



Evidence-Based Series 2-5

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

**Strategies of Sequential Therapies in Unresectable, Metastatic
Colorectal Cancer Treated with Palliative Intent**

*T. Asmis, S. Berry, R. Cosby, K. Chan, N. Coburn, M. Rother,
and the Gastrointestinal Disease Site Group*

Report Date: January 28, 2014

An assessment conducted in December 2023 deferred the review of Evidence-based Series (EBS) 2-5. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

Evidence-Based Series 2-5 is comprised of 3 sections. You can access the summary and full report here:

<https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/396>

Section 1:	Guideline Recommendations
Section 2:	Evidentiary Base
Section 3:	Development Methods, Recommendations Development and External Review Process

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Table of Contents

Section 1: Guideline Recommendations	1
Section 2: Evidentiary Base	5
Section 3: EBS Development Methods and External Review Process	31

Evidence-Based Series 2-5: Section 1

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

**Strategies of Sequential Therapies in Unresectable, Metastatic
Colorectal Cancer Treated with Palliative Intent:
Guideline Recommendations**

*T. Asmis, S. Berry, R. Cosby, K. Chan, N. Coburn, M. Rother,
and the Gastrointestinal Disease Site Group*

Report Date: January 28, 2014

QUESTION

What is the impact of different strategies of sequential and combination chemotherapy on efficacy (including overall survival), toxicity and quality of life in unresectable metastatic colorectal cancer treated with palliative intent?

TARGET POPULATION

These recommendations apply to adult patients (≥ 18 years old) with unresectable metastatic colorectal cancer. The cytotoxic agents covered in this guideline include initial fluoropyrimidine (5-FU or capecitabine) either alone or in combination, irinotecan and oxaliplatin.

INTENDED USERS

This guideline is intended for use by clinicians and healthcare providers involved in the management of patients with unresectable, metastatic colorectal cancer treated with palliative intent.

RECOMMENDATIONS AND KEY EVIDENCE

Planned sequential chemotherapy and upfront combination chemotherapy are both acceptable standards of care. While there is a statistically significant difference in overall survival in favour of combination chemotherapy, the magnitude of the difference between the two strategies may not be clinically significant. Furthermore, sequential therapies may reduce upfront toxicities. Therefore, choice of treatment should be made on a case-by-case basis based on considerations that include patient and tumour characteristics, toxicity of each strategy and patient preference.

Sequential chemotherapy consists of a fluoropyrimidine monotherapy followed by either:

- a. another monotherapy with irinotecan *OR*
- b. combination chemotherapy consists of a doublet of a fluoropyrimidine with irinotecan or oxaliplatin

Combination chemotherapy consists of an upfront doublet of a fluoropyrimidine with irinotecan or oxaliplatin.

A meta-analysis of five trials (1-5) demonstrates a survival advantage for combination chemotherapy (HR, 0.92; 95%CI, 0.86-0.99, $p=0.02$). Median survival advantage in most trials is 3 to 6 weeks (range <1 week to 12 weeks). Therefore, any survival advantage that exists is likely to be very small and not clinically significant. First-line toxicities are reported by three trials (1,2,4). Hematological toxicities include significantly more neutropenia (1,4), febrile neutropenia (1) and thrombocytopenia (4) with upfront combination chemotherapy. Non-hematological toxicities include significantly more diarrhea (1), nausea (1,4), vomiting (1,4) and sensory neuropathy (4) in the upfront combination chemotherapy arm, and significantly more hand-foot syndrome in the sequential chemotherapy arm (1).

QUALIFYING STATEMENTS

- The FOCUS (2) trial is the largest trial of the five included trials. The individual hazard ratio for the FOCUS (2) trial only includes two arms of this trial. Therefore, one third of the data from this trial is missing from the overall meta-analysis of the five trials.
- Based on the results of this systematic review, patients should have access to all effective cytotoxic drugs using a sequential strategy.
- Combination chemotherapy may be more appropriate for patients with rapidly progressing, very symptomatic or bulky life-threatening visceral disease given their higher overall response rates.
- The studies included in this systematic review were done in an era prior to the use of biologics in the treatment of mCRC. Definitive statements about the integration of biologics into a sequential strategy cannot be made at this time.

FUTURE RESEARCH

Future research of strategies of care should also include biologically targeted therapies.

RELATED GUIDELINES

- PEBC Evidence-based Series #2-25: *The Role of Bevacizumab (Avastin®) Combined with Chemotherapy in the Treatment of Patients with Advanced Colorectal Cancer* (available from: <https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1506?redirect=true>).

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Evidence-Based Series 2-5: Section 2

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

**Strategies of Sequential Therapies in Unresectable, Metastatic
Colorectal Cancer Treated with Palliative Intent:
Evidentiary Base**

*T. Asmis, S. Berry, R. Cosby, K. Chan, N. Coburn, M. Rother,
and the Gastrointestinal Disease Site Group*

Report Date: January 28, 2014

QUESTION

What is the impact of different strategies of sequential and combination chemotherapy on efficacy (including overall survival), toxicity and quality of life in unresectable, metastatic colorectal cancer treated with palliative intent?

INTRODUCTION

Colorectal cancer is the third most common cancer in Ontario in both sexes, with an estimated 8700 new cases in 2012. This represents 12% of all new cases of cancer in Ontario for 2012 (1). The incidence of colorectal cancer has varied over the last 30 years. Between 1982 and 1985, incidence rose in males and was fairly stable in females. Incidence then rose through 2000, followed by a significant decline. Although mortality rates have been declining in males and females in the last decade, it is estimated that there will be 3450 colorectal cancer deaths in Ontario in 2012, representing 12.4% of all cancer deaths (1). Therefore, there is interest in improving treatment results as well as quality of life for people with colorectal cancer.

The current, commonly used strategy for unresectable metastatic colorectal cancer (mCRC) in Ontario is upfront combination chemotherapy with a fluoropyrimidine (5-fluorouracil or capecitabine) and either oxaliplatin or irinotecan, with or without a biologic. Less often, monotherapy with capecitabine followed by irinotecan is used. Prior to the emergence of first-line combination chemotherapy, the standard of care was first-line monotherapy with modulated 5-fluorouracil. There have now been several large, randomized phase III trials completed that assess whether a planned sequential chemotherapy strategy, beginning with fluoropyrimidine monotherapy until treatment failure followed by another regimen (either monotherapy or combination chemotherapy) until treatment failure, could result in the same survival benefit as an initial combination chemotherapy strategy but with less toxicity for patients. The Gastrointestinal Disease Site Group (GI DSG) of the PEBC decided that a systematic review of the evidence and a synthesis of the available data that could guide clinicians' treatment recommendations for their patients with unresectable mCRC being treated with palliative intent would be useful.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (2). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC Gastrointestinal Disease Site Group (GI DSG) working group and one methodologist (Appendix 1).

The systematic review is a convenient and up-to-date source of the best available evidence on strategies of sequential therapies in advanced colorectal cancer. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of the recommendations developed by the GI DSG (Appendix 2) and presented in Section 1. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

The MEDLINE (2000 through July [week5] 2013) and EMBASE (2000 through week 32 2013) databases were searched for relevant evidence. The year 2000 was chosen as the starting point as it predates the approval of irinotecan and oxaliplatin for use in metastatic colorectal cancer. The full MEDLINE and EMBASE literature search strategies can be found in Appendix 3). The reference lists from retained articles were also searched for additional relevant trials. In addition, the proceedings of the 2004-2013 American Society of Clinical Oncology (ASCO) and the 2002-2012 European Society of Medical Oncology (ESMO) annual meetings were searched for abstract reports of relevant studies.

Study Selection Criteria

Inclusion Criteria

Articles were included if they were published English-language abstracts or fully published reports of RCTS comparing a sequential strategy of chemotherapy to upfront combination chemotherapy in adult patients with metastatic colorectal cancer and included at least one of the outcomes of interest. Syntheses of RCTs in the form of systematic review or meta-analyses were also eligible. If more than one study evaluated the same data set, only the most recent paper was selected for inclusion.

Exclusion Criteria

Abstract reports of preliminary or interim data only were excluded. Letters, editorials, notes, case-reports, commentaries and non-systematic reviews were not eligible.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, the data were pooled using the Review Manager software (RevMan 5.1) provided by the Cochrane Collaboration (3). Since hazard ratios (HRs), rather than the number of events at a certain time point, is the preferred statistic for pooling time-to-event outcomes (4), those were extracted directly from the most recently reported trial results. The variances of the HR estimates were calculated from the reported CIs using the methods described by Parmar et al. (4). A random-effects model was used for all pooling, as it provides a more conservative estimate of effect (5).

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% were considered indicative of statistical heterogeneity. Results are expressed as HRs with 95%CI. An HR <1.0 indicates that patients receiving the experimental treatment had a lower probability of experiencing an event (death); conversely, an HR >1.0 suggests that patients in the experimental arm experienced a higher probability of an event.

RESULTS

Literature Search Results

The MEDLINE search yielded 3383 hits, of which 42 were potentially relevant and were fully reviewed. Five were retained (Table 1, Appendix 4). The EMBASE search yielded 8507 hits, of which 19 were potentially relevant and were fully reviewed. None of these were retained. No abstracts from ASCO or ESMO were retained.

Table 1. Literature search results.

Database	Dates Searched	Hits	Fully Reviewed	Retained
MEDLINE	2000 - July [week5] 2013	3383	42	5
EMBASE	2000 - week 32 2013	8507	19	0
ASCO	2004-2013	5617	8	0
ESMO	2002-2012	914	2	0
Reference Mining	Not Applicable	0	0	0

Study/Trial Design and Quality

Randomized trials were assessed for key methodological characteristics, using information provided in the trial reports. The following elements were assessed: generation of allocation sequence, allocation concealment, blinding, intention-to-treat analysis, withdrawals, loss to follow-up, funding source, statistical power calculations, length of follow-up, differences in baseline patient characteristics, and early termination.

Outcomes

Study/Trial Design and Quality

All five trials (6-10) involved adult patients with advanced unresectable or metastatic colorectal cancer comparing a planned sequential chemotherapy strategy to upfront combination chemotherapy (Table 2). The vast majority of patients had tumours of the colon or rectum. None of the patients had previous systemic therapy for advanced colorectal cancer. All patients had World Health Organization (WHO) performance status (PS) of 0-2. Only three studies (6,7,9) reported median follow-up time (Table 2). All of the trials were superiority trials. FOCUS2 (10) was a trial specifically designed for elderly and frail patients who were considered unsuitable for full-dose chemotherapy. In this trial, starting doses were 80% of the standard dose with the option of increasing to the full dose after six weeks at the discretion of the treating oncologist.

Table 3 outlines the specific planned details of the treatment strategies for each of the trials. The sequential arm in all the trials consisted of a first-line fluoropyrimidine (6-10). CAIRO (6), FOCUS (7) and LIFE (8) followed the upfront fluoropyrimidine monotherapy with second-line irinotecan monotherapy. CAIRO also allowed for third-line combination chemotherapy (capecitabine/oxaliplatin). FFCD (9) and FOCUS2 (10) followed the upfront monotherapy with second-line combination chemotherapy. FFCD (9) also included another combination chemotherapy regimen as third-line treatment. The combination chemotherapy

arm in all the trials began with upfront combination chemotherapy followed by nothing else planned (7,10), although further unplanned treatment could be instituted at the discretion of the treating physician (10), another combination regimen (6,9) or monotherapy (8). FOCUS (7) had a third strategy, which they called 'deferred combination'. This arm consisted of first-line monotherapy with a fluoropyrimidine followed by a combination regimen and was similar to the sequential arm in FOCUS2 (10).

With respect to trial quality, all five trials reported on the generation of allocation sequences, described withdrawals, had industry funding, provided statistical power calculations, used intent-to-treat analysis and had balanced baseline patient characteristics. One of the studies reported on loss to follow-up (9), and one of the studies was terminated early (9) (Table 4).

Table 2. Characteristics of identified randomized controlled trials.

Trial	Patient Characteristics	Site of Tumour (%)	Treatment	Primary Endpoint	Number of Patients Randomized (Evaluated)	Median Follow-up for Patients Still Alive (months)
Koopman 2007 (CAIRO) (6)	Colorectal cancer Advanced, not amenable to surgery No previous systemic treatment for advanced disease Aged ≥ 18 WHO PS 0-2	Colon - 60 Rectosigmoid - 8 Rectum - 32 Multiple tumours - <1 Missing - <1	Sequential (Cape then Irino then Cape/Ox) Combination (Cape/Irino then Cape/Ox)	Overall Survival	410 (401) 410 (402)	31.5
Seymour 2007 (FOCUS) (7)	Colorectal adenocarcinoma Inoperable metastatic or locoregional disease No prior chemotherapy for metastatic disease Age >18 WHO PS 0-2	Colon - 66 Rectum - 33	Sequential (FU then Irino) Deferred Combination A (FU then FU/Irino) Deferred Combination B (FU then FU/Ox) Combination A (FU/Irino) Combination B (FU/Ox)	2-year Survival	710 356 356 356 357	26.5
Cunningham 2009 (LIFE) (8)	Colorectal cancer Distant metastases (excluding CNS) No prior chemotherapy for metastatic disease Aged ≥ 18 WHO PS 0-2	Colon - 56 Rectum - 37 Other - 7	Sequential (FU then Irino) Combination (FU/Ox then Irino)	2-year Survival	363 (363) 362 (362)	NR
Ducieux 2011 (FFCD) (9)	Colorectal cancer Metastatic, no amenable to curative intent surgery No prior chemotherapy for metastatic disease Age >18 WHO PS 0-2	Colon - 76 Rectum - 22	Sequential (FU then FOLFOX6 then FOLFIRI) Combination (FOLFOX6 then FOLFIRI)	PFS for first and second line treatment	205 (205) 205 (205)	36
Seymour 2011 (FOCUS2) (10)	Colorectal adenocarcinoma Inoperable advanced or metastatic disease No prior systemic therapy for metastatic disease No upper or lower age limit. Patients had to be unsuitable for standard <i>full-dose</i> combination therapy. WHO PS 0-2	Colon - 74 Rectum - 26	Sequential A (FU then FU/Ox) Sequential B (Cape then Cape/Ox) Combination A (FU/Ox) Combination B (Cape/Ox)	PFS	115 115 115 114	NR

Cape = capecitabine; CNS = central nervous system; FOLFIRI = folinic acid/5-fluorouracil/irinotecan; FOLFOX = folinic acid/5-fluorouracil/oxaliplatin; FU = 5-fluorouracil; Irino = irinotecan; NR = not reported; Ox = oxaliplatin; PFS = progression-free survival; PS = performance status; WHO = World Health Organization

Table 3. Planned treatment strategy details of included randomized controlled trials.

Trial	Treatment Strategy	Planned Treatment Strategy Details
Koopman 2007 (CAIRO) (6)	Sequential Combination	Monotherapy → another monotherapy → combination chemotherapy Upfront combination chemotherapy → another combination regimen
Seymour 2007 (FOCUS) (7)	Sequential Deferred Combination Combination	Monotherapy → another monotherapy Monotherapy → combination chemotherapy Upfront combination chemotherapy
Cunningham 2009 (LIFE) (8)	Sequential Combination	Monotherapy → another monotherapy Upfront combination chemotherapy → monotherapy
Ducreux 2011 (FFCD) (9)	Sequential Combination	Monotherapy → combination chemotherapy → another combination regimen Upfront combination chemotherapy → another combination regimen
Seymour 2011 (FOCUS2) (10)	Sequential Combination	Monotherapy → combination chemotherapy Upfront combination chemotherapy

→ = followed by

Table 4. Methodological quality characteristics of identified randomized controlled trials.

Trial	Generation of Allocation Sequence Reported	Allocation Concealment	Blinding	ITT	Withdrawals Described	Industry Funding	Statistical Power and Target Sample Size	Loss to Follow-up	Baseline Characteristics Balanced	Terminated Early
Koopman 2007 (CAIRO) (6)	Yes	No	No	Yes	Yes	Yes	80% power to detect 20% reduction in the hazard of death with 800 pts. Actual accrual 820 pts.	NR	Yes	No
Seymour 2007 (FOCUS) (7)	Yes	NR	NR	Yes	Yes	Yes	80% power to detect a 7.5% improvement in 2-yr survival with 2100 pts. Actual accrual 2135 pts.	NR	Yes	No
Cunningham 2009 (LIFE) (8)	Yes	No	No	Yes	Yes	Yes	90% power to detect 10% improvement in 2-yr survival with 700 pts. Actual accrual 725 pts.	NR	Yes	No
Ducreux 2011 (FFCD) (9)	Yes	No	No	Yes	Yes	Yes	90% power to detect 3-month improvement in median PFS for first-line and second-line treatment with 570 patients. Actual accrual 410 pts.	Yes	Yes	Yes, for decrease in accrual
Seymour 2011 (FOCUS2) (10)	Yes	No	No	Yes	Yes	Yes	90% power to detect 3-month improvement in median PFS with 460 pts. Actual accrual 459 pts.	NR	Yes	No

ITT = intent-to-treat analysis; NR = not reported; PFS = progression-free survival; pts = patients; yr = year

Response and Survival

In each of the five studies (6-10), the overall response rate (ORR) (complete and partial response) was significantly greater in the upfront combination chemotherapy arm than in the sequential chemotherapy arm (Table 5). Similarly, progression-free survival (PFS) was significantly greater in the combination chemotherapy arm in four of the studies (6-9). In FOCUS2 (10), there was no significant difference between the treatment arms with respect to PFS. Meta-analysis of the four trials that report HRs for PFS (6,8-10) demonstrates a significant benefit for combination chemotherapy (HR, 0.74; 95%CI, 0.67-0.81; $p < 0.00001$) (Figure 1). There was no significant heterogeneity among these trials with respect to progression-free survival.

Figure 1. Meta-analysis of progression-free survival hazard ratios from randomized trials comparing upfront combination versus sequential chemotherapy in unresectable, metastatic colorectal cancer.

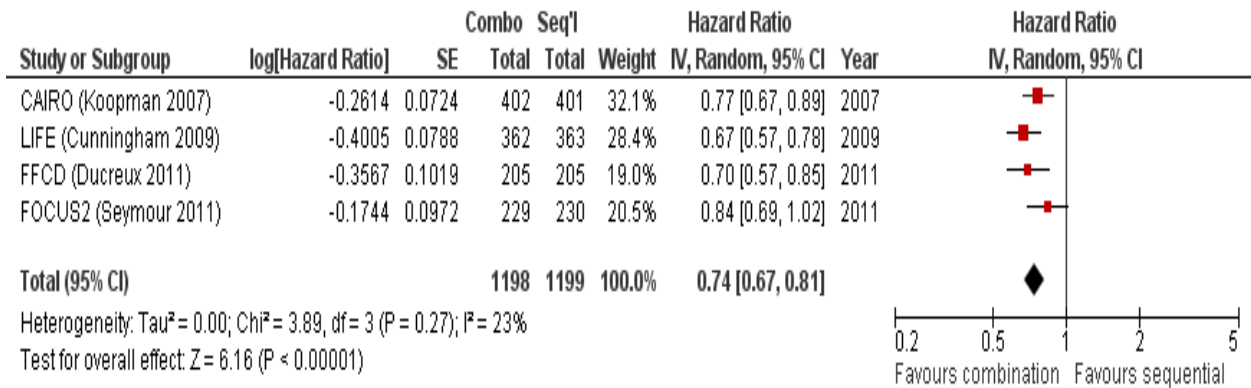


Table 5. Survival and response outcomes of identified randomized controlled trials.

Trial	Treatment ^a	N	Overall Survival			Progression-Free Survival 1 ^b		ORR (%)
			2-year (%)	Median (months)	HR (95%CI)	Median (months)	HR (95%CI)	
Koopman 2007 (CAIRO) (6)	Sequential (Cape then Irino then Cape/Ox) Combination (Cape/Irino then Cape/Ox)	401	1-year 64	16.3	0.92 (0.79-1.08) p=ns	5.8	0.77 (0.67-0.89) p=0.0002	20
		402	67 p=ns	17.4 p=ns		7.8 p=0.0002		41 p<0.0001
Seymour 2007 (FOCUS) (7)	Sequential (FU then Irino)	710	22	13.9	Combo vs. Seq'l 0.88 (0.79-0.98) p=0.02 (ns) ^c	} 6.3	NR	} 28
	Deferred Combination A (FU then FU/Irino)	356	} 25	15.0 (ns)				
	Deferred Combination B (FU then FU/Ox)	356		15.2 (ns)	Combo vs. Deferred Combo 0.94 (0.84-1.05) ^d	8.5 (p<0.001) 8.7 (p<0.001)	49 (p<0.001) 57 (p<0.001)	
	Combination A (FU/Irino)	356	} 28	16.7 (p=0.01)				
	Combination B (FU/Ox)	357		15.4 (ns)				
Cunningham 2009 (LIFE) (8)	Sequential (FU then Irino)	363	24.8	15.2	0.93 (0.78-1.10) p=ns	5.9	0.67 (0.58-0.79) p<0.0001	29.8
	Combination (FU/Ox then Irino)	362	27.3	15.9		7.9		54.1 p<0.0001
Ducreux 2011 (FFCD) (9)	Sequential (FU then FOLFOX6 then FOLFIRI)	205	30	16.4	1.02 (0.82-1.27) p=ns	5.3	0.70 (0.57-0.85) p=0.0004	24
	Combination (FOLFOX6 then FOLFIRI)	205	30	16.2		7.6		58 p<0.0001
Seymour 2011 (FOCUS2) (10)	Sequential A (FU then FU/Ox)	115	NR	10.1	0.99 (0.81-1.18) p=ns	3.5	Combo vs. Seq'l 0.84 (0.69-1.01) p=ns	11
	Sequential B (Cape then Cape/Ox)	115		11.0		5.2		14
	Combination A (FU/Ox)	115		10.7		5.8		38
	Combination B (Cape/Ox)	114		12.4		5.8		32 p<0.0001

Cape = capecitabine; CI = confidence interval; combo = combination; FOLFIRI = folinic acid/5-fluorouracil/irinotecan; FOLFOX = folinic acid/5-fluorouracil/oxaliplatin; FU = 5-fluorouracil; HR = hazard ratio; Irino = irinotecan; NR = not reported; ns = not significant; ORR = overall response rate; Ox = oxaliplatin; seq'l = sequential; vs. = versus.

^aPlanned lines of therapy as shown and then followed by salvage treatment at the discretion of the treating oncologist.

^bProgression-Free Survival 1 - the time from randomization to first progression or death

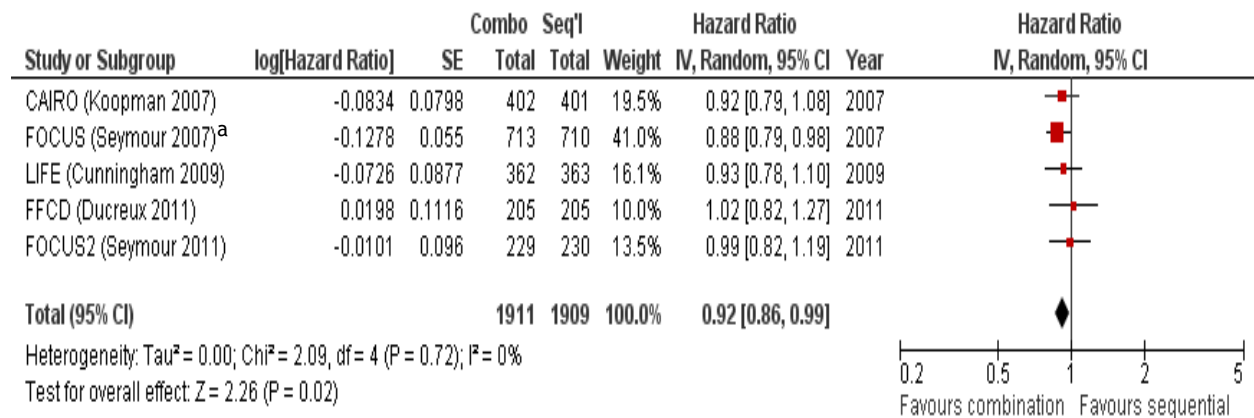
^cAuthors set significance level at p<0.01 to confirm superiority, at the 99% confidence level, owing to adjustments made to account for multiple testing.

^dSeymour 2007 reports an HR of 1.06 and 90%CI of 0.97-1.17. These data were inverted so that all the comparisons were in the same direction. Also, the 95%CI was calculated for this systematic review to make it consistent with the other included studies and is reported in the table.

In each of the five included studies (6-10), overall survival was not significantly longer for the combination chemotherapy strategy (Table 5) compared to the sequential strategy. The FOCUS study (7) does report that median survival in one of the upfront combination arms consisting of fluorouracil and irinotecan was significantly greater compared to the sequential chemotherapy arm (16.7 vs. 13.9 months, $p=0.01$). However, the other upfront combination chemotherapy arm consisting of fluorouracil and oxaliplatin did not result in longer survival compared to sequential chemotherapy. Moreover, a comparison of upfront combination chemotherapy and sequential chemotherapy, without including the ‘deferred combination’ arms, did not result in a statistically significant longer survival (HR, 0.88; 95%CI, 0.79-0.98), as the authors of this trial used a very stringent significance level ($p<0.01$, see Table 5, Footnote c) to account to the multiple testing they performed.

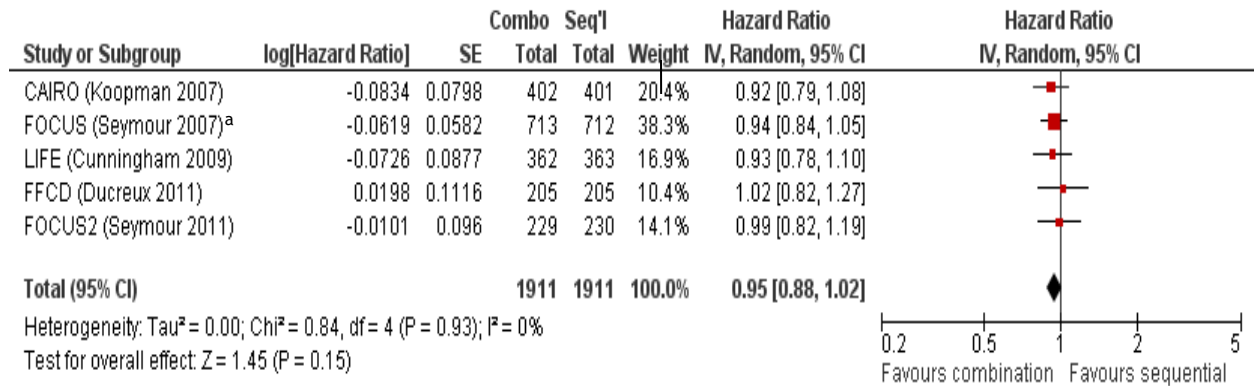
Meta-analysis of these five trials does demonstrate significant benefit for combination chemotherapy (HR, 0.92; 95%CI, 0.86-0.99, $p=0.02$) and no heterogeneity ($I^2=0\%$, $p=0.72$) (Figure 2). However, this meta-analysis may be problematic in that for the FOCUS trial (7), a hazard ratio for survival that included all the data was not available. A HR for survival was available for the comparison of upfront combination chemotherapy (N=713) versus sequential chemotherapy (N=710) strategies (and was used in this meta-analysis), but the deferred combination strategy arm (N=712) was not included. Thus, one third of the trial data is not included in this HR (N=712). Therefore, a second meta-analysis was performed (Figure 3) that used the HR for the comparison of upfront combination (N=713) versus deferred combination (essentially sequential) chemotherapy (N=712) strategies. The data from the sequential arm are not included (N=710). This second analysis demonstrates no significant survival benefit for combination chemotherapy (HR, 0.95; 95%CI, 0.88-1.02, $p=0.15$) compared to a sequential chemotherapy strategy and no heterogeneity among the trials ($I^2=0\%$, $p=0.93$).

Figure 2. Initial meta-analysis of survival hazard ratios from randomized trials of upfront combination versus sequential/initial monotherapy chemotherapy strategies in unresectable, metastatic colorectal cancer.



^adata for upfront combination versus sequential chemotherapy arms included; data for deferred combination arm is not included.

Figure 3. Alternate meta-analysis of survival hazard ratios from randomized trials of upfront combination versus sequential/initial monotherapy chemotherapy in unresectable, metastatic colorectal cancer.



^adata for upfront combination versus deferred combination chemotherapy arms included; data for sequential monotherapy chemotherapy arm not included.

After the initiation of FOCUS (7), standard practice changed from first-line fluorouracil to combination chemotherapy. These authors then decided to conduct an analysis using combination chemotherapy as the reference for the deferred combination strategy in a type of non-inferiority analysis. They use the confidence interval from the trial to calculate a non-inferiority boundary of 1.18. This analysis results in a HR of 0.94, and a 95%CI of 0.84-1.05 (results inverted to make the comparison consistent with the other trials). To conclude that one strategy is non-inferior to the other, a properly designed non-inferiority trial would have to be conducted.

Toxicity

Toxicity data are reported differently in the various trials. LIFE (8) and FOCUS2 (10) report toxicity data over the entire trial (Table 6), and FOCUS (7) reports the toxicities from the first-line treatment only (Table 7). CAIRO (6) and FFCD (9) report toxicity data both ways (Tables 6 and 7).

Looking at the toxicity data reported over the entire trial, the incidence of grade 3-4 anemia, febrile neutropenia and thrombocytopenia were not significantly different in the sequential versus upfront combination chemotherapy arms in the trials that reported on these specific toxicities (Table 6). Neutropenia is the only hematologic toxicity that was reported on in all included trials. In two trials (6,10), there was no difference in the rate of neutropenia between the study arms. In the LIFE (8) trial, there were more cases of neutropenia in the upfront combination chemotherapy arm than in the sequential chemotherapy arm, although a significance level is not provided, and in the FFCD (9) trial there were significantly more cases of neutropenia in the upfront combination chemotherapy arm.

In the CAIRO study (6), there were no significant differences between arms with respect to grade 3-4 non-hematologic toxicities. Several non-hematologic toxicities (diarrhea, nausea and/or vomiting, sensory neuropathy) occur more often in the upfront combination chemotherapy arms in the LIFE (8) trial, although no p-values are reported. Hand-foot syndrome occurred significantly more often in the sequential arm of the CAIRO (6) trial. In the FFCD trial (9), sensory neuropathy occurred significantly more often in the upfront combination

chemotherapy arm. In the FOCUS2 trial (10), which only included elderly and frail participants, there was significantly more diarrhea and sensory neuropathy in the upfront combination chemotherapy arm and significantly more hand-foot syndrome in the sequential chemotherapy arm.

With respect to hematologic toxicities in first-line treatment only (Table 7), two studies (6,9) report significantly higher incidence of grade 3-4 neutropenia, and one study (6) reports significantly higher incidence of febrile neutropenia in the upfront combination chemotherapy arm compared to the sequential chemotherapy arm. No differences were found for anemia, and one study (9) reports significantly more thrombocytopenia with the upfront combination chemotherapy strategy. FOCUS (7) only reports on neutropenia. There are more cases of neutropenia in the upfront combination chemotherapy arm, but a significance level is not provided. The following non-hematologic grade 3-4 toxicities occurred significantly more in the upfront combination chemotherapy arm: diarrhea (6), nausea (6,9) and vomiting (6,9). There was significantly more grade 3 hand-foot syndrome in the sequential chemotherapy arm in the CAIRO (6) study. FOCUS (7) reports more diarrhea, nausea or vomiting, and sensory neuropathy in the combination chemotherapy arm; however, significance levels are not provided.

Table 6. Grade 3-4 hematologic and non-hematologic toxicities of identified randomized controlled trials over the entire trial.

Trial	Treatment	Hematologic Toxicities (%)				Non-Hematologic Toxicities (%)						
		Anemia	Neutropenia	Febrile Neutropenia	Thrombocytopenia	Diarrhea	Nausea	Vomiting	Stomatitis	Sensory Neuropathy	Hand-foot Syndrome	Cardiac Ischemia/infarction (total)
Koopman 2007 (CAIRO) (6)	Sequential Combination	<1 <1 p=ns	5 7 p=ns	5 7 p=ns	1 1 p=ns	23 27 p=ns	8 9 p=ns	7 10 p=ns	3 2 p=ns	2 3 p=ns	13 ^a 7 p=0.004	4 4 p=ns
Cunningham 2009 (LIFE) ^b (8)	Sequential Combination	NR	5 33 p=NR	NR	NR	8 14 p=NR	NR	3 6 p=NR	NR	1 13 p=NR	NR	1 <1 p=NR
Ducreux 2011 (FFCD) (9)	Sequential Combination	8 6 p=ns	25 39 p=0.002	NR	8 6 p=ns	8 11 p=ns	(nausea or vomiting) 6 11 p=ns		3 6 p=ns	41 ^c 66 p<0.0001	NR	2 2 p=ns
Seymour 2011 (FOCUS2) (10)	Sequential Combination	2 2 p=ns	2 4 p=ns	NR	<1 1 p=ns	7 12 p=0.05	3 3 p=ns	2 2 p=ns	1 2 p=ns	0 2 p=0.02	5 1 p=0.01	NR

NR = not reported; ns = not significant

^aGrade 3 only^bGrade 3-4 toxicities occurring in at least 5% of patients in either treatment arm^cGrade 2-4

Table 7. Grade 3-4 hematologic and non-hematologic toxicities of identified randomized controlled trials for first-line treatment.

Trial	Treatment	Hematologic Toxicities %				Non-Hematologic Toxicities %						
		Anemia	Neutropenia	Febrile Neutropenia	Thrombocytopenia	Diarrhea	Nausea	Vomiting	Stomatitis	Sensory Neuropathy	Hand-foot Syndrome	Cardiac Ischaemia/infarction (total)
Koopman 2007 (CAIRO) (6)	Sequential Combination	<1 <1 p=ns	<1 7 p<0.0001	<1 7 p<0.0001	0 <1 p=ns	11 26 p<0.0001	4 10 p=0.004	3 9 p=0.0002	<1 2 p= ns	NR	12 ^a 6 p=0.002	3 3 p=ns
Seymour 2007 (FOCUS) (7)	Sequential (FU) Combination (FU/Irino) Combination (FU/Ox)	NR	9 19 28 p=NR	NR	NR	6 12 10 p=NR	(nausea or vomiting) 4 10 9 p=NR		2 2 2 p=NR	1 2 10 p=NR	2 1 1 p=NR	NR
Ducreux 2011 (FFCD) (9)	Sequential Combination	2 5 p=ns	2 31 p<0.0001	NR	1 5 p=0.05	5 5 p=ns	1 8 p=0.001	1 8 p=0.001	1 3 p=ns	1 ^b 64 p<0.0001	NR	1 1 p=ns

NR = not reported; ns = not significant

^aGrade 3 only

^bGrade 2-4

Quality of Life

Quality of life (QOL) was assessed using the EORTC QLQ-C30 instrument in CAIRO (6), FOCUS (7) and FFCD (9). The authors of the CAIRO study report similar changes in financial problems and in global health status in both arms of the study. They also report a greater decrease in emotional, physical, role and social functioning with the upfront combination chemotherapy arm compared to the sequential chemotherapy arm. Moreover, the changes on the symptomatic scales were generally greater, indicating worse symptoms, for the upfront combination chemotherapy arm with the exception of pain and dyspnea. However, the only significant change on the symptomatic scales was for the diarrhea scale ($p=0.002$), which was worse in the upfront combination chemotherapy arm (6). In the FOCUS trial (7), overall QOL was similar between regimens and over time. These authors conclude that there is no advantage or disadvantage at three and six months with combination chemotherapy. In the FFCD (9) trial, there were no significant differences between the arms with respect to the global and physical dimensions. There was, however, a significant difference between the arms with respect to the emotional dimension in favour of the upfront combination group ($p=0.009$)

In the FOCUS2 trial (10), QOL was assessed using the Comprehensive Health Assessment (CHA) instrument. These authors report an improved global QOL at weeks 12 to 14 in 62% of patients in the sequential chemotherapy arm and in 49% of patients in the combination chemotherapy arm ($p=0.04$). Based on the CHA results, they conclude that the addition of oxaliplatin has a detrimental effect on global QOL. The LIFE trial (8) did not report on QOL.

Ongoing Trials

The NCI® database of ongoing clinical trials (http://www.cancer.gov/search/clinical_trials/) was searched on August 14, 2013. No relevant phase III trials were identified.

DISCUSSION

In the late 1990s and early 2000s, evidence emerged demonstrating a response and survival advantage (progression-free and overall survival) for upfront combination chemotherapy with new cytotoxics (oxaliplatin and irinotecan) compared to fluoropyrimidine monotherapy (11-14) in the treatment of unresectable, metastatic colorectal cancer. Subsequently, several trials (6-10) were designed to determine whether efficacy could be maintained, toxicity reduced and quality of life improved by deferred introduction of the new cytotoxic agents. In the standard arms of these trials, an effective chemotherapy doublet combination was given as first-line treatment and compared to alternate strategies where first-line therapy was a single agent fluoropyrimidine with differing plans for subsequent administration of the remaining active therapies. With the completion and publication of these trials, we have performed a pooled analysis to assess the outcomes of these alternate strategies to first-line combination chemotherapy.

All five of the trials (6-10) demonstrate a significantly better overall response rate for upfront combination chemotherapy (all trials, $p < 0.0001$). Similarly, four of these trials report significantly better progression-free survival in the upfront combination chemotherapy arm (6-9). PFS was also superior in the upfront combination arm of FOCUS2 (10), although it did not reach statistical significance (HR, 0.84; 95%CI, 0.69-1.01, $p = \text{ns}$). Meta-analysis of the four trials that report HRs for PFS (6,8-10) demonstrates this overall benefit for upfront combination chemotherapy (Figure 1; HR, 0.74; 95%CI, 0.67-0.81; $p < 0.00001$). The superior PFS for combination chemotherapy only occurs in first-line treatment. During later lines of treatment, PFS was not significantly different between treatment arms (6,9) (data not shown).

With respect to overall survival, upfront combination chemotherapy was not superior to planned serial administration of chemotherapy in any of the five trials (6-10) individually. However, when they were pooled meta-analytically (Figure 2), a significant survival benefit for upfront combination chemotherapy does emerge (Figure 2; HR, 0.92; 95%CI, 0.86-0.99, $p = 0.02$). This meta-analysis is somewhat problematic in that the HR for the FOCUS trial (7) only included the comparison of upfront combination strategy compared to the sequential monotherapy arm and accounts for only 67% of the patients involved in the trial. For our present purpose, it would have been ideal to include a hazard ratio in this meta-analysis that included data on all of the patients and that described a comparison of the upfront combination strategy to the arms that contained upfront monotherapy. The data from the deferred combination strategy arm were not included in that hazard ratio. The FOCUS trial (7) does report a HR for the comparison of the upfront combination strategy and the deferred combination strategy, which is essentially a sequential strategy beginning with single-agent 5FU. Therefore, a second meta-analysis was carried out that used this HR from the FOCUS trial. This meta-analysis demonstrates that there is no significant survival benefit for upfront combination chemotherapy compared to a sequential/deferred combination chemotherapy strategy (Figure 3; HR, 0.95; 95%CI, 0.88-1.02). Notwithstanding the difference in statistical significance observed in the two meta-analyses, we can conclude that the overall survival difference between upfront combination and initial monotherapy strategies is likely to be of minimal clinical significance given the hazard ratios observed in the two meta-analyses.

Looking at the grade 3-4 toxicity data reported over the entire trial (Table 6, 4 studies reporting), most toxicities were either not significantly different in the sequential and combination chemotherapy arms or the p-values were not reported. The exceptions to this were significantly more of the following toxicities in the combination arm: neutropenia in the FFCD trial (9), diarrhea in the FOCUS2 trial (10), and sensory neuropathy in the FFCD (9) and FOCUS2 (10) trials. There was also significantly more hand-foot syndrome in the sequential arm of the FOCUS2 (10) and CAIRO (6) trials.

With respect to hematologic toxicities in first-line treatment only (Table 7, 3 studies reporting), significantly higher grade 3-4 toxicity is reported for neutropenia (6,9), febrile neutropenia (6) and thrombocytopenia (9) in the upfront combination chemotherapy arm compared to the sequential chemotherapy arm. The following non-hematologic grade 3-4 toxicities occurred significantly more in the upfront combination chemotherapy arm: diarrhea (6), nausea (6,9), and vomiting (6,9). There was significantly more grade 3 hand-foot syndrome in the sequential chemotherapy arm in the CAIRO (6) study. FOCUS (7) reports more diarrhea, nausea or vomiting, and sensory neuropathy in the upfront combination chemotherapy arm; however, significance levels are not provided. These results are not surprising, in that toxicity would be higher for upfront combination chemotherapy than for initial monotherapy.

Quality of life (QOL) was assessed using the EORTC QLQ-C30 instrument in three studies (6,7,9). The authors of the CAIRO study (6) report similar changes in financial problems and in global health status in both arms of the study. They also report that the decrease in emotional, physical, role and social functioning was generally greater for the upfront combination chemotherapy arm compared to the sequential chemotherapy arm. Moreover, the changes on the symptomatic scales were generally greater (i.e., the symptoms were worse) for the upfront combination chemotherapy arm, with the exception of pain and dyspnea. However, the only significant change on the symptomatic scales was for the diarrhea scale ($p=0.002$), with diarrhea being worse in the upfront combination chemotherapy arm (6). In the FOCUS trial (7), overall QOL was similar between regimens and over time. In the FFCD (9) trial, there were no significant differences between the trial arms with respect to the global and physical dimensions. There was, however, a significant difference between the arms with respect to the emotional dimension in favour of the upfront combination group ($p=0.009$). In the FOCUS2 trial (10) QOL was assessed using the Comprehensive Health Assessment (CHA) instrument. These authors report an improved global QOL at weeks 12 to 14 in 62% of patients in the sequential chemotherapy arm and in 49% of patients in the combination chemotherapy arm ($p=0.04$). Based on the CHA data they conclude that the addition of oxalipatin has a detrimental effect on global QOL.

There has been criticism (15) that the trials comparing upfront combination and sequential chemotherapy strategies achieve a considerably lower median survival than most other recent trials. There are several possible explanations for this. All five of the trials included in the systematic review enrolled patients who were less fit and would likely not be candidates for curative surgery if the first-line chemotherapy was successful enough. In fact, in several of the trials, recruiting physicians were specifically asked *not* to enroll patients they thought might become operable if they responded well enough to first-line chemotherapy. Moreover, FOCUS2 (10) only included the frail and elderly, a population that is traditionally under-represented in clinical trials. These patients would also never be considered for resection. Therefore, it is not surprising that the median survival in the studies included in this review is lower than that seen in contemporaneous trials. Another possible explanation is the use of capecitabine and irinotecan in some of the trials, which has been shown to have inferior survival (16) and/or toxicity profiles (16,17) compared to FOLFIRI. Additionally, the superior PFS seen with first-line combination chemotherapy, in the trials included in this systematic review, is not maintained over subsequent lines of treatment. This combined with a lack of superior survival between upfront combination chemotherapy and sequential chemotherapy suggests that the survival benefit seen in other recent trials may be owing to the inadequate use of salvage treatments in the monotherapy arm. One other possible explanation relates to the number of patients in the sequential strategies who were actually exposed to all of the effective drugs to which they were planned to be exposed. In these five trials, only 36% to 61% of patients in the sequential arms received all planned lines of therapy and, therefore, exposure to all planned effective drugs. It is notable that the FFCD trial, which only used FOLFIRI

chemotherapy and had appropriate access to all three cancer drugs, showed similar overall survival to other recent trials.

The current document is a systematic review of trials done in an era prior to targeted therapies being included as part of mCRC treatment. We now have good evidence that the addition of biologics has further improved outcomes in first-line treatment and the Ontario standard is chemotherapy and bevacizumab (18-21). The addition of bevacizumab to a single-agent fluoropyrimidine has been shown to be safe and effective (18,19,22). As the authors of both the FOCUS and FFCD trials point out, bevacizumab and fluoropyrimidine monotherapy is generally reserved for patients thought to be unfit for combination therapy, and suggest that the results of their trials would support extending this approach to patients receiving upfront monotherapy in a sequential approach (7,9). However, given that none of the randomized trials included in this analysis included biologics, definitive statements about the integration of biologics into a sequential strategy cannot be made at this time.

The ultimate goal for the treatment of mCRC cancer is to improve the length and quality of life of patients. For patients with unresectable, metastatic colorectal cancer, the use of effective cytotoxic agents in a sequential approach with less toxicity and negligible compromise in survival is a feasible option. Appropriate patient selection and choice of treatment should be made on a case-by-case basis. Strategies that involve initial monotherapy have less toxicity, improve QOL in some trials and produce no clinically significant detriment in overall survival compared with upfront combination chemotherapy strategies, and are an acceptable option for patients with unresectable mCRC. Alternatively, combination chemotherapy may be more appropriate for patients with rapidly progressing, very symptomatic or bulky life-threatening visceral disease given their higher overall response rates.

CONCLUSIONS

Based on the currently available evidence, the use of sequential chemotherapy in the palliative treatment of mCRC is an appropriate option for some patients. This treatment strategy appears to offer similar overall survival to patients as compared to upfront combination chemotherapy. Sequential therapy has the added advantage in that it is simpler and less toxic. However, patients and medical oncologists may still choose, after an informed discussion, to use combination systemic therapy up front if there is a clinical need for an improved response rate. Patients should not be restricted to a specific number of lines of therapy, as this report does show that patients can benefit from strategies that include more lines of therapy. More study is required in this area, especially given the recent advances in targeted therapy.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, GI DSG members, and internal and external reviewers were asked to disclose potential conflicts of interest. Five authors declared they had no conflicts. One author (TA) declared conflicts and reported receiving more than \$5000 in a single year from consulting fees, honoraria, and/or other support from Sanofi-Aventis, Roche and Pfizer pharmaceutical companies. This author also declared receiving research grant support from Sanofi-Aventis, Roche and Pfizer Pharmaceutical companies as well as being a co-investigator on metastatic colorectal trials, providing an opinion piece for the Globe and Mail and being the Ontario Medical Association vice-chair for the section on Hematology and Medical Oncology. A waiver was granted for this author to serve as the lead on this project, as the initiation of the project preceded the implementation of the current PEBC COI Policy and as provided for in the PEBC COI Policy.

For the Expert Panel, 20 members declared they had no conflicts of interest, and six (CB, PK, CL, MM, AM, and KZ) declared conflicts. CB reported receiving \$5000 or more in 2010-2011 to act in a consulting capacity (Advisory Board) and was a principal investigator on the CRC5 and CO-20 trials. PK reported receiving a \$25,000 grant from Sanofi-Aventis. CL received conference travel support from Novartis and Amgen of \$5000 or more in a single year as well as grant support from Novartis and Sanofi. MM has been principal investigator on several trials including CRC2, CRC3, COZO and a Phase II robotumumab trial. AM received a \$10,000 non-restricted research grant from Sanofi Aventis as well as a \$5000 non-restricted educational and research grant from Paladin Labs Incorporated. KZ received travel support of \$5000 or more in a single year to attend an international oncology meeting.

Both RAP reviewers declared they had no conflicts. All three targeted peer reviews declared conflicts of interest. SD received \$5000 or more in a single year in a consulting capacity for AMGEN, and HK received a grant for an investigational Phase II study from AMGEN. SG received \$5000 or more in a single year as speaker honoraria from Roche and is the Principal Investigator for the Pancreox Trial.

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

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6. Bruce Histed for copy editing

For a complete list of the GI DSG members, please visit the CCO Web site at <http://www.cancercare.on.ca/>

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Tim Asmis Medical Oncologist, The Ottawa Hospital Cancer Centre, Ottawa, ON

Panel Members:

Scott Berry Medical Oncologist, Odette Cancer Centre, Toronto, ON
Kelvin Chan Medical Oncologist, Odette Cancer Centre, Toronto, ON
Natalie Coburn Surgical Oncologist, Odette Cancer Centre, Toronto, ON
Roxanne Cosby Methodologist, McMaster University, Hamilton, ON
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Jim Biagi	Medical Oncologist
Rebecca Wong	Radiation Oncologist

Members:

Tim Asmis	Medical Oncologist
Scott Berry	Medical Oncologist
Christine Brezden-Masley	Medical Oncologist
Kelvin Chan	Medical Oncologist
Charles Cho	Radiation Oncologist
Murray Citron	Patient Representative
Natalie Coburn	Surgical Oncologist
Roxanne Cosby	Research Coordinator
Craig Earle	Medical Oncologist
Tarek Elfiki	Medical Oncologist
Barbara Fisher	Radiation Oncologist
Nazik Hammad	Medical Oncologist
Derek Jonker	Medical Oncologist
Juhu Kamra	Radiation Oncologist
Paul Karanicolas	Surgical Oncologist
Gregory Knight	Medical Oncologist
Jennifer Knox	Medical Oncologist
Calvin Law	Surgical Oncologist
Mary Mackenzie	Medical Oncologist
Aamer Mahmud	Radiation Oncologist
Richard Malthaner	Surgical Oncologist
Jason Pantarotto	Radiation Oncologist
Mark Rother	Medical Oncologist
Marko Simunovic	Surgical Oncologist
Simron Singh	Medical Oncologist
Andy Smith	Surgical Oncologist
Stephen Welch	Medical Oncologist
Raimond Wong	Radiation Oncologist
Youssef Youssef	Radiation Oncologist
Kevin Zbuk	Medical Oncologist

Appendix 3: Literature search strategy.

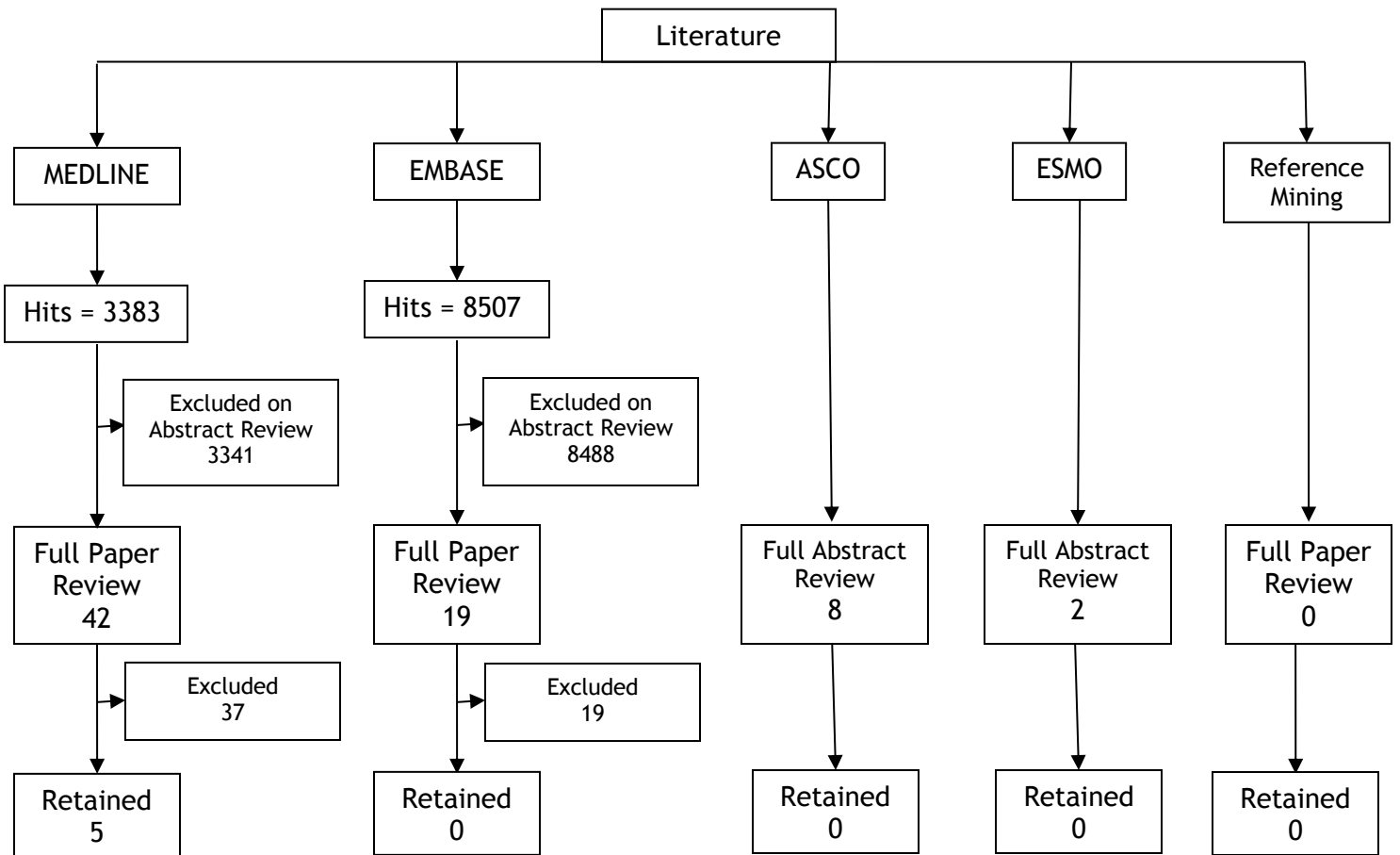
MEDLINE

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5. 1 and 4
6. exp Antineoplastic Combined Chemotherapy Protocols/
7. exp Drug Therapy, Combination/
8. exp Drug Therapy/
9. or/6-8
10. 5 and 9
11. comment.pt.
12. letter.pt.
13. editorial.pt.
14. historical article.pt.
15. case report.tw.
16. or/11-15
17. 10 not 16
18. limit 17 to english language
19. limit 18 to yr="2000 - 2011"

EMBASE

1. exp colorectal tumor/
2. exp colorectal cancer/
3. 1 or 2
4. metastas\$.mp.
5. advanced.mp.
6. 4 or 5
7. 3 and 6
8. exp combination chemotherapy/
9. exp drug therapy/
10. exp CHEMOTHERAPY/
11. or/8-10
12. 7 and 11
13. letter.pt.
14. editorial.pt.
15. case report.tw.
16. or/13-15
17. 12 not 16
18. limit 17 to english language
19. limit 18 to yr="2000 - 2011"

Appendix 4: Literature search results flow diagram.



Evidence-Based Series 2-5: Section 3

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

**Strategies of Sequential Therapies in Unresectable, Metastatic
Colorectal Cancer Treated with Palliative Intent:
Development Methods, Recommendations Development
and External Review Process**

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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) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations.* Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process.* Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Gastrointestinal Disease Site Group of the CCO PEBC (see Section 2, Appendices 1 and 2 for a complete list of working group and DSG members respectively). The series is a convenient and up-to-date source of the best available evidence on strategies of sequential therapies in unresectable, metastatic colorectal cancer treated with palliative intent, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. There were challenges when reviewing the evidence owing to the fact that the largest trial (FOCUS) did not provide a hazard ratio for survival that included all the data. As a result, two meta-analyses had to be done, one using the data for upfront combination versus sequential chemotherapy (Figure 2) and one using the data for upfront combination versus deferred combination chemotherapy (Figure 3). Unfortunately, the two meta-analyses are not in the same direction: the former demonstrating a significant survival benefit for upfront combination chemotherapy and the latter not demonstrating a significant survival benefit. For our purpose, it would have been ideal to have a single hazard ratio that included data on all of the patients and that described a comparison of the upfront combination strategy to the arms that contained upfront monotherapy. We did try to obtain this information from the study authors but were unable to do so. Notwithstanding the difference in statistical significance observed in the two meta-analyses, the clear consensus of the working group was that the overall survival difference between upfront combination and initial monotherapy strategies is likely to be of minimal clinical significance given the hazard ratios observed in the two meta-analyses.

Report Approval Panel Review and Approval

Prior to the submission of this EBS draft report for External Review, the report was reviewed and approved by the PEBC Report Approval Panel, a panel that includes oncologists and whose members have clinical and methodological expertise. Key issues raised by the Report Approval Panel, along with the response of the working group in italics included the following:

- a suggestion that the population the guideline applied to should be more explicit in Section 2. *This was made more explicit in the Introduction in Section 2.*
- a query that the GI DSG has no members from radiology or pathology. *DSGs do not always have radiology or pathology representation. If they are needed for a particular guideline, they are brought in to join the working group.*

- a concern that the risks and benefits considered in formulating the recommendations were found in Section 2 but not Section 3. The working group believed it was more appropriate for this to be kept in Section 2.
- a concern that the recommendation does not specify specific drugs. *The recommendation was revised to include this information.*
- a suggestion that Section 1 should focus on the sequential versus upfront combination chemotherapy comparison and that the information on deferred combination strategy was confusing in Section 1. The implications of a deferred combination strategy were best left to a more thorough explanation in Section 2. *The working group removed information regarding deferred combination chemotherapy from Section 1.*

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of [Section 1: Recommendations](#) and [Section 2: Evidentiary Base](#) of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the Gastrointestinal Disease Site Group (GI DSG) circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the GI DSG.

BOX 1:

QUESTION

What is the impact of different strategies of sequential and combination chemotherapy on efficacy (including overall survival), toxicity and quality of life in unresectable metastatic colorectal cancer treated with palliative intent?

TARGET POPULATION

These recommendations apply to adult patients (≥ 18 years old) with unresectable metastatic colorectal cancer. The cytotoxic agents covered in this guideline include initial fluoropyrimidine (5-FU or capecitabine) either alone or in combination, irinotecan and oxaliplatin.

Patients who are not surgical candidates owing to locally advanced cancers may also be considered for palliative chemoradiation.

DRAFT RECOMMENDATIONS and KEY EVIDENCE (approved for external review September 13, 2013)

Planned sequential chemotherapy and upfront combination chemotherapy are both acceptable standards of care. While there is a statistically significant difference in overall survival in favour of combination chemotherapy, the magnitude of the difference between the two strategies may not be clinically significant. Furthermore, sequential therapies may reduce upfront toxicities. Therefore, choice of treatment should be made on a case-by-case basis based on considerations that include patient and tumour characteristics, toxicity of each strategy and patient preference.

Sequential chemotherapy consists of a fluoropyrimidine monotherapy followed by either:

- a. another monotherapy with irinotecan *OR*
- b. combination chemotherapy consists of a doublet of a fluoropyrimidine with irinotecan or oxaliplatin

Combination chemotherapy consists of an upfront doublet of a fluoropyrimidine with irinotecan or oxaliplatin.

A meta-analysis of five trials (1-5) demonstrates a survival advantage for combination chemotherapy (HR, 0.92; 95%CI, 0.86-0.99, p=0.02). Median survival advantage in most trials is 3 to 6 weeks (range <1 week to 12 weeks). Therefore, any survival advantage that exists is likely to be very small and not clinically significant. First-line toxicities are reported by three trials (1,2,4). Hematological toxicities include significantly more neutropenia (1,4), febrile neutropenia (1) and thrombocytopenia (4) with upfront combination chemotherapy. Non-hematological toxicities include significantly more diarrhea (1), nausea (1,4), vomiting (1,4) and sensory neuropathy (4) in the upfront combination chemotherapy arm, and significantly more hand-foot syndrome in the sequential chemotherapy arm (1).

QUALIFYING STATEMENTS

- The FOCUS (2) trial is the largest trial of the five included trials. The individual hazard ratio for the FOCUS (2) trial only includes two arms of this trial. Therefore, one third of the data from this trial is missing from the overall meta-analysis of the five trials.
- Based on the results of this systematic review, patients should have access to all effective cytotoxic drugs using a sequential strategy.
- Combination chemotherapy may be more appropriate for patients with rapidly progressing, very symptomatic or bulky life-threatening visceral disease given their higher overall response rates.

Methods

Targeted Peer Review: During the guideline development process, seven targeted peer reviewers from British Columbia, Alberta, Manitoba, Quebec, the USA and Netherlands considered to be clinical and/or methodological experts on the topic were identified by working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on September 11, 2013. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The working group from the GI DSG reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All medical oncologists in the PEBC database were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and

directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on September 13, 2013. The consultation period ended on October 25, 2013. The working group from the GI DSG reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received from three reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Reviewer Ratings (N=x)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				2	1
2. Rate the guideline presentation.			1	1	1
3. Rate the guideline recommendations.			2	1	
4. Rate the completeness of reporting.				2	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	2	
6. Rate the overall quality of the guideline report.				3	
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			2	1	
8. I would recommend this guideline for use in practice.			1	1	1

9. What are the barriers or enablers to the implementation of this guideline report?

Two reviewers commented that a barrier may be the generalizability of the results as the trials included in the systematic review were conducted in a time prior to the use of biologics in the treatment of mCRC. One reviewer commented that the funding process in Ontario seemed to be a huge barrier.

Summary of Written Comments

The main points contained in the written comments along with the modification(s) made by the working group (*in italics*) were:

- i. A concern about the generalizability of the results as the trials included in the systematic review were conducted in a time prior to the use of biologics in the treatment of mCRC. *This issue is examined in the discussion. However, it was decided to add a qualifying statement to Section 1 to add clarity the issue.*
- ii. A concern that the title of the document should be changed to reflect that treatment with bevacizumab is not included in the guideline. *It was decided that the title would remain the same as every contingency could not be reflected in the title.*

- iii. A suggestion to change the way the toxicity data was presented. *It was decided that the toxicity data was adequately presented.*
- iv. A suggestion to include the primary endpoint of each study. *This information was added to Table 2.*
- v. To clarify the time of the PFS endpoint. *This information is already available in Table 5.*
- vi. A concern that the conclusion of the document indicated that a sequential chemotherapeutic approach was suitable for all mCRC patients. *This was not the intent of the document; therefore, the conclusion was modified to indicate that a sequential approach was suitable for some patients.*

Professional Consultation: Fifteen responses were received. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to four items on the professional consultation survey.

General Questions: Overall Guideline Assessment	Number (%)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			3(20)	8(53)	4(27)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.		1(7)	3(20)	6(40)	5(33)
3. I would recommend this guideline for use in practice.		1(7)	4(27)	5(33)	5(33)

4. What are the barriers or enablers to the implementation of this guideline report?

It was noted that current funding policies may be a barrier to choosing the best option for each patient. It was also noted that the use of biologics was not included. It was also noted that the document was generally concordant with oncologic practice.

Summary of Written Comments

The main points contained in the written comments were:

- i. A concern that funding policies may influence the choice of therapy rather than the patient and physician being the primary driver of the decision.
- ii. A concern that the document indicates that a sequential chemotherapeutic approach is suitable for all mCRC patients.
- iii. A suggestion that the second sentence of the “Target Population” in Section 1 was unnecessary.

Modifications/Actions

- i. This issue is covered in the second Qualifying Statement in Section 1.

- ii. The conclusion was modified to indicate that a sequential approach was suitable for some patients.
- iii. The sentence was removed.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the GI DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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