td><td colspan="2">0.55 (0.24,1.21)</td><td colspan="2">0.10 (0.01,1.11)</td></tr>
<tr><td>Consolidation 2 (n/N)</td><td>9/23</td><td>12/12</td><td>14/23</td><td>0/12</td></tr>
<tr><td>Median OS (mo)</td><td>Not reached</td><td>14.31</td><td>26.32</td><td>-</td></tr>
<tr><td>HR (95%CI)</td><td colspan="2">0.45 (0.09,2.36)</td><td></td><td></td></tr>
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Table 2. Summary of Relevant Guidelines

Citation (ref)	Search dates	Recommendations
Bittencourt et al. 2016; Associacao Medica Brasileira [11]	Search dates not specified.	• On comparing the efficacy of induction therapy using the anthracyclines, idarubicin and daunorubicin in AML pts of difference ages, although the reduction in the blast count was faster with the first cycle of idarubicin, there were no significant differences in the complete remission or toxicity of the two drugs. • Due to the lower risk of death using 100 mg/m^2/day of cytarabine compared to 200 mg/m^2/day of cytarabine in the induction therapy of AML pts and no significant difference in the CR between the two groups, the lower dose is more appropriate. This is true for all age groups. • In adults with AML, high doses of daunorubicin (60-90 mg/m^2/day) associated with cytarabine (100-200 mg/m^2/day) increase the complete remission rate in induction therapy, both after the first and second cycles of chemotherapy without increasing the hematologic or non-hematologic toxicity when compared to a dose of 45 mg/ m^2/day of daunorubicin. • There is controversy about the use of conventional doses and high doses of daunorubicin in induction therapy in relation to the complete response of elderly AML pts. However increasing the dose does not increase the hematological and non-hematological toxicity, or the number of treatment-related deaths. • Is it common to perform a second induction cycle of chemotherapy in pts with AML who have 5% or more blasts in the bone marrow 10-14 days after the first cycle; the complete response rate increases significantly after the second chemotherapy. • There is no significant difference between different doses of cytarabine in the consolidation therapy of AML in respect to DFS and OS. However the study that compared standard-dose cytarabine (100mg/m^2/day with high dose (6g/ m^2/day) did not inform the

Citation (ref)	Search dates	Recommendations
		cytogenetic risk. There are no studies comparing dose of 1g/m^2/day, 1.5g/m^2/day, 2g/m^2/day and 3g/m^2/day. The total dose of 6g/ m^2/day for three days seems to be associated with greater hematologic toxicity, and compared with the standard regimen of 100mg/ m^2/day, it is also associated with higher hematologic toxicity. • The overall survival and disease free survival of 15 to 65 year old AML pts with a favorable prognosis does not improve using a higher dose of cytarabine in the consolidation regimen. However, hematological and non-hematological grade 3 and 4 toxicity increases as the dose increases. • In consolidation of 15 to 64 year old AML pts and intermediate or unfavorable prognosis, there is no significant difference in overall survival or disease-free survival using the different doses of cytarabine evaluated. • There is no consensus on the best practice consolidation strategy for elderly pts. • Autologous bone marrow transplantation or intensive chemotherapy with cytarabine is indicated for pts without HLA-compatible donors or with favorable cytogenetics. However there is controversy about the best consolidation treatment options for pts at intermediate risk, who are not candidates for allogeneic transplantation.
Miyawaki 2017 [12]	Search dates not specified	-The standard induction therapy regimen for de novo AML in younger adult patients (<60 years) used to be the "3 + 7" regimen consisting of 45–60 mg/m2 of daunorubicin for 3 days plus continuous infusion of 100 or 200 mg/m2 of cytarabine for 7 days. -Addition of other drugs to standard induction therapy with an anthracycline (idarubicin or daunorubicin) plus standard-dose cytarabine has not been shown to yield superior outcomes in younger adult patients with de novo AML. There is also little evidence to support the superiority of intensification to high-dose cytarabine, and it is not recommended due to the higher risk of adverse events. -The same induction therapy regimens that are used in younger patients yield good remission and survival rates in older patients with AML between the ages of 60 and 65 years. However, it may be necessary to consider lower-intensity treatment or best supportive care in elderly patients with AML depending on performance status or severity of comorbidities. -There is no evidence indicating whether the same induction therapy regimen should be repeated or the regimen should be changed. However, it is reasonable to repeat the same induction therapy regimen because it may be possible to achieve remission at a certain frequency. -High-dose cytarabine is recommended as postremission therapy for patients 60 years and younger with core binding factor (CBF) AML as it has been shown to prolong disease-free survival (DFS) in this group. There are no clear standards for the number of cycles and duration for high-dose cytarabine therapy. Three or more cycles of high-dose cytarabine are recommended for CBF leukemia. -If a regimen with a non–cross-resistant anthracycline is used as consolidation therapy for AML in first remission, 4 cycles of treatment are recommended. * High-dose cytarabine has long been the most popular consolidation therapy in the West, but was not possible to be performed in Japan for a long time due to insurance restrictions. -There is no clear clinical benefit to postremission therapy in elderly patients with AML who are not candidates for transplantation, but it may be effective in some patients.

Table 3. Summary of Relevant Systematic Reviews

Citation (ref)	Search details	Inclusion criteria	Intervention/comparison	Results	Included studies
Xie et al. 2016[13] *Meta analysis*	PubMed, EMBASE, China National Knowledge Infrastructure,Wanf	(1) a minimum of 20 patients with MDS or AML; (2) treatment with the HAG regimen, and without	HAG vs intensive chemotherapy Daunorubicin+ cytarabine HHT+cytarabine	CR rate HAG = 55% (95% CI,46%-63%) Intensive therapy =30% (95% CI, 26%-35%)	See Table 2 in article. 16 trials included in meta analyses.

Citation (ref)	Search details	Inclusion criteria	Intervention/comparison	Results	Included studies
	ang Data, and the American Society of Hematology (ASH) meeting abstracts were searched for articles published in English or Chinese between January 2005 and December 2014. Eligible studies were relevant clinical trials of AML or MDS patients treated with HAG (low dose homoharringtonine + cytarabine + G-CSF priming).	additional chemotherapy, immunotherapy,epigenetic therapy or hematopoietic stem cell transplantation; (3) reported in English or Chinese; (4) reporting of complete response (CR) rate, partial response (PR) rate,overall response (OR) rate, ED rate, or other toxicity data.	Mitoxantrone+cytarabine Mitoxantron+ cytarabine+etoposide	OR = 2.41 (95% CI, 1.77– 3.28; *P* = 0.000).	
Yun et al. [14] *Meta analysis*	PubMed, EMBASE, and Cochrane Database of Systematic Reviews up to October 2015. Additional relevant abstracts from the American Society of Hematology, the American Society of Clinical Oncology, and the European Hematology Association were also included into the literature search. CCR included best supportive care,	Eligible studies were (1) RCTs, (2) assessing adult patients age ≥18 years with (3) morphologically proven diagnosis of AML or MDS with no previous allogeneic SCT, (4) treated with either HMA (azacitidine or decitabine) or CCR (BSC, LDAC or IC) in a setting of first-line treatment, and (5) including OS and treatment response outcomes.	HMA vs CCR Azacitidine vs CCR Decitabine vs CCR HMA vs LDAC	OS : 33.2 vs 21.4% (RR 0.83, 95 % CI 0.71–0.98, p = 0.03) ORR: 23.7 vs. 13.4 % (RR 0.87, 95 % CI 0.81–0.93, p = 0.0001) OS : HR 0.67, 95 % CI 0.56–0.79, p < 0.00001 ORR: RR 0.87, 95 % CI 0.78–0.97, p = 0.01 OS : HR 0.86, 95 % CI 0.73–1.02, p = 0.08 ORR: RR 0.86, 95 % CI 0.76–0.98, p = 0.03) OS: 21.8 vs.12.1 %, RR 0.77, 95 % CI 0.52–1.16, p = 0.21 OS RR 0.66, 95 % CI 0.49–0.87, p = 0.004 OS: RR 0.97, 95 % CI 0.92–1.02, p = 0.24)	Silverman, 2002; Fenaux 2009; Lubbert 2011; Kantarjian 2012; Dombret 2014

Citation (ref)	Search details	Inclusion criteria	Intervention/comparison	Results	Included studies
	intensive chemotherapy and low dose cytarabine.		Azacititidine vs LDAC Decitabine vs LDAC		

Table 4. Summary of Relevant Primary Studies

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
Induction					
NILG trial 02/06 NCT00495287 2006-2012 Bassan 2017 (abstract)	Patients with AML, stratified by age 60	ICE (idarubicin 12 mg/m2/d iv. dd1-3, cytarabine 100 mg/m2/bd iv. dd 1-7, etoposide 100 mg/m2/d iv. dd1-5) n= 286 SHD (cytarabine 2 g [1 g if age >65]/m2 /bd iv. dd 1-2 and 8-9, idarubicin 18 mg/m2/d iv. dd 3 and 10), plus G-CSF from d11. N=286 Postremission consolidation consisted of IC (cycle 2), intermediate-dose cytarabine 1 g/m2/bd iv. dd 1-4, with harvest of CD34+ blood stem cells (cycle 3), and allogeneic SCT if high-risk or second randomization to BUCY2-conditioned autograft or repetitive HD cycles (cytarabine 2 g/m2/bd iv. dd 1-5 and idarubicin 8 mg/m2/d dd 1-2, cycles 4-6) supported by 1-2 x106/kg CD34+ cells	CR, OS, DFS	NR	After induction (ICE vs SHD) CR= 69.2% vs 81.5%, p=0.001 The benefit was confirmed in high-risk AML (n=201 vs 218: CR 64.2% vs 77.6%; P .002) and in patients aged ≤60 years with de novo AML (n=190 vs 189: CR 74.2% vs 86.2%; P .003). Median and 5 yr OS ICE = 2.14 years and 38% SHD= 4.51 years and 48%, p =0.0125 standard-risk subset (5-year OS 55% vs 72%, P .0068) Patients aged ≤60 years with de novo AML (5-year OS 43% vs 58%; P .0026) Median and 5 yr DFS ICE =1.48 yrs and 36% SHD = 3.41 yrs vs 48%, p =0.030 standard-risk subset (5-year DFS 40% vs 64%; P .0064) patients aged ≤60 years with de novo AML (5-year DFS 38% vs 54%; P .0023).
UK NCRI AML16 August 2006-December 2008; 124 centres in UK, Denmark and New Zealand Burnett 2017 *[15]*	Pts > 60 years (median was 67 years (range 56–84), 59% were male, 72% had de novo AML, 17% secondary AML and 11% had high-risk MDS)	(DClo) daunorubicin 50 mg/m2 day 1,3, 5 combined with clofarabine 20 mg/m2 days 1–5 (N = 404); 2 courses (DA) daunorubicin 50 mg/m2 combined with ara-C 100 mg/m2 b.i.d. days 1–10 in course 1 and days 1–8 in course 2. (N=404); 2 courses	OS ; CR	NR	DA vs DClo: CR 64% vs 58%, OR = 1.30 (0.98–1.73), p = 0.07 OS 14% vs 15%, HR= 1.04 (0.90–1.21), p = 0.6 The five-year cumulative incidence of relapse was 75% (DA 78% vs DClo 72%; HR 0.93 (0.77–1.13), P=0.5) There was no suggestion of a benefit of any particular demographic or cytogenetic subgroup, whether an FLT3 or NPM1c mutation as present or whether the

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
		Pts were also included in additional randomisations; +/- one dose of gemtuzumab ozogamicin in course 1; 2v3 courses and +/- azacitidine maintenance. Results not presented in this article.			patient received gemtuzumab ozogamicin or not
Dumas 2017 [16]	Older pts with non de novo AML= 199	Intensive chemotherapy - three-drug schedule that combined idarubicin, standard-dose cytarabine, and lomustine (n=92) Azacitidine (n= 107) Dosing not mentioned in abstract	Overall response; CR; OS	Median f/u 3.4 yrs	Azacitidinne vs intensive chemo Overall response: 19.6% vs 63.0%, p<0.001 Complete response: 11.2% vs 51.1%, p<0.001 OS: 10.8 (IQR: 4.8-26.4) vs 9.6 month (IQR: 3.6-22.8), p = 0.899 After 1.6 yrs, pts that received chemo had a lower risk of death compared to those that received azacitidine (adjusted HR 0.61, 95%CI: 0.38-0.99) Adjusted for main prognostic factors.
Feng 2016 [17] *abstract*	elderly patients with newly diagnosed AML	etoposide combine with low-dose CAG (E-CAG) DA Dosing not mentioned in abstract	CR	NR	E-CAG vs DA CR: 55.1% vs 48.9%, p=0.158 Median survival: 14.3 months vs 10.3 months, 0=0.042 2yr OS probability: 24.2% and 11.3%
ECOG-acrin cancer research group (E2906) Foran 2016 [18]	Newly diagnosed AML patients aged >=60 years (n=727)	CLO [30mg/m2 x 5 days induction; 20 mg/m2 re-induction (if indicated) & 2 cycles Consol.] standard DA therapy [Dauno 60mg/m2 D1-3 & Ara-C 100mg/m2 D1-7 induction x 1-2 cycles; 2 cycles Consol. with Ara-C (1.5g/m2 Q12hrs D1-6 age 60-69; once daily if age 70+	OS	7.6 months	HR CLO/Standard (95% CI) Weighted OS : 1.41 (1.12-1.78) Age 60-69: 1.48 (1.10-1.99) Age 70+: 1.34 (0.93-1.93)
SWOG S1203 Garcia-Manero 2016 [19] Abstract	Previously untreated non-APL AML by WHO criteria, age 15 to 60 years, and preserved cardiac function but no severe comorbidities	7+3: 7+3 arm: dauno 90 mg/m^2 IV QD x 3 on days 1-3 with ara-C CI 100 mg/m^2 QD x 7 days on days 1 to 7 (N= 261) IA: ida 12 mg/m^2 QD x 3 on days 1 to 3 with 24 hours CI ara-C 1.5 gm/m^{2}QD for 4 days on days 1 to 4 (N= 261) IA+V: IA but with vorinostat 500 mg orally	EFS; OS; Relapse free survival (RFS); CR	NR	CR rates were 75% for 7+3, 79% for IA, and 77% for IA+V (p=0.58). More pts received reinduction with 7+3 (24%) versus 11% with IA and 9% with IA+V (p=0.001) No significant differences in EFS, RFS or OS among all three arms

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
		TID for 3 days on days 1 to 3 (N=216) Consolidation: 7+3 : standard high-dose ara-c at 3 gm/m^2over 3 hrs q12 hours x 6 doses for 1 to 4 cycles depending on transplant availability IA: idarubicin 8 mg/m^2 IV QD x 2 days on days 1 to 2 with ara-C 0.75 gm/m^2 CI for 3 days on days 1 to 3 for 4 cycles IA+V: N/R			30% of pts received 1 consolidation cycle, 18% 2, 16% 3, and 37% 4 cycles
Hu 2015 abstract [20]	Older pts with AML	decitabine plus cytarabine/anthracycline (DCA) n=31 cytarabine/anthracycline (CA) n=31 induction therapy included decitabine 30mg/m^2/days1-4, cytarabine 100 mg/m^2/days 1-7 & daunorubicin 45 mg/m^2 days 1-3, or idarubicin 12 mg/m^2 days 1-3, or mitoxantrone 10 mg/m^2 days 1-3, or aclarubicin 10mg /m^2 days 1-7 followed by intravenous infusion of GPBSC 24h after cytarabine therapy	CR; DFS; OS	NR	CR: DCA 70.0% vs.CA 80.6 %, p=0.38 OS DCA 28.4 vs CA 28.1 months, p 0.19 DFS: DCA 26.5 vs CA 22.8 months p= 0.90
NCT01289457 Issa 2017 abstract [21] Jabbour 2017	Adults with newly diagnosed AML (n=182)	All pts received idarubicin 10 mg/ m^2 IV daily on Days 1-3 and cytarabine 1 g/ m^2 IV daily on Days 1-5. Pts with FLT3 mutations could receive sorafenib. Pts randomized to: Clofarabine 15 mg/ m^2 IV daily on Days 1-5 (n=106) fludarabine 30 mg/ m^2 IV daily on Days 1-5 (n=76)	CR, EFS, OS	27 mths (range 1-58 mths)	CR without platelet recovery rate= CIA 80%, FIA 82% p=0.84 Median EFS= CIA 13 mths, FIA 12 mths. 2 year EFS rate was 44% in both arms (p=0.91) 2 yr OS was 51% and 57%, p=0.23 Pts < 50 years of age: FIA vs CIA : 2-year EFS rate: 58% vs 30%, P = 0.05; 2-year OS rate: 72% vs 36%; P = 0.009

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
		Fludarabine and clofarabine were given 4 hours before cytarabine to optimize Ara-CTP formation			
Issa 2015 [22]	patients with AML aged >=60 years with no prior intensive chemotherapy or high dose cytarabine or prior azacitidine >=3 cycles or prior decitabine for >=2 cycles were eligible. MDS pts also included but not reported.	A: decitabine 20 mg/m2 intravenously over 1 hour daily for 5 days; B: decitabine at the same dose schedule with oral valproic acid 50 mg/kg daily for 7 days (on days 1-7; simultaneous therapy with decitabine)	CR, ORR,	NR	A vs B: CR rates: 33% vs 9%(P= .029), ORR 51% vs 35% (P=.208) estimated median survival 9.6 vs 7.9 months (P=.729) estimated 2-year survival rates: 23% vs 22%
RAS-AZIC East German Study Group Planned Interim analysis Jaekel 2016[23]	Patients >60 y with newly diagnosed AML and eligible for IC (n=40). Planned interim analysis of first 40 patients.	"up front" Azacitidine (75 mg/m2/day s.c.) for 7 days days followed by one of the following on d15 bone marrow blast count (<45 versus >=45%) and CR and CRi on D56. Azacitidine Or Intensive chemotherapy (mitoxantrone 10 mg/ m2/day on day (d) 1-3 and cytarabine 1g/ m2</BID on d 1, 3, 5, 7)	OR at day 90; OS	202 days	in the 33 (82.5%) pts who continued therapy per protocol until d90, an OR was achieved in 27 (82%) pts At 202 days, OS = 84.5% (entire cohort) and OS = 95.5% (responding pts)
Jin 2017[24] abstract	Pts with de novo AML (n=198)	A: idarubicin 10 mg/m2 for 3 days and subcutaneous cytarabine 50 mg/m2 injection twice daily for 7 days B: idarubicin 10 mg/m2 for 3 days and intravenous cytarabine 100 mg/m2 by continuous infusion daily for 7 days	CR	NR	A: 74% B: 68%
Kim 2017; 2015 [25] [26] abstract	young adults with newly diagnosed AML	All receive cytarabine (200 mg/m2/d for 7 day) combined with either: idarubicin (12 mg/m2/d for 3 days) n=149 high-dose daunorubicin (90 mg/m2/d for	OS, EFS; CR	34.9 months	AI vs AD OS: 51.1% v 54.7%, respectively; P = .756 Cumulative incidence of relapse: 35.2% v 25.1%, P = .194 EFS: 45.5% v 50.8%, P = .772

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
		3 days (n=150)			CR: 80.5% (120 of 149, AI) vs. 74.7% (112 of 150, AD) (P=0.224) Pts with FLT3 internal tandem duplication mutation: AI v AD: median OS, 15.5 months v not reached, respectively; P = .030; EFS, 11.9 months v not reached; P = .028
UK MRC AML15; NCRI AML17 Knapper 2017 [27]	Pts with previously untreated AML and confirmed FLT3-activating mutations (mostly <60yrs) (n=500)	randomly assigned either to receive oral After each of 4 cycles of induction and consolidation, patients were randomly assigned to receive lestaurtinib (CEP701. Lestaurtinib was commenced 2 days after completing chemotherapy and administered in cycles of up to 28 days. Induction chemotherapy (courses 1-2) was with ADE, DA, or FLAG-Ida, with or without GO in course 1; consolidation (courses 3-4) comprised high-dose cytarabine (1.5 g/m2 or 3 g/m2) orMACE/MidAC.	OS; EFS	median follow-up of 50.5 months	5-year OS = lestaurtinib 46% vs control 45%; HR, 0.90; 95% CI 0.70-1.15; P=.3) or 5-year relapse-free survival (40% vs 36%; HR, 0.88; 95% CI 0.69-1.12;=5.3)
Liu 2017[28] (abstract)	newly diagnosed elderly acute myeloid leukemia (AML) patients aged 55-71 yrs (n=41)	Randomized to Homoharringtonine, cytarabine, aclacinomycin and G-CSF (HCAG) or IA for induction and consolidation therapy *Dosing not specified.*	OS; RFS	E yrs	A total of 29 pts (70.7%) achieved CR Estimated 2 yr OS was 66.8% in Group HCAG and 75.4% in Group IA (P=0.913) Estimated 2-year RFS was 61.8% in Group HCAG and 49.1% in Group IA (P=0.411)
HOVON-102 Lowenberg 2017[29]	Previously untreated adults who were 18 to 65 years of age with a cytopathologically confirmed diagnosis of AML, or with RAEBand an international prognostic score of >=1.5 IPSS and WHO <=2	Cycle I of the control arm included idarubicin at 12mg/m2 (3-hour infusion on days 1, 2, and 3) and cytarabine at a doseof 200 mg/m2 (per continuous infusion on days 1-7) *with (n=393) or without(n=402)* clofarabine at 10 mg/m2 per 1 hour of infusion on days 1 to 5. Cycle II contained amsacrine 120 mg/m2 per 1-hour infusion on days 4, 5, and 6 plus cytarabine 1000 mg/m2 given intravenously for 3 hours twice daily on days 1-67 *with or without* the addition of	EFS; OS; RFS	36 mths	<u>Control vs Clo</u> **CR**: 355 (88%) vs 352 (90%), HR 1.14 95%CI 0.73-1.77, p=0.57 **EFS**: 35% (SE = 3%) vs 38% (SE = 3%), HR 0.90 95%CI (0.75-1.07), p =0.24 **OS at 4 yrs**: 43% vs 44%, OR 0.95 95%CI (0.78-1.15), p=0.57 **RFS at 4 yrs**: 41% vs 44%, OR 0.90 95%CI (0.74-1.10), p=0.32 The data indicate a favorable effect of the clofarabine regimen in the largest ELN intermediate I prognostic

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
		clofarabine 10 mg/m2 given intravenously for 1 hour on days 1 to 5.			risk subset (n=121 vs 123; EFS 26%±4 vs 40%±5; Cox P=.002; OS 29%±5 vs 50%±6; Cox P < .001. This positive effect of the clofarabine schedule on EFS and OS in part depended on a favorable effect in the molecular subset NPM1 wild-type/FLT3 without internal-tandem duplications (FLT3-ITD negative) (n=68 vs 67; EFS, 18%±5 vs 40%± 7; Cox P<.001 and OS, 22% ± 6 vs 49% ± 8; P <.001.
ECOG E1900 #NCT00049517 Luskin 2016 (abstract)	Untreated AML pts (age 17-60 yr)	High dose daunorubicin (90 mg/m2/d for 3 d + AraC; vs daunorubicin std dose (45 mg/m2/d for 3 d) + AraC		Median f/u 80.1 months among survivors	Compared to std dose, high dose associated with HR for death of 0.74 (<0.001) Those that benefited from HD: Younger pts (<50 years) HR, 0.66; P < .002; Favourable cytogentics HR, 0.51; P < .03; intermediate cytogenetics HR, 0.68;P<.01 Patients with FLT3-ITD (24%), DNMT3A (24%), and NPM1 (26%) mutant AML all benefited from HD daunorubicin (HR, 0.61, P=.009; HR, 0.62, P=.02; and HR, 0.50, P=.002
NCT00780598 Mawad 2016 [30]	Patients > 60 years or older, with untreated AML or high-risk MDS [10–19% marrow blasts; refractory anaemia with excess blasts type 2 (RAEB-2)], including those with prior MDS, therapy-related AML or AML with tri-lineage dysplasia.	tosedostat 120 mg daily by mouth on days 1–21 of each 35-d cycle, combined with either: A: decitabine 20 mg intravenously (IV) daily (n=17) ; or B: cytarabine 1 g IV daily for the first 5 d of each 35-d cycle (n=17)	OS	median follow-up of 11.2 months (range, 0.5–22.3)	A total of 18 achieved complete response (CR+CRi), 54% in each group. Median OS in months: Decitabine = 16.7 (5.2-N/A) Cytarabine = 10.9 month (3.3-N/A)
Niederwieser 2016 abstract[31]	Patients >=60 years with all AML subtypes except M3. n=1286	Standard Arm (CSA): Induction: (1-2 rounds) araC 100 mg/m2/d continuous IV (CI) d 1-7 d and daunorubicin (dauno) 60 mg/m2/d IV d 3, 4, 5 Consolidaton: two courses of araC 1 g/m2/d BID IV d 1, 3 and 5 AMLCG arm (Group A):	EFS	67 motnhs	Three-year EFS was 12.4% (95% CI: 6.7 - 19.9%) in the CSA, 15.6% (95% CI: 13.1 - 18.3%) in group A and 11.4% (95% CI, 7.4% to 16.4%) in group B (n.s) Three-year survival probability was 22.3% (95% CI: 14.7-30.9%) in the CSA, 24.7% (95% CI: 21.6- 27.9%) in group A and 22.4% (95% CI, 16.7% - 18.3%) in group B Proportion of patients in CR in the CSA [51% (95% CI:

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
		Induction: araC 100 mg/m2/d CI d1-2 followed by BID d 3-8, dauno 60 mg/m2/d IV d 3-5 and 6-thioguanine 100 mg/m2/d po BID d 3-9) and HAM [araC 1 mg/m2/d IV BID d 1-3 and mitoxantrone (mito) 10 mg/m2/d IV d 3-5] versus two courses of HAM with any 2nd course only given if blasts persisted +/- G-CSF. Consolidation: Two courses of TAD followed by maintenance chemotherapy over three years OSHO Arm (Group B): Induction: araC 1 g/m2/d BID IV d 1 + 3 + 5 + 7 and mito 10 mg/m2/d IV d 1 - 3 for one or two induction courses and ara-C 500 mg/m2 BID 1h IV d 1 + 3 + 5 in combination with mito10 mg/m2/d IV d 1 + 2 as consolidation. Pegfilgrastim 6 mg s.c. was applied on day 10 of induction and on d 8 of consolidation.			42-61%)] was comparable to the 50% (95% CI: 47-54%) and 48% (95% CI: 41-55%) of the study group arms (p=n.s.)
AML 17 Russell 2016 abstract[32] f/u to Burnett 2015 (in original search)	Pts with AML (84% had de novo AML, 10% secondary, and 6% high risk MDS)	DA90: Daunorubicin 90mg/m2/d DA60: Daunorubicin 60mg/m2/d1,3,5 in course 1, 50mg/m2/d1,3,5 in course 2 with Ara-C 100mg/m2/12 hourly d1-10 (course 1) and d1-8 (course 2)	3 yr OS	28 months	60-day mortality remained higher with DA90 (10% vs. 5%, p = 0.002) 3-year OS did not differ (50% vs. 47%, p = 0.7) In ITD WT patients: DA90 did not improve outcome (51% vs. 49%, p = 0.3), but in ITD mutant patients a survival significant benefit (54% vs. 34%, p = 0.03) emerged post 1-year
AMLSG 07-04 NCT00151242 Schlenk 2016 [33] August 2004 to January 2006	Patients aged between 18 and 60 years with newly diagnosed AML including de novo AML, secondary AML with a preceding history of myelodysplastic or myeloproliferative disorder (sAML) and therapy-related AML	*Induction:* Standard: ICE (idarubicin, 12mg/m2 i.v., days 1, 3 and 5; cytarabine, 100 mg/m2 cont. i.v., days 1–7; etoposide 100 mg/m2 i.v., days 1–3), n =556 ASTRA: ATRA (p.o., 45 mg/m2, days 6–8 and 15 mg/m2, days 9–21) + ICE, n=544 Originally a 4 arm study but VPA arms were terminated due to increased hematologic toxicity	EFS, RFS, OS	5.23 years (95 % CI, 5.02–5.37)	no significant difference on an ITT basis (ATRA, 50.9%; STANDARD, 48.7 %) in achieving of CR/CRi (p = 0.47) survival analyses on an ITT basis revealed no significant differences for EFS (p = 0.93), RFS (p =0.25) and OS (p = 0.24) ITT analyses revealed no significant impact of ATRA in the NPM1-mutated and NPM1-wildtype subgroups for EFS (p=0.17, p=0.48) for RFS (p=0.38, p = 0.28) and OS (p = 0.44 and p = 0.70)

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
		Consolidation: Transplant if high risk or FLT3-ITD, transplant or 3 cycles AraC. All others assigned to 3 cycles of HiDAC with cytarabine 3 g/m2 bid, days 1, 3 and 5 (Aug 2004-Nov 2006) and from November 2006 with a condensed schedule with application of cytarabine 3 g/m2 bid, days 1, 2 and 3.			Explorative analyses in molecularly defined subsets on OS revealed a significant beneficial effect on an ITT and PP basis of ATRA in patients in the ELN favorable-risk category (p=0.05 and p = 0.05) and in particular, those patients exhibiting biallelic CEBPA mutations (p=0.04 and p =0.03)
Short 2016 abstract [34] August 2011- June 2016	Adult pts <=60 years of age with newly diagnosed non-APL AML	All pts received induction with idarubicin 10 mg/m2/IV daily on days 1-3 and cytarabine 1000 mg/m2/IV daily for on days 1-5 Randomized to either CIA arm: clofarabine 15mg/m2/IV daily D1-5 (n=106) FAI arm: fludarabine 30mg/m2/IV daily D1-5 (n=76) Responding pts could receive up to 6 cycles of consolidation with attenuated doses of the same drug combination	EFS, CR/CRp rates, OS	27 months	CIA vs FAI CR/CRp rate :80% vs 81% Median EFS : 13 months vs 12 months, respectively, P=0.91 2-year OS rates : 51% and 57%, P=0.24 When compared to a historical cohort of pts treated with IA alone (subgroup of pts < 40years): the median EFS for CIA/FAI (n=38) and IA (n=16) were 25 months and 9 months, with a 2-year EFS rate of 52% and 33% respectively (P=0.27) Strong trend in OS for CIA/FAI compared to the IA groups (median OS: not reached vs. 20 months; 2-year OS rate 68% vs. 47%; P=0.08).
AZA-AML-001 NCT01074047 2010-2014 Schuh 2015[35] Post-hoc exploratory analysis	Older patients >=65 with newly diagnosed AML. Post hoc analysis on subgroup of patients who did not attain CR on-study.	Before randomization, a convention care regimen was chosen (standard induction, low-dose AraC, or supportive care) and then pts randomized to azacitidine or conventional care; only subgroup initially randomized to standard induction is relevant to this review Azacitidine, 75 mg/m2/d sc, 7 consecutive days per 28-d treatment cycle, at least 6 cycles Standard induction: [AraC (100-200 mg/m2/d CI, 7 d) + either DNR (45-60 mg/m2/d)or IDA (9-12 mg/m2/d)] for one cycle then up to 2 cycles consolidation with same regimen but for	OS	N/R	For pts with no CR who were preselected to receive IC, median OS with AZA (n=30) vs IC (n=28) was 8.0 vs 7.5 months, respectively (HR=0.81 [95%CI 0.46, 1.44], p=0.4765), with 1-year survival of 40.0% vs 40.2% **Author notes: Results should be interpreted cautiously, as OS comparisons of pt subgroups defined by post-randomization outcomes may be biased. The current analysis did not control for time-dependency of response or interactions between Tx and response that could influence OS.*

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
		AraC given for 3-7 d for pts with CR or partial response			
ChiCTR-TRC-10001202 Wei 2017 [36]	Newly diagnosed pts with de novo AML (median age 36 (15-55 yrs).	Intermediate-dose cytarabine, 100 mg/m2 per day as a 12-hour IV infusion on days 1 through 4 and 1,000 mg/m2 every 12 hours as a 3-hour IV infusion on days 5, 6, and 7 (n=295) Conventional dose cytarabine, 100 mg/m2 per day as a 12-hour IV infusion for 7 days, combined with homoharringtonine 2mg/m2 for 7 days and daunorubicin 40mg/m2 for 3 days (n=296) All patients who achieved CR were randomly assigned to receive either high dose of cytarabine (3,000 mg/m2 every 12 hours as a 3-hour IV infusion on days 1, 2, and 3) or intermediate dose of cytarabine (1,500 mg/m2 every 12 hours as a 3-hour IV infusion on days 1, 2, and 3) combined with anthracycline (daunorubicin or mitoxane)	DFS	30.4 mths (5.1-74.4)	Conventional vs Intermediate CR = 77.4% vs 86.8%, p =0.003 3 yr DFS= 66.7% (95% CI 60.4% to 72.9%) vs 55.4% (95% CI 48.3% to 62.4%), p =0.013 Probability of 3 yr OS 67.7% (95% CI 61.8% to 73.7%) vs 59.3% (95% CI 53.1% to 65.5%), p =0.0604 Pts in non-adverse risk subgroup: 3 yr DSF 69.7% vs 56.1% (p=0.004) 3 yr OS= 72.0% vs 60.8%, p = 0.017
Yilmaz 2015	Patients with newly diagnosed AML (non-CBF and non-APL)	CIA ((clofarabine 15 mg/m2 D1-5, idarubicin 10 mg/m2 D1-3, cytarabine 1 g/m2 D1-5) n=97 FIA ((fludarabine 30 mg/m2 D1-5, idarubicin 10 mg/m2 IV D1-3, cytarabine 1 g/m2 D1-5) n=61 Patients could receive to up to 6 cycles of consolidation at an attenuated schedule.	EFS; OS; CR	CIA: 21.3 (0.9-44.7) FIA: 16.3 (4.3-42.0)	EFS : CIA 14 mths vs FIA 11 mths, p=0.81 No difference in OS between CIA and FIA was observed. Compared to IA regimen, the triplet showed better median EFS (9 vs NR; p¼0.05) and OS (19.6 vs NR; p¼0.05) in younger patients (<=40 years).
Post Remission Consolidation					
ALLG M12 Bradstock 2016[37] (abstract)	Patients with AML in complete remission after induction therapy (16 to 60 years of age)	two cycles of consolidation therapy with cytarabine 100 mg/m2 daily for 5 days, etoposide 75 mg/m2 daily for 5 days, and idarubicin 9 mg/m2 daily for either 2 (standard (n=146) or 3	3 yr leukemia free survival (LFS); 3 yr	Median f/u 5.3 yrs	3-year LFS (intensive v standard): 47% [95% CI, 40% to 56%] v 35% [95% CI, 28% to 44%]; HR for intensive arm, 0.74 [95% CI, 0.55 to 0.99]; P = .045; 3 yr OS (intensive v standard): 61% (95%CI, 54% to

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
		days (intensive arms (n=147) 120 in the standard arm (82%) and 95 in the intensive arm (66%) completed both planned consolidation cycles (P < .001)	OS		70%) v 50% (95% CI, 43% to 59%); HR for intensive arm, 0.75 (95% CI, 0.54 to 1.05; P = .092
NILG trial 02/06 (ClinicalTrials.gov Identifier: NCT00495287) Bassan 2016[38]	AML patients with complete remission and did not relapse following consolidation or ASCT.	ICE (idarubicin 12 mg/m^2/d iv. Dd1-3, cytarabine 100 mg/m^2/bd iv. Dd 1-7, etoposide 100 mg/m^2/d iv. Dd1-5); n= 286 SHD (cytarabine 2 g [1 g if age >65]/m^2/bd iv. Dd 1-2 and 8-9, idarubicin 18 mg/m^2/d iv. Dd 3 and 10), plus G-CSF from d11; n = 286 Postremission consolidation consisted of IC (cycle 2), intermediate-dose cytarabine 1 g/m^2/bd iv. Dd 1-4, with harvest of CD34+ blood stem cells (cycle 3), and allogeneic SCT if high-risk or second randomization to BUCY2-conditioned autograft or repetitive HD cycles (cytarabine 2 g/m^2/bd iv. Dd 1-5 and idarubicin 8 mg/m^2/d dd 1-2, cycles 4-6) supported by 1-2 x10^6/kg CD34+ cells	Primary CR rate	5 yr f/u	After induction course (ICE vs SHD): 69.2 vs 81.5%, p=0.001 Subgroup analysis: highrisk AML (n=201 vs 218: CR 64.2% vs 77.6%; P .002) patients <=60 pts with de novo AML (n=190 vs 189: CR 74.2% vs 86.2%; P .003) Median and 5 yr OS ICE 2.14 yrs; 38% SDH 4.51 yrs; 48%, P =0.0125 Subgroup analysis Standard-risk subset: 5-yr OS 55% vs 72%, P .0068 patients <=60 pts with de novo AML: 5 yr OS 43% vs 58%; P .0026).
Cuzzola 2016 (abstract) [39] Interim analysis	>60 years of age; have newly diagnosed "de novo" AML or evolving from myelodysplastic syndrome; >30% bone marrow blasts; no contraindications for intensive chemotherapy; and an ECOG performance status<3	Induction chemotherapy: two courses of "3+7" (Daunorubicin 40 mg/m^2 daily days 1-3 and cytarabine 100 mg/m^2 daily continuous IV infusion days 1-7). Pts in CR receive consolidation therapy (cytarabine 800 mg/ m^2/ 3 hour infusion bid days 1-3) after which they are randomized 1:1 to receive best supportive care (BSC; n=13) or 5-Azacitidine maintenance (n=18) therapy up to 4 years and six months until AML relapse	Time of Relapse	N/R	21 of the 31 patients have relapsed (10 in BSC arm, 11 in 5-Azacitidine arm), while the remaining 10 are alive in CR. Median time to relapse was 296 days, 95% CI 73 -519
Jaramillo 2016 [40]	568 AML pts (18-60 yrs) receiving 1376	two cycles of idarubicin, cytarabine and etoposide +/- all-trans retionoic acid	RFS; OS	NR	Relapse-free and overall survival were similar with HDAC-123 and HDAC-135 (p=0.48, p=0.90)

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
	consolidation cycles.	(ATRA) and +/- valproic acid (VPA). Consolidation: HDAC-135: cytarabine 3g/m2 bidaily, on days 1, 3, 5 and pegfilgrastim on day 10 (n=135) HDAC-123: condensed schedule with cytarabine 3g/m2 bidaily, on days 1,2,3 and pegfilgrastim on day 8 (n=392)			
Kenneth 2016 [41] abstract	AML pts aged 16-60yrs achieving CR after 1 or 2 cycles of induction.	Induction: idarubicin 9 mg/m2 daily x3, cytarabine 3 g/m2 twice daily on days 1,3,5 and 7, and etoposide 75 mg/m2 daily x7; ICE protocol randomized to receive 2 cycles of consolidation therapy with cytarabine 100 mg/m2 per day for 5 days, etoposide 75 mg/m2 for 5 days, and idarubicin 9mg/m2 daily for either 2 (standard; n=146) or 3 days (intensive; n=147).	Leukemia free survival; OS	5.3 years (range 0.6 - 9.9)	3 year LFS for the intensive arm was 47% (95% CI 40-56%) versus 35% (28-44%) for the standard arm; HR 0.74 (95% CI 0.55-0.99); p=0.045 3 year OS for the intensive arm was 61% (95% CI 54-70%) and 50% (95% CI 43- 59%) for the standard arm; HR 0.75 (95% CI 0.54-1.05); p=0.092
NCT# 02024308 Li 2017	Patients aged 13–66 years with previously untreated CBFα-AML after achieving complete remission	Induction: DA or IA regimens (D: daunorubicin 60 mg m22 per day 1–3; I: idarubicin 8 mg m22 per day 1–3; A: cytarabine 100–200 mg m22 per day 1–7) If patients did not achieve PR with one cycle of induction, they received HAG regimen which comprised of homoharringtonine (HHT, 1 mg day 21, intravenously, on days 1–14); cytarabine (25 mg m22 per 24hr divided into twice, subcutaneously, on days 1–14), and G-CSF (5 mg kg21 day21 from day 0 until the neutrophil counts above 1.5 3 109 cells/L) Consolidation: randomized into FAfludarabine (30 mg m22 by 30-min infusion on days 1–5) and cytarabine (1.4 g m22 infusion starting 3.5 hr after fludarabine for over 4 hr on days 1–5) or	RFS; OS	37.5 months (5.5-77.5 mths)	RFS at 36 months (FA vs HD-Ara-C): 81.73% (95% CI, 67–99.7%) vs 50.73% (95% CI, 32.8–78.5%) in HD-Ara-C arm; HR: 0.323, 95%CI (0.101, 1.032), P=0.04 by the log-rank test) RFS of those with/without c-kit mutations: HR 18.806 95%CI (3.277, 107.938), P=0.001 OS of CR pts at 36 mths (FA vs HD-Ara-C): 91.1% (95%CI 80-100% vs 48.4% (95%CI 30-78%), HR: 0.185, 95%CI (0.041, 0.846), p=0.01 log rank test).

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
		HD-Ara-C (fludarabine (30 mg m22 by 30-min infusion on days 1–5) and cytarabine (1.4 g m22 infusion starting 3.5 hr after fludarabine for over 4 hr on days 1–5)			
Post remission maintenance					
HOVON97 Huls 2017 [42] abstract	Older patients (>= 60 years) with AML or MDS-RAEB in CR/CRi after at least 2 cycles of intensive chemotherapy	Observation (n=56) azacitidine maintenance (aza group), 50 mg/ m^2 day 1-5, q 4 weeks, until relapse for a maximum of 12 cycles (n=52). Subsequently, 44, 40, 34 and 32 patients received at least 3, 6, 9 and 12 cycles	DFS; OS		The difference in DFS between the two arms was statistically significant in the cohort of patients in this pre-final analysis (Cox regression; p=0.005). The 12 months DFS was estimated at 39% for the control group and at 63% for the aza group The difference in OS between the two groups currently is not statistically significant in the cohort of patients in this pre-final analysis (Cox regression; p=0.35). The 12 months OS (after censoring allo transplanted patients) was estimated at 64% for the control group and 83% for the aza group.
NCT00700544 Pigneux et al 2017 [43] multicenter, phase III, randomized open-label trial	patients 60 years of age or older with AML de novo or secondary to chemotherapy or radiotherapy	Induction: idarubicin 8 mg/m2 on days 1 to 5, cytarabine 100 mg/m2 on days 1 to 7, and lomustine 200 mg/m2 on day 1. Patients in complete remission or partial remission received six reinduction courses, alternating idarubicin 8 mg/m2 on day 1, cytarabine 100 mg/m2 on days 1 to 5, and a regimen of methotrexate and mercaptopurine. Maintenance: norethandrolone 10 or 20 mg/day, according to body weight (n=165), or no norethandrolone (n=165) for a 2-year maintenance therapy regimen	Disease free survival by intention to treat; event free survival, OS,	NR	norethandrolone significantly improved survival for patients still in remission at 1 year after induction norethandrolone Vs none 5-year disease-free survival was 31.2% and 16.2%, event-free survival was 21.5% and 12.9% overall survival was 26.3% and 17.2%
NCT01687387 Vey 2017 [44] November 2012 and November 2014	Patients were aged 60 to 80 yrs, diagnosed with non-APL AML, in CR1 following standard induction (1 to 2 cycles) and consolidation (1 to 2 cycles) and had: ECOG	All had received 7+3 induction therapy. Most pts (81%) received 2 cycles of consolidation prior to inclusion. Consolidation chemotherapy consisted of intermediate-dose single agent cytarabine (IDAC) in 53%, and 5+1 in 47% of the pts. Pts were randomly allocated to receive placebo or lirilumab given at	LFS	36.6 mo	Median LFS INT group: 17.6 [11.2; 25.0) HR (compared to placebo)= 0.98 (0.61-1.56) CONT group: 6.7 (2.9;14.8) HR (compared to placebo)=1.42 (0.88-2.28)

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
	performance status of 0-1, adequate hematologic, liver and renal function.	either 0.1 mg/kg q 12 weeks (INT) or 1mg/kg q 4 weeks (CONT). * pts in CONT was discontinued in light of an excess of early relapses. Major reasons for study discontinuation were relapse (63%) and adverse events (AE) (10%).			Placebo: 13.9 (7.9-27.9)
R/R pts					
Eslamijouybari 2017 [45] abstract	Elderly patients (including those who are older than 60 with comorbidity and all patients over 65 years of age), treatment resistant patients (primary refractory) and relapsed patients who were not candidates for chemotherapy due to lack of compatible donors	Group A: Ara-c 20 mg/Bid (LDAC) by subcutaneous injection 5 days each week and arsenic trioxide 10 mg/day by infusion over 2 hours for 10 days each month (n=22) Group B: Ara-c 20 mg/Bid (LDAC) 5 days each week (n=20)	OS; Partial remission	3 yrs	PR at +60 days: Group A (n=20): 60% Group B (n=14): 71.4% PR at +120 days: Group A (n=18) 27.8% Group B (n = 12) = 58.3% OS was 16 months in both groups
VALOR (NCT01191801) Phase 3, 101 sites in North America, South Korea, Australia, New Zealand Rovandi 2015 (primary analysis: all patients) December 2010-September 2013 (f/u September 2014)	AML patients > 18 yrs with first relapse or had refractory disease (n=711). All pts must have received previous induction with anthracycline (or antrhacenedione) + cytarabine. Subgroup analysis of pts >=60yrs (63% of total sample). Vos/cyt n=226 Pla/cyt n=225	cytarabine (1 g/m2 IV over 2 h, d 1-5) plus Vos/cyt: vosaroxin (90 mg/m2 IV over 10 min d 1 and 4; 70 mg/m2 in subsequent cycles) (n=356) or; Plat/cyt: placebo (n=355) A second induction cycle could be started between 2-8 weeks after initiation of cycle 1. Up to two additional cycles could be given as consolidation therapy in CR or CR with incomplete platelet recovery	OS; all-cause mortality at 30 and 60 days; CR	Median follow up 24.4 mths	vos/cyt vs pla/cyt OS: 7.5 mths (95% CI 6.4–8.5) vs 6.1 mths (5.2–7.1), HR 0·87, 95% CI 0·73–1·02; unstratified log-rank p=0·061 CR: 107/356 vs 58/355 (16%), p<0.0001 EFS: 1·9 months [95% CI 1·6–2·2] vs 1·3 months [1·2–1·4]; HR 0·67, 0·57–0·79; log-rank p<0.0001 30 day mortality: 28 [8%] of 355 vs 23 [7%] of 350 60 day mortality: 70 [20%] vs 68 [19%] *Subgroup analysis:* Pts with early relapse OS: 6.7 months vs 5.2 months; HR 0.77, 0.59–1.00; log-rank p=0.039 *OS ns different in pts younger than 60 yrs, late relapse or refractory disease. Pts>=60 yrs OS: 7·1 mths vs 5.0 mths; HR 0.75, 95% CI 0.62–0.92; log-rank p=0·0030

Trial Name Citations (ref)	Population	Arms / Dose (n)	Outcomes	Follow-up	Results
Carella 2015[46] Krug 2015 abstract [47] (abstracts on primary study, pts >= 60 yrs only)					Pts>=60 yrs: CR: 72/226 (32%) vs 31/225 (14%), p<0.0001 median leukemia-free survival in patients who achieved CR was 10.3 mo vs 6.5 mo (p = 0.20) Pts>=60 yrs: EFS: 2.1 mo vs 1.3 mo with pla/cyt; HR=0.61; P<0.0001 30-day mortality: 10.2% vs 9.0%; 60-day mortality: 20.4% vs 22.6%
Horst 2016 [48] Pigneux 2016 abstract [49] (abstracts on f/u January 2016 all pts) Ravandi 2016 (abstract) f/u January 2016 pts >= 60 yrs				Median follow up 39.9 mths	All pts: 134/711 (19%) alive at f/u CR: 70% in vos/cyt vs 51% pla/cyt Pts >= 60 yrs 33/451 pts were alive, 23/226 (10.2%) in vos/cyt vs 10/225 (4.4% pla/cyt OS (for addition of Vos): HR = 0.75 [95% CI: 0.62-0.91]; P = 0.0017 OS benefit was consistent across various age subgroups in the population >= 60 years of age; 60-64 years (n = 124), 65-74 years (n = 293), and 75-84 years (n = 34), vosaroxin/cytarabine treatment increased median survival by 2.9 mo (8.1 vs 5.2 mo; HR = 0.72 [95% CI: 0.49-1.06]), 2.0 mo (7.0 vs 5.0 mo; HR = 0.76 [95% CI: 0.60- 0.97]), and 2.2 mo (5.5 vs 3.3 mo; HR = 0.72 [95% CI: 0.36-1.45]) over placebo/cytarabine treatments
Webster 2015[50]; 2017[51] June 2013-September 2014 Multi-institution study	Patients aged 18–75 years with a pathologically confirmed diagnosis of relapsed or primary refractory AML. Patients were eligible if they received ≤2 prior cytotoxic induction regimens and were>2 weeks beyond previous cytotoxic chemo or radiation.	Arm A: AraC 2 g/m2 over 72 h intravenous continuous infusion beginning on Day 1 and Day 10 with MK-8776 100 mg over 30 min by IV infusion beginning 24 ± 4 h and 48 ± 4 h after the start of each AraC infusion on Days 2, 3, 11, and 12 (n=13) Arm B: AraC alone (n=18) Accrual to this randomized study was stopped due to the termination of the clinical development of MK-8776	CR	NR	no significant difference in response rates between the arms, with 5 patients (36%) in Arm A and 8 patients (44%) in Arm B achieving CR/CRi and 1 patient in each arm achieving a PR

Table 5. Ongoing trials

NCT Number	Title
NCT00046930	Daunorubicin & Cytarabine +/- Zosuquidar inTreating Older Patients With Newly Diagnosed Acute Myeloid
NCT00121303	Cytarabine and Daunorubicin With or Without Gemtuzumab Ozogamicin in Treating Older Patients With Acute Myeloid Leukemia or Myelodysplastic Syndromes
NCT00860639	Efficacy of Gemtuzumab Ozogamycin for Patients Presenting an Acute Myeloid Leukemia (AML) With Intermediate Risk
NCT01802333	Cytarabine and Daunorubicin Hydrochloride or Idarubicin and Cytarabine With or Without Vorinostat in Treating Younger Patients With Previously Untreated Acute Myeloid Leukemia

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Appendix 1. Members of the Expert Panel

Name	Affiliation	Conflict of Interest Declaration
Tom Kouroukis	Provincial Head, Complex Malignant Hematology, Cancer Care Ontario	None declared
Mitchell Sabloff	Hematologist, Ottawa	Received $500 or more to act in a consulting capacity: Pfizer Canada Oct 2018; Celgene Jun 2018; Jazz Pharmaceuticals April 2018; Novartis Canada Feb 2018/2017. Received research support Sanofi Canada 2016/2017 Principal investigator for a clinical trial involving any of the objects of study: A Phase 3, Randomized, Open-Label, Crossover Study of ASTX727 (Cedazuridine and Decitabine Fixed-Dose Combination) vs IV Decitabine in Subjects with Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML) A Randomized, Double-Blind, Placebo Controlled Phase 3 Study of Venetoclax in Combination with Azacitidine vs Azacitidine in Treatment Naïve Subjects with Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy An Open-Label, Multicenter, Extension Study for Subjects Who Participated in Prior Guadecitabine Clinical Studies A Phase 3, Multicenter, Open-label, Randomized Study of SGI-110 vs Treatment Choice (TC) in Adults with Previously Untreated Acute Myeloid Leukemia (AML) Who Are Not Considered Candidates for Intensive Remission Induction Chemotherapy A Multicenter, Pivotal Phase 3 Study of Iomab-B Prior to Allogeneic Hematopoietic Cell Transplantation vs Conventional Care in Older Subjects with Active, Relapsed or Refractory Acute Myeloid Leukemia A randomized, multicenter, open-label, phase 2 study evaluating the efficacy and safety of azacitidine subcutaneous in combination with durvalumab (medi4736) in previously untreated subjects with higher-risk myelodysplastic syndromes (MDS) or in elderly (≥ 65 years) acute myeloid leukemia (AML) subjects not eligible for hematopoietic stem cell transplantation (HSCT).
Rena Buckstein	Hematologist, Odette Cancer Centre, Toronto	Received $500 or more to act in a consulting capacity: Advisory board attendance Celgene. Received grant or other research support from Celgene for MDS registry: 150K/year; Takeda support for MDS registry: 75 K x 1 Principal investigator for Pevonedistat clinical trial in MDS; Takeda ASTEX clinical studies of decitabine oral in MDS.
Jill Dudebout	Hematologist, Kingston	None declared
Lianne Dupras	Patient and Family Advisor,	None declared

	CCO	
Sindu Kanjeekal	Hematologist, Windsor	None declared
Kardi Kennedy	Regional Systemic Treatment Program Lead, Kingston	None declared
Rouslan Kotchekov	Hematologist, Barrie	None declared
Kit McCann	Nurse Practitioner, Windsor	Received $500 or more to act in a consulting capacity: Talk for Teva for nurses on APL Ad Board for Fragmin- Pfizer.
Anthony Naassan	Hematologist, Lakeridge Health, Oshawa	Received $500 or more to act in a consulting capacity: Participated as an investigator (both principal and sub) in industry supported trials. Served on advisory boards, as a consultant and also as a speaker. These are in the field of hematology but none relate to the management of Acute Leukemia. Had managerial responsibility for an organization or department that has received $5,000 or more in a single year from a relevant business entity: Section head for hematology at the Durham Regional Cancer Centre. Recieve funds exceeding $5000 from Cancer Care Ontario and Ministry of Health and Long Term Care.
Sue Nugent	Administrator, London Health Sciences Centre, London	None declared
Lalit Saini	Hematologist, London	Received $500 or more to act in a consulting capacity: Various pharmaceutical companies' advisory boards. Principal investigator for various clinical trials evaluating novel agents in AML.
Judy Costello	Senior Clinical Director, Malignant Hematology, Princess Margaret Hospital, Toronto	Received $500 or more to act in a consulting capacity: As an Accreditation Canada Surveyor I have completed a consultation for a Canadian Cancer Center one year prior to their actual survey (I was on their previous survey team.). This consultation was provided as an agent of Accreditation Canada And was carried out utilizing approved tools of that organization.

Appendix 2. Search Strategy

#	Search Terms	# hits
1	exp phase 3 clinical trial/ or exp "phase 3 clinical trial (topic)"/ or exp clinical trial, phase iii/ or exp clinical trials, phase iii as topic/ or exp phase 4 clinical trial/ or exp "phase 4 clinical trial (topic)"/ or exp clinical trial, phase iv/ or exp clinical trials, phase iv as topic/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or exp controlled clinical trial/ or exp randomized controlled trials as topic/ or exp randomization/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/ or exp placebos/ or exp placebo/ or ((exp phase 2 clinical trial/ or exp "phase 2 clinical trial (topic)"/ or exp clinical trial, phase ii/ or exp clinical trials, phase ii as topic/ or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/) and random$.tw.) or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or ((singl$ or double$ or treple$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw. or placebo?.tw. or (allocat: adj2 random:).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.	1424463
2	exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw.	468888
3	exp evidence based practice/ or exp practice guideline/ or guideline.pt. or practice parameter$.tw. or practice guideline$.mp. or (guideline: or recommend: or consensus or standards).ti. or (guideline: or recommend: or consensus or standards).kw.	1454391
4	2 not 1	300265
5	3 not (1 or 2)	711668
6	(exp Acute granulocytic leukemia/ or exp acute megakaryocytic leukemia/ or exp acute monocytic leukemia/ or exp acute myeloblastic leukemia/ or exp acute myelomonocytic leukemia/ or exp Leukemia, Myeloid, Acute/ or (Acute adj2 leuk?emia$ adj2 (granulocytic or megakaryocytic or monocytic or myeloblastic or myelomonocytic or myeloid or myelocytic or myelogenous or nonlymphoblastic or non-lymphoblastic or nonlymphocytic or non-lymphocytic or erythroid or monoblastic or basophilic or erythroid or monoblastic or nonlymphoid or non-lymphoid)).tw. or (acute panmyelosis with myelofibrosis or pure erythroid leuk?emia$ or erythroleuk?emia$ or myeloid sarcoma or myeloid leuk?emia$ associated with Down syndrome or myeloid proliferations related to Down syndrome or transient abnormal myelopoiesis or blastic plasmacytoid dendritic cell neoplasm or therapy-related myeloid neoplasms).tw. or ANLL.mp. or (AML not (angiomyol: or amylose or amlodipine)).mp.) not ((comment or letter or editorial or case reports or historical article or note).pt. or exp case report/ or exp case study/)	77278
7	6 and ((201508: or 201509: or 20151: or 2016: or 2017: or 2018:).ed. or (201508: or 201509: or 20151: or 2016: or 2017: or 2018:).dd. or (201508: or 201509: or 20151: or 2016: or 2017: or 2018:).em.)	23439
8	1 and 7	2199
9	7 and 4	289
10	7 and 5	461
11	remove duplicates from 8	1989
12	remove duplicates from 9	233
13	remove duplicates from 10	447

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document, however, may still be useful for education or other information purposes. The document is designated archived on the CCO website and each page is watermarked with the words "ARCHIVED."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.