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Guideline Endorsement 9-10 Version 2

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

An Endorsement of the ASCO-SNO Guideline on Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults

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This document describes the OH (CCO)-CNS Program endorsement of the 2021 ASCO-SNO Guideline on Therapy for Diffuse Astrocytic and Oligodendoglial Tumors in Adults. The original publication is available at https://ascopubs.org/doi/full/10.1200/JCO.21.02036.

An assessment conducted in November 2023 deferred the review of Guideline Endorsement (GL-END) 9-10 Version 2. 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)

GL-END 9-10 Version 2 consists of 3 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/54246

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An Endorsement of the ASCO-SNO Guideline on Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults

Section 1: Guideline Endorsement

GUIDELINE OBJECTIVES

The objectives of this guideline are to provide guidance to clinicians regarding therapy for diffuse astrocytic and oligodendroglial tumours in adults. Our recommendations are based on the 2021 guideline on "Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO[1] Guideline" [1].

TARGET POPULATION

The target population is adults with gliomas who have received maximum safe surgical resection.

INTENDED USERS

The guideline is intended for oncologists (medical, radiation, neuro-oncology) and neurologists who provide care to people with glioma.

ENDORSEMENT

The Adult Gliomas Guideline Development Group of Ontario Health (Cancer Care Ontario) endorses the recommendations of Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO Guideline modified by the endorsement process described in this document. The recommendations are reprinted with the permission of Wolters Kluwer Health, Inc. and Copyright Clearance Center.

Eight of the 16 recommendations were endorsed without changes. Seven recommendations (R 1.1, R 1.3, R 1.4, R 1.6, R 2.1, R 2.8, and R 2.9) were endorsed with modifications and/or clarifications and one recommendation (R 2.4) was not endorsed (Table 1.1).

For all adults with central nervous system (CNS) tumours, whenever medically/surgically feasible, a tissue diagnosis should be considered. This includes high-risk locations, such as midline brainstem lesions, if molecular/pathologic diagnosis will affect treatment choice.

Table 1.1. Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO Guideline

Recommendations	Assessment
Isocitrate dehydrogenase (IDH)- mutant astrocytic and oligodendroglial tumours	
Oligodendroglioma, IDH-mutant, 1p19q, CNS WHO grade 2	
R 1.1. People with oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 2 should be offered radiation in combination with procarbazine, lomustine, and vincristine (PCV) (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong). Temozolomide (TMZ) is a reasonable alternative to PCV when toxicity is a concern (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak). **Modification:** Procarbazine and lomustine (PC) is also a reasonable alternative to PCV when toxicity is a concern. TMZ as a monotherapy is not routinely recommended.	**ENDORSED (with modification and clarification)**

[1] ASCO: American Society of Clinical Oncology; SNO: Society for Neuro-Oncology

Ontario-based guidelines for chemotherapy agents can be found on the OH (CCO) website and can be based on patient needs.	
R 1.2. Within the group of people with oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 2, initial therapy may be deferred until radiographic or symptomatic progression in some people with positive prognostic factors (e.g., complete resection and younger age) or concerns about toxicity. (Type: informal consensus; Evidence quality; low; Strength of recommendation: weak).	**ENDORSED**
Oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 3 (formerly anaplastic oligodendroglioma)	
R 1.3. People with oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 3 should be offered RT in combination with PCV (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong). TMZ is a reasonable alternative to PCV when toxicity is a concern (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak). **Clarification:** TMZ as a monotherapy is not routinely recommended.	**ENDORSED (with clarification)**
Astrocytoma, IDH-mutant, 1p19q non-codeleted, CNS WHO grade 2 (formerly diffuse astrocytoma)	
R 1.4. People with astrocytoma, IDH-mutant, 1p19q non-codeleted, CNS WHO grade 2 (low-grade diffuse glioma) should be offered RT with adjuvant chemotherapy (TMZ or PCV) (Type: evidence-based [informal consensus regarding TMZ], benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong). **Modification:** Could consider RT with concurrent and adjuvant TMZ. TMZ as a monotherapy is not routinely recommended. Ontario-based guidelines for chemotherapy agents can be found on the OH (CCO) website and can be based on patient needs.	**ENDORSED (with modification)**
R 1.5. In astrocytoma, IDH-mutant, 1p19q non-codeleted, CNS WHO grade 2, initial therapy may be deferred until radiographic or symptomatic progression in some people with positive prognostic factors (e.g., complete resection, younger age) or concerns about short- and long-term toxicity given the natural history of the disease. (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).	**ENDORSED**
Astrocytoma, IDH-mutant, 1p19q non-codeleted, CNS WHO grade 3 (formerly diffuse astrocytoma)	
R 1.6. People with astrocytoma, IDH-mutant, 1p19q non-codeleted CNS WHO grade 3 should be offered RT with adjuvant TMZ (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong). **Modification:** Could consider concurrent TMZ in addition to adjuvant TMZ. PCV is reasonable to consider in but given the CATNON results showing a clear prospectively derived survival advantage associated with less toxic regimen, TMZ is recommended [2,3].	**ENDORSED (with modification)**
Astrocytoma, IDH-mutant, CNS WHO grade 4 (formerly IDH-mutant glioblastoma)	
R 1.7. People with astrocytoma, IDH mutant CNS WHO grade 4 may be treated like an astrocytoma, IDH-mutant, non-codeleted, CNS WHO grade 3 (formerly anaplastic astrocytoma; see Recommendation 1.6) or like a glioblastoma, IDH-wildtype, CNS WHO grade 4 (formerly IDH-wildtype glioblastoma; see Recommendation 2.2) Type:	**ENDORSED**

informal consensus; Evidence quality: very low; Strength of recommendation: weak).	
Glioblastoma and other IDH-wildtype diffuse glioma	
R 2.1. People with astrocytomas, IDH-wildtype, CNS WHO grade 2 or 3 may be treated according to recommendations for glioblastoma, IDH-wildtype, CNS WHO grade 4 found in this guideline (Type: informal consensus: Evidence quality: very low; Strength of recommendation: weak). **Modification and clarification:** In a glioma with diffuse astrocytoma or oligodendroglioma morphology lacking high-grade histology features (necrosis and/or microvascular proliferation) and without IDH mutation, clinicians should consider the following two possibilities: 1. Pediatric-type diffuse low-grade glioma (e.g., MYB/MYBL1 fusion or MAPK alterations such as *BRAF* or *FGFR* point mutation or fusions); 2. Molecular glioblastoma (defined by the presence of any of a mutation in TERT promoter, EGFR amplification, or gain of chromosome 7/ loss of chromosome 10 [4,5].	**ENDORSED (with modification and clarification)**
R 2.2. Concurrent TMZ and RT should be offered to people with newly diagnosed glioblastoma, IDH-wildtype, CNS WHO grade 4 (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong). *Qualifying statement:* With the exception of studies addressing glioblastoma diagnosis in people with older age or poor performance status, no prospective, randomized evidence provides a sufficient basis to guide decision making based on MGMT promoters methylation status.	**ENDORSED**
R 2.3. Six months of adjuvant TMZ should be offered to people with newly diagnosed glioblastoma, IDH-wildtype, CNS WHO grade 4 who have received concurrent RT plus TMZ (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).	**ENDORSED**
R 2.4. Alternating electric field therapy may be added to adjuvant TMZ in people with newly diagnosed supratentorial glioblastoma, IDH-wildtype, CNS WHO grade 4 who have completed chemoradiation therapy (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: weak). **Explanation:** This is currently not approved by Health Canada.	**NOT ENDORSED (with explanation)**
R 2.5. Bevacizumab is not recommended for people with newly diagnosed glioblastoma, IDH-wildtype, CNS WHO grade 4 (Type: evidence-based, benefits do not outweigh harms; Evidence quality: moderate; Strength of recommendation: weak).	**ENDORSED**
R 2.6. In people with glioblastoma, IDH-wildtype, CNS WHO grade 4 where the expected survival benefits of a six-week radiation course combined with TMZ may not outweigh the harms, hypofractionated RT combined with TMZ is a reasonable alternative. (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: weak).	**ENDORSED**
R 2.7. In people with glioblastoma, IDH-wildtype, CNS WHO grade 4 with older age, poor performance status or with concerns about toxicity or prognosis, best supportive care alone, hypofractionated RT alone (for MGMT promoter	**ENDORSED**

unmethylated tumors), or TMZ alone (for MGMT promoter methylated tumors) are reasonable options. (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).	
R 2.8. No recommendation for or against any therapeutic strategy can be made for treatment of recurrent glioblastoma, IDH-wildtype, CNS WHO grade 4 (Type: informal consensus; Certainty of evidence: low; Strength of recommendation: no recommendation). People with recurrent glioblastoma should be referred for participation in a clinical trial where possible (Type: informal consensus; Evidence quality: no evidence considered; Strength of recommendation: strong). **Clarification:** TMZ rechallenge, lomustine, and bevacizumab are available systemic therapy options for recurrent glioblastoma; however, none of these have shown benefit in controlled studies, and no evidence-based recommendation for or against a particular therapy can be made. Clinical trials enrolling patients with recurrent glioblastoma are recommended where available.	**ENDORSED with clarification**
R 2.9. No recommendation for or against any therapeutic strategy can be made for treatment of diffuse midline glioma (Type: informal consensus: Certainty of the evidence: low; Strength of recommendation: no recommendation). People with diffuse midline glioma should be referred for participation in a clinical trial when possible (Type: informal consensus; Evidence quality: no evidence considered; Strength of recommendation: strong). **Modification:** Urgent radiation oncology consult should be considered for these patients.	**ENDORSED (with modification)**
ASCO: American Society of Clinical Oncology; CNS: central nervous system; EGFR: Epidermal Growth Factor Receptor; FGFR: Fibroblast Growth Factor Receptor; IDH: isocitrate dehydrogenase; MGMT: O^6-methylguanine-DNA methyltransferase; OH (CCO): Ontario Health (Cancer Care Ontario); PC: procarbazine and lomustine; PCV: procarbazine, lomustine and vincristine; RT: radiation therapy; SNO: Society for Neuro-Oncology; TERT: Telomerase reverse transcriptase; TMZ: temoxolomide; WHO: World Health Organization	

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Section 2: Endorsement Methods Overview

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario). 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 is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

BACKGROUND FOR GUIDELINE

During the annual document assessment and review in December 2021, the OH (CCO) 2017 endorsement of the European Association for Neuro-Oncology (EANO) Guideline on the Diagnosis and Treatment of Adult Astrocytic and Olidendroglial Gliomas was identified as needing an update because the recommendations no longer reflect current practice. There is new evidence that has guided changes in glioma taxonomy, biomarker testing, and treatment.

GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was developed by the Adult Gliomas Guideline Development Group (GDG) (Appendix 1), which was convened at the request of the OH (CCO) CNS Advisory Committee. The project was led by a small Working Group of the Adult Gliomas GDG, which was responsible for reviewing the evidence base and recommendations in "Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO Guideline" in detail and making an initial determination as to any necessary changes, drafting the first version of the endorsement document, and responding to comments received during the document review process. The Working Group members had expertise in neuro-oncology, CNS radiation oncology, neuropathology, and neurosurgery. Other members of the Adult Gliomas 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 1 and were managed in accordance with the *PEBC Conflict of Interest Policy*.

ENDORSEMENT METHODS

The PEBC endorses guidelines using the process outlined in the OH (CCO) Guideline Endorsement Protocol [6]. This process includes selection of a guideline, assessment of the recommendations (if applicable), drafting the endorsement document by the Working Group, and internal review by content and methodology experts.

The PEBC assesses the quality of guidelines using the AGREE II tool [7]. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

Implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations may be provided along with the recommendations for information purposes.

Selection of Guidelines

The Working Group reviewed the ASCO evidence-based guideline on "Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO Guideline" and accepted it as potentially useful and relevant to guide practice in Ontario.

Assessment of Guideline(s)

Details of the AGREE II assessment can be found in Appendix 2. The overall quality of the guideline was rated as "6" by both appraisers (on a scale from 1 [low] to 7 [high]). Both appraisers stated that they would recommend this guideline for use. The AGREE II quality ratings for the individual domains varied; they were assessed at 86% for scope and purpose, 94% for stakeholder involvement, 85% for rigour of development, 92% for clarity of presentation, 48% for applicability, and 75% for editorial independence [7].

DESCRIPTION OF ENDORSED GUIDELINE

The guideline was developed jointly effort by ASCO and SNO and addressed four clinical questions on the therapy for diffuse astrocytic and oligodendroglial tumours in adults [1]. A multidisciplinary Expert Panel (including a patient representative and health research methodologist) was convened to conduct a systematic review of the literature and to develop clinical practice guideline recommendations based on the results of the systematic review of randomized clinical trials (RCTs). The recommendations were informed by 59 RCTs focusing on therapeutic management; specifically, 30 trials in newly diagnosed glioblastoma, 14 trials in recurrent glioblastoma, 11 trials of nonglioblastoma, and four trials of mixed glioblastoma and nonglioblastoma. The Expert Panel organized the gliomas recommendations based on isocitrate dehydrogenase (IDH)-mutation status and diagnostic categories in the WHO 2016 and 2021 classification systems for tumours of the CNS [4,8]. A complete list of recommendations from the ASCO-SNO guideline are presented in Table 1-1.

ENDORSEMENT PROCESS

The Working Group reviewed the 2021 Guideline in detail and reviewed each recommendation of that guideline to determine whether it could be endorsed, endorsed with changes, or rejected (not endorsed). There are 16 recommendations based on five research questions. The Working Group considered the following issues for each of the recommendations:

1. Does the Working Group agree with the interpretation of the evidence and the justification of the original recommendation?
2. Are modifications required to align with the Ontario context?
3. Is it likely there is new, unidentified evidence that would call into question the recommendation?
4. Are statements of qualification/clarification to the recommendation required?

ENDORSEMENT REVIEW AND APPROVAL

Internal Review

For the endorsement document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. The Expert Panel may specify that approval is conditional, and that changes to the document are required.

DISSEMINATION AND IMPLEMENTATION

The endorsement document will be published on the OH (CCO) website. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

UPDATING THE ENDORSEMENT

OH (CCO)/PEBC will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for use in Ontario.

ENDORSEMENT AND MODIFICATIONS

Eight of the 16 Recommendations were endorsed without changes. The table below highlights the eight recommendations that were endorsed with modifications and/or clarifications or not endorsed. See Table 1-1 for a list of all 16 recommendations.

Table 2.1. Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO Guideline

Recommendations	Assessment
Isocitrate dehydrogenase (IDH)- mutant astrocytic and oligodendroglial tumors	
Oligodendroglioma, IDH-mutant, 1p19q, CNS WHO grade 2.	
R 1.1. People with oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 2 should be offered radiation in combination with procarbazine, lomustine, and vincristine (PCV) (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong). Temozolomide (TMZ) is a reasonable alternative to PCV when toxicity is a concern (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak). **Modification:** Procarbazine and lomustine (PC) is also a reasonable alternative to PCV when toxicity is a concern. TMZ as a monotherapy is not routinely recommended. Ontario-based guidelines for chemotherapy agents can be found on the OH (CCO) website and can be based on patient needs.	**ENDORSED (with modification and clarification)**
Oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 3 (formerly anaplastic oligodendroglioma).	
R 1.3. People with oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 3 should be offered RT in combination with PCV (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong). TMZ is a reasonable alternative to PCV when toxicity is a concern (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak). **Clarification:** TMZ as a monotherapy is not routinely recommended.	**ENDORSED (with clarification)**
Astrocytoma, IDH-mutant, 1p19q non-codeleted, CNS WHO grade 2 (formerly diffuse astrocytoma).	
R 1.4. People with astrocytoma, IDH-mutant, 1p19q non-codeleted, CNS WHO grade 2 (low-grade diffuse glioma) should be offered RT with adjuvant chemotherapy (TMZ or PCV) (Type: evidence-based [informal consensus regarding TMZ], benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong). **Modification:** Could consider RT with concurrent and adjuvant TMZ. TMZ as a monotherapy is not routinely recommended. Ontario-based guidelines for chemotherapy agents can be found on the OH (CCO) website and can be based on patient needs.	**ENDORSED (with modification)**

Astrocytoma, IDH-mutant, 1p19q non-codeleted, CNS WHO grade 3 (formerly diffuse astrocytoma).	
R 1.6. People with astrocytoma, IDH-mutant, 1p19q non-codeleted CNS WHO grade 3 should be offered RT with adjuvant TMZ (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong). **Modification:** Could consider concurrent TMZ in addition to adjuvant TMZ. PCV is reasonable to consider in but given the CATNON results showing a clear prospectively derived survival advantage associated with less toxic regimen, TMZ is recommended [2,3].	**ENDORSED (with modification)**
Glioblastoma and other IDH-wildtype diffuse glioma.	
R 2.1. People with astrocytomas, IDH-wildtype, CNS WHO grade 2 or 3 may be treated according to recommendations for glioblastoma, IDH-wildtype, CNS WHO grade 4 found in this guideline (Type: informal consensus: Evidence quality: very low; Strength of recommendation: weak). **Modification and clarification:** In a glioma with diffuse astrocytoma or oligodendroglioma morphology lacking high-grade histology features (necrosis and/or microvascular proliferation) and without IDH mutation, clinicians should consider the following two possibilities: 1. Pediatric-type diffuse low-grade glioma (e.g., MYB/MYBL1 fusion or MAPK alterations such as BRAF or FGFR point mutation or fusions). 2. Molecular glioblastoma (defined by the presence of any of a mutation in TERT promoter, EGFR amplification, or gain of chromosome 7/ loss of chromosome 10 [4,5].	**ENDORSED (with modification and clarification)**
R 2.4. Alternating electric field therapy may be added to adjuvant TMZ in people with newly diagnosed supratentorial glioblastoma, IDH-wildtype, CNS WHO grade 4 who have completed chemoradiation therapy (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: weak). **Explanation:** This is currently not approved by Health Canada.	**NOT ENDORSED (with explanation)**
R 2.8. No recommendation for or against any therapeutic strategy can be made for treatment of recurrent glioblastoma, IDH-wildtype, CNS WHO grade 4 (Type: informal consensus; Certainty of evidence: low; Strength of recommendation: no recommendation). People with recurrent glioblastoma should be referred for participation in a clinical trial where possible (Type: informal consensus; Evidence quality: no evidence considered; Strength of recommendation: strong). **Clarification:** TMZ rechallenge, lomustine, and bevacizumab are available systemic therapy options for recurrent glioblastoma; however, none of these have shown benefit in controlled studies, and no evidence-based recommendation for or against a particular therapy can be made. Clinical trials enrolling patients with recurrent glioblastoma are recommended where available.	**ENDORSED with clarification**
R 2.9. No recommendation for or against any therapeutic strategy can be made for treatment of diffuse midline glioma (Type: informal consensus: Certainty of the evidence: low; Strength of recommendation: no recommendation). People with diffuse midline glioma should be referred for participation in a clinical trial when possible (Type: informal consensus; Evidence quality: no evidence considered; Strength of recommendation: strong). **Modification:** Urgent radiation oncology consult should be considered for these patients.	**ENDORSED (with modification)**
ASCO: American Society of Clinical Oncology; CNS: central nervous system; EGFR: Epidermal Growth Factor Receptor; FGFR: Fibroblast Growth Factor Receptor; IDH: isocitrate dehydrogenase; MGMT: O^6-methylguanine-DNA methyltransferase;	

OH (CCO): Ontario Health (Cancer Care Ontario); PC: procarbazine and lomustine; PCV: procarbazine, lomustine and vincristine; RT: radiation therapy; SNO: Society for Neuro-Oncology; TERT: Telomerase reverse transcriptase; TMZ: temoxolomide; WHO: World Health Organization

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- Sara Miller for copy editing

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Section 3: Internal Review

INTERNAL REVIEW

The endorsement was evaluated by the GDG Expert Panel (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 12 members of the GDG Expert Panel, 11 members voted, for a total of 92% response in June 2022. Of those who voted, 11 approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized below.

Table 3-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. In the recommendations for all adjuvant TMZ, could specify the number of cycles (e.g., 12 cycles per CATNON trial)	The Working Group discussed this and decided to exclude length of regimen. Ontario-based guidelines for chemotherapy agents can be found on the OH (CCO) website and can be based on individual patient needs.
2. Change R 1.1, R 1.3, and R 1.4 Modification as "TMZ as monotherapy (without radiation) is not routinely recommended" for better clarity.	The Working Group has decided to keep the recommendation wording as is.
3. For R 1.1 add parentheses with the type and evidence quality which is present for all the other recommendations	We have added the parentheses with type and evidence quality to R 1.1
4. For R 1.3, add except from 2021 EANO guideline that "the distinction of the two grades (2 and 3) of IDH mutant 1P/19q codeleted tumours remains controversial. Accordingly, watching weight strategies after complete resection can also be considered for younger patients with grade 3 tumours, specifically for those without homozygous CDKN2A/B deletion."	The Working Group discussed this and decided not to implement these suggested changes as there are no supporting evidence at this time. While the Working Group agrees there are some data to suggest that grade 2 vs 3 astrocytoma may be hard to distinguish (based on mitotic figures), this is not true for grade 2 versus 3 oligodendrogliomas (this would be necrosis and/or vascular endothelial proliferation or CDKN2A homozygous deletion.
5. For R 1.6, the recommendation is about Grade 3 astrocytoma and it is under the heading of grade 2 astrocytoma. Consider adding a new heading for grade 3 or changing the current heading to grade 2 and 3 astrocytomas.	A heading for grade 3 astrocytomas has been added.
6. For R 1.6 modification, remove parenthetical remark "(i.e., AA)" as it has not been defined or is not current nomenclature to describe this entity.	The Working Group has removed it.

7. For R 2.1, consider rephrasing "if negative *TERT*, *EGFR* or +7/-10 then rule out *BRAF V600E* mutation or fusion, *MYBL*, *MYB*, *FGFR* mutation or fusion" to "Testing for a molecular glioblastoma should be pursued (defined by the presence of any of a mutation in *TERT*, *EGFR*, or +7/-10). In the absence of these findings of a molecular glioblastoma, then a *BRAF V600E* mutation or fusion, *MYBL*, *MYB*, *FGFR* mutation or fusion [4,5] should be ruled out."	We have implemented the suggested wording and a few modifications. The final medication will be read as: "In a glioma with diffuse astrocytoma or oligodendroglioma morphology lacking high-grade histology features (necrosis and/or microvascular proliferation) and without IDH mutation, clinicians should consider the following two possibilities: 1. Pediatric-type diffuse low-grade glioma (e.g., *MYB*/*MYBL1* fusion or *MAPK* alteration such as *BRAF* or *FGFR* point mutation or fusions). 2. Molecular glioblastoma (defined by the presence of any of a mutation in *TERT* promoter, *EGFR* amplification, or +7/-10) [4,5]
8. There has not been a specific recommendation advising the need for tissue for any other glioma subtype. It is unclear why there is a statement specifically recommending it under the heading of diffuse midline glioma. If there is going to be recommendations about tissue diagnosis, consider making one blanket statement about the utility of tissue diagnosis in adults with glioma whenever medically feasible.	The Working Group agrees and has added a blanket statement at the beginning of the recommendations table about the utility of tissue diagnosis in adults with glioma whenever medically feasible.
9. Table 2.1 should only include recommendations with modifications/clarifications and not endorsed.	We have modified the Table.
10. For R 2.3, maybe add that in some cases 12 cycles can be considered.	The Working Group discussed this and decided to exclude length of regimen. Ontario-based guidelines for chemotherapy agents can be found on the OH (CCO) website and can be based on individual patient needs.

CONCLUSION

The final endorsed recommendations contained 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.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Table 1: Members of the Adult Gliomas Guideline Development Group

Name	Affiliation	Conflict of Interest
Working Group		
Sunit Das Working Group Chair, Neurosurgical Oncology	St Michael's Hospital: Unity Health Toronto Toronto, ON	See below.[a]
Lisa Durocher-Allen Health Research Methodologist	McMaster University Department of Oncology, Program in Evidence-Based Care, Hamilton, ON	None declared.
Cynthia Hawkins Neuropathology	Sick Kids Hospital Toronto, ON	See below.[b]
Maria MacDonald Neuro-oncology	London Health Sciences Centre - London Regional Cancer Program, London, ON	None declared.
James Perry Neuro-oncology	Sunnybrook Health Sciences Toronto, ON	See below.[c]
Arjun Sahgal CNS Radiation Oncology	Sunnybrook Health Sciences Centre Toronto, ON	See below.[d]
Expert Panel		
Fabio Ynoe De Moraes Radiation Oncology	Kingston General Hospital Kingston, ON	See below.[e]
Joe Del-Paggio Medical Oncology	Lake Head University Thunder Bay, ON	
Mary Jane Lim Fat Neuro-Oncology	Sunnybrook Health Sciences Centre Toronto, ON	See below.[f]
Navya Kalidindi Neuro-Oncology	Hamilton Health Sciences Hamilton, ON	None declared.
Julia Keith Neuropathology	Sunnybook Health Science Centre Toronto, ON	None declared.
Amy Lin Radiation Oncology	St Michael's Hospital Toronto, ON	None declared.
Warren Mason Neuro-Oncology	Princess Margaret Hospital Cancer Centre Toronto, ON	See below.[g]
Garth Nicholas Medical Oncology	The Ottawa Hospital Ottawa, ON	See below.[h]
Ken Schneider CNS Radiation Oncology	Windsor Regional Hospital Windsor, ON	None declared.
John Sinclair Neurosurgical Oncology	The Ottawa Hospital Ottawa, ON	See below.[i]
Amparo Wolf Neurosurgical Oncology	Health Sciences North Sudbury, ON	None declared.
Jason Yu Medical Oncology	Royal Victoria Regional Health Centre Barrie, ON	None declared.

[a] Has received $500 or more in a single year to act in a consulting capacity on behalf of Medexus for training exercises to train neurosurgeons on the use of 5-ALA for glioma surgery; conference support travel and accommodations from Congress of Neurological Surgeons, the American Association of Neurological Surgeons, and the Society for NeuroOncology; Laboratory received grant funding from Alkermes and Medicenna; participated as site lead for clinical trial with Agios; has advised OH(CCO) in the development of molecular testing platform for patients with primary brain tumours; has published editorial, commentary, or other clear opinion regarding any of the objects of study.

[b] Has received $500 or more in a single year to act in a consulting capacity with Bayer Canada on CanTRK study; has published editorial, commentary, or other clear opinion regarding any of the objects of study; has participated with OH(CCO) to develop guidelines for brain cancer molecular testing.

[c] Has received $500 of more in a single year from Global Coalition for Adaptive Research (GCAR, a non-profit clinical trial organization, study PI) and Enveric Biosciences (Advisory Board, company has no marketed products); has been the co-principal investigator of CCTG CE.6 Cooperative group trial.

[d] Has received $500 or more in a single year as consultant with Varian (Medical Advisory Group), Elekta (Gamma Knife Icon), BrainLAB, MERCK, Abbvie, Roche Advisory; has received fianancial or material support of $500 or more as a board member with ISRS, co-chair with AO Spine Knowledge Forum Tumor, past educational seminars (honorarium) with AstraZeneca, Elekta AB, Varian (CNS Teaching Faculty), BrainLAB, Medtronic Kyphon, Accuray Research Grant: Elekta AB, Varian, and travel accommodations/expenses from Elekta, Varian and BrainLAB; slso belong to the Elekta MR Linac Research Consortium, Elekta Spine, Oligometastases and Linac Based SRS Consortia; has received grants or other research support as either principal or co-investigator from Elekta AB and Varian

[e] Has received $500 or more in a single year to act in a consulting capacity for Astra Zeneca, IASLC, and CTAQ Queen's University

[f] Has received $500 or more in a single year to act in a consulting capacity for Bayer as a one time expert panel member in April 2021.

[g] Has received $500 or more in a single year to act in a consulting capacity for advisory boards for Viatris, Apotex, GSK Consultant for Century Therapeutics; has been an investigator for clinical trials involved the objects of study (e.g. Selenixor, Roche, Agile, Optune, SOLDI, Stellar; and has published an editorial/commentary in the Neuro-Oncology Practice in 2022.

[h] Has been the principal investigator for a clinical trial involving any of the objects of study (Novocure studies, EF-14 and EF-32 and has provided guidance regarding the object of the study in a public capacity for CTV news 2017 regarding the results of EF-14 trial.

[i] Has received $500 or more in a single year to act in a consulting capacity for Medexus as a teaching lecturer.

Appendix 2: AGREE II Score Sheet

Domain	Item	AGREE II Appraiser Ratings[1]	
		1	2
1) Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.	7	6
	2. The health question(s) covered by the guideline is (are) specifically described.	6	5
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7	6
Domain score[2] - (37-6/42-6)*100 = 31/36 *100 = .8611 *100 = **86.1%**		Score 37	
2) Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	7	7
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	6	6
	6. The target users of the guideline are clearly defined.	7	7
Domain score[2] - (40-6/42-6)*100 = 34/36 *100 = .9444*100 = **94.4%**		Score 37	
3) Rigour of development	7. Systematic methods were used to search for evidence.	7	7
	8. The criteria for selecting the evidence are clearly described.	7	7
	9. The strengths and limitations of the body of evidence are clearly described.	5	5
	10. The methods for formulating the recommendations are clearly described.	4	3
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.	6	7
	12. There is an explicit link between the recommendations and the supporting evidence.	6	6
	13. The guideline has been externally reviewed by experts prior to its publication.	7	7
	14. A procedure for updating the guideline is provided.	7	7
Domain score[2] - (98-16/112-16)*100 = 82/96 *100 = .8541 *100 = **85.4%**		Score 98	
4) Clarity of presentation	15. The recommendations are specific and unambiguous.	6	6
	16. The different options for management of the condition or health issue are clearly presented.	6	7
	17. Key recommendations are easily identifiable.	7	7
Domain score[2] - (39-6/42-6)*100 = 32/36 *100 = .9167 *100 = **91.7%**		Score 39	
5) Applicability	18. The guideline describes facilitators and barriers to its application.	5	4
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	4	3
	20. The potential resource implications of applying the recommendations have been considered.	5	4
	21. The guideline presents monitoring and/ or auditing criteria.	4	2
Domain Score[2] - (31-8/56-8)*100 =23/48 *100 = .4792 *100 = **47.9%**		Score 31	

6) **Editorial independence**	22. The views of the funding body have not influenced the content of the guideline. 23. Competing interests of guideline development group members have been recorded and addressed.	4 7	4 7
Domain Score[2] - (22-4/28-4)*100 = 18/24 *100 = .7500 *100 = **75.0%**		Score 22	
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	**6**	**6**
Overall Guideline Assessment	2. I would recommend this guideline for use.	**Yes**	**Yes**

[1] Rated on a scale from 1 to 7, [2] Domain score = (Obtained score – Minimum possible score)/(Maximum possible score – Minimum possible score)