ASCO special articles

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

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abstract

PURPOSE To provide guidance to clinicians regarding therapy for diffuse astrocytic and oligodendroglial tumors in adults.

METHODS ASCO and the Society for Neuro-Oncology convened an Expert Panel and conducted a systematic review of the literature.

RESULTS Fifty-nine randomized trials focusing on therapeutic management were identified.

RECOMMENDATIONS Adults with newly diagnosed oligodendroglioma, isocitrate dehydrogenase (IDH)–mutant, 1p19q codeleted CNS WHO grade 2 and 3 should be offered radiation therapy (RT) and procarbazine, lomustine, and vincristine (PCV). Temozolomide (TMZ) is a reasonable alternative for patients who may not tolerate PCV, but no high-level evidence supports upfront TMZ in this setting. People with newly diagnosed astrocytoma, IDH-mutant, 1p19q non-codeleted CNS WHO grade 2 should be offered RT with adjuvant chemotherapy (TMZ or PCV). People with astrocytoma, IDH-mutant, 1p19q non-codeleted CNS WHO grade 3 should be offered RT and adjuvant TMZ. People with astrocytoma, IDH-mutant, CNS WHO grade 4 may follow recommendations for either astrocytoma, IDH-mutant, 1p19q non-codeleted CNS WHO grade 3 or glioblastoma, IDH-wildtype, CNS WHO grade 4. Concurrent TMZ and RT should be offered to patients with newly diagnosed glioblastoma, IDH-wildtype, CNS WHO grade 4 followed by 6 months of adjuvant TMZ. Alternating electric field therapy, approved by the US Food and Drug Administration, should be considered for these patients. Bevacizumab is not recommended. In situations in which the benefits of 6-week RT plus TMZ may not outweigh the harms, hypofractionated RT plus TMZ is reasonable. In patients age ≥ 60 to ≥ 70 years, with poor performance status or for whom toxicity or prognosis are concerns, best supportive care alone, RT alone (for *MGMT* promoter unmethylated tumors), or TMZ alone (for *MGMT* promoter methylated tumors) are reasonable treatment options. Additional information is available at www.asco.org/neurooncology-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Each year, more than 15,000 people in the United States are newly diagnosed with diffuse astrocytic and oligodendroglial tumors, including glioblastoma, the most common type of malignant primary brain tumor encountered by oncologists.[1] The clinical care of people with these tumors is in the midst of a paradigm shift because of the evolving role of systemic and device therapies. For decades, the treatment of most primary brain tumors in adults relied exclusively on neurosurgical resection and cranial radiotherapy. More recently, several systemic agents and a device have demonstrated improvements in survival when added to surgical and radiation therapies. This has changed the approach to treatment, decision making, prognosis, and survivorship for adults with gliomas. As a result, oncologists face an increasingly complicated calculus of weighing benefits of therapy against potential harms. The Expert Panel devised these guidelines with these concerns in mind and aimed to provide recommendations for oncology practice based on the evidence but also consistent with the challenges of real-life clinical care.

Another transformation in neurooncology began with exploration of the cancer genome and, more specifically, with the discovery of the isocitrate dehydrogenase (IDH) 1 and 2 mutations.[2] These genetic alterations are critical prognostic biomarkers and are central to

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

Guideline Questions

With reference to each WHO 2016 and 2021 classifications of glioma (Table 1):

- After maximal safe surgical resection, what are the evidence-based therapies for adults with newly diagnosed glioma, including optimal regimens, settings, and timing of therapy?
- What are the appropriate therapies for adults with recurrent glioma, including optimal regimens, settings, and timing of therapy?
- What should the effect of *MGMT* promoter methylation status be on choice of therapy?
- Are there subpopulations that should affect choice of therapy?

Target Population

Adult people with glioma who have received maximal safe surgical resection.

Target Audience

Oncologists (medical, radiation, neuro) and neurologists who provide care to people with glioma.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Isocitrate dehydrogenase (IDH)–mutant astrocytic and oligodendroglial tumors.

Oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 2.

Recommendation 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).

Recommendation 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 (eg, complete resection and younger age) or concerns about toxicity. See the Clinical Interpretation section for more details (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 3 (formerly anaplastic oligodendroglioma).

Recommendation 1.3.

People with oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 3 should be offered radiation therapy (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).

Astrocytoma, IDH-mutant, 1p19q non-codeleted, CNS WHO grade 2 (formerly diffuse astrocytoma).

Recommendation 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).

Recommendation 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 (eg, complete resection, younger age) or concerns about short- and long-term toxicity given the natural history of the disease. See the Clinical Interpretation section for more details (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Astrocytoma, IDH-mutant, 1p19q non-codeleted, CNS WHO grade 3 (formerly anaplastic astrocytoma).

Recommendation 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).

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Astrocytoma, IDH-mutant, CNS WHO grade 4 (formerly IDH-mutant glioblastoma).

Recommendation 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: informal consensus; Evidence quality: very low; Strength of recommendation: weak).

Glioblastoma and other IDH-wildtype diffuse glioma.

Recommendation 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).

Recommendation 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 of older age or poor performance status, no prospective, randomized evidence provides a sufficient basis to guide decision making based on *MGMT* promoter methylation status.

Recommendation 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).

Recommendation 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).

Recommendation 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).

Recommendation 2.6.

In people with glioblastoma, IDH-wildtype, CNS WHO grade 4 where the expected survival benefits of a 6-week radiation course combined with TMZ may not outweigh the harms, hypofractionated RT combined with TMZ is a reasonable alternative. See the Clinical Interpretation section for further explanation (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: weak).

Recommendation 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 unmethylated tumors), or TMZ alone (for *MGMT* promoter methylated tumors) are reasonable options. See the Clinical Interpretation section for further explanation (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 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 the 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).

Recommendation 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).

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Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A2 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/neurooncology-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

modern classification of adult-type diffuse gliomas.[2,3] The WHO organizes adult-type diffuse gliomas based on the presence or absence of IDH mutations, bisecting them into two key categories—the slower growing, IDH-mutant tumors and the more aggressive, IDH-wildtype tumors.

The 2016 and 2021 WHO classifications[4] rely on the combination of molecular alterations, histology, and traditional grade classifications to yield an integrated and layered diagnosis. In Table 1, we portray the key recent changes in classification and nomenclature of adult gliomas. The modern transition to a molecular-based nomenclature significantly complicates the ability to interpret clinical trials completed in adults with newly diagnosed and recurrent gliomas when traditional histologic criteria were the basis for enrollment and cohort assessment. Outcomes from the practice-defining clinical trials for gliomas in adults must therefore be reinterpreted in the context of contemporary nomenclature such that recommendations built on past evidence are relevant and interpretable in the context of the information an oncology provider will receive in modern pathology reports. In order to address these complexities and to reconcile the therapeutic advances seen in clinical trials with the recent reorganization to a nomenclature based on molecular alterations, ASCO and the Society for Neuro-Oncology (SNO) developed a comprehensive guideline for the treatment of diffuse astrocytic and oligodendroglial tumors in adults.

As the new 2021 WHO classification is not yet fully implemented in clinical practice, the Expert Panel has attempted to present the recommendations in this guideline as much as possible so that they can be understood and implemented both at the time of publication (while the 2016 WHO classification is still widely in use) and in the future as the new classification system is adopted. For example, in this guideline, we have used Arabic and not Roman numerals for the grade of disease in the recommendations per the 2021 WHO CNS5 recommendations, but have continued to use Roman numerals in the description of trials where earlier classification schemes were in use. Table 1 describes the differences between the 2021 and prior classification systems and should be used to guide interpretation of the recommendations.

GUIDELINE QUESTIONS

With reference to each WHO 2016 classifications of glioma (Table 1):

- After maximal safe surgical resection, what are the evidence-based therapies for newly diagnosed patients with glioma, including optimal regimens, settings, and timing of therapy?
- What are the appropriate therapies for patients with recurrent glioma, including optimal regimens, settings, and timing of therapy?
- What should the effect of *MGMT* promoter methylation status be on choice of therapy?
- Are there subpopulations that should affect choice of therapy?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a joint ASCO-SNO multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel met via teleconference and/or webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology* and *Neuro-Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee prior to publication. This guideline was also approved by the SNO Guideline Committee. All funding for the administration of the project was provided by ASCO.

TABLE 1. Glioma Classifications Included in This Guideline[5]

Molecular Diagnostic Features	Additional Characteristic Genetic Alterations	WHO 2021—CNS 5th Edition: Adult-Type Diffuse Gliomas	WHO 2016: Diffuse Astrocytic and Oligodendroglial Tumors	WHO 2007[a]: Astrocytic Tumors and Oligodendroglial Tumors
IDH1 or IDH2 mutation[a,b] 1p19q codeletion	*TERT* promoter mutation *CIC* mutation *FUBP1* mutation *NOTCH1* overexpression	Oligodendroglioma, IDH-mutant and 1p19q codeleted CNS WHO grade 2	Oligodendroglioma, IDH-mutant and 1p19q codeleted WHO grade II	Oligodendroglioma WHO grade II
		Oligodendroglioma, IDH-mutant and 1p19q codeleted CNS WHO grade 3	Anaplastic oligodendroglioma, IDH-mutant and 1p19q co-deleted WHO grade III	Anaplastic oligodendroglioma WHO grade III
IDH1 or IDH2 mutation[b] Non-codeleted	*ATRX* loss *TP53* mutation *CDKN2A* or *CDKN2B* homozygous deletion	Astrocytoma, IDH-mutant CNS WHO grade 2	Diffuse astrocytoma, IDH-mutant WHO grade	Diffuse astrocytoma WHO grade II
		Astrocytoma, IDH-mutant CNS WHO grade 3	Anaplastic astrocytoma, IDH-mutant WHO grade III	Anaplastic astroctyoma WHO grade III
		Astrocytoma, IDH-mutant CNS WHO grade 4	Glioblastoma, IDH-mutant WHO grade IV	Glioblastoma WHO grade IV
IDH-wildtype[b]	*TERT* promoter mutations Chromosome +7 and –10 *EGFR* amplification	Glioblastoma, IDH-wildtype CNS WHO grade 4	Diffuse astrocytoma, IDH-wildtype WHO grade II	Diffuse astrocytoma WHO grade II
			Anaplastic astrocytoma, IDH-wildtype WHO grade III	Anaplastic astroctyoma WHO grade III
			Glioblastoma, IDH-wildtype WHO grade IV	Glioblastoma WHO grade IV
Pediatric-type diffuse high grade gliomas				
H3K27 mutation		Diffuse midline glioma, H3K27 altered CNS WHO grade 4	Diffuse midline glioma, H3K27M-mutant WHO grade IV	Diffuse intrinsic pontine glioma

Abbreviation: IDH, isocitrate dehydrogenase.

[a]The WHO 2007 classification is not based on any molecular diagnostic features. The WHO 2007 classification included a category oligoastrocytoma WHO grade II and grade III. In 2016 and 2021, these tumors are reclassified as either astrocytomas or oligodendrogliomas based on the absence or presence of 1p19q codeletion.

[b]IDH status confirmed by gene sequencing. Absence of mutation by immunohistochemistry in IDH1 codon 132 or IDH2 codon 172 should be confirmed by gene sequencing[1] in people with grade 2 or 3 tumors under the age of 55.[5]

The recommendations were developed by using a systematic review of randomized clinical trials (RCTs) included in PubMed published between January 1, 2001, and August 17, 2020. Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- Inclusion of adults (age ≥ 18 years)
- Reports of randomized trials, including subgroup analyses, indexed in PubMed with at least 30 patients per arm
- Patients had glioma of any classification
- If newly diagnosed, must have received maximally feasible surgery
- Reported on at least one of these outcomes: overall survival (OS), disease-free survival or progression-free survival (PFS) or recurrence-free survival or event-free survival, time to recurrence or treatment failure or progression, quality of life (QOL), and toxicity or adverse events
- Randomly assigned patients to any form of systemic antineoplastic therapy (including chemotherapy, immunotherapy, targeted agents, etc), RT, and/or device-based therapy (defined as tumor treatment fields, implanted wafers, or laser interstitial thermal therapy). Vaccine-based therapy trials were excluded based on an a priori assumption that they would not influence recommendations in order to reduce the labor associated with the systematic review based on initial assessment showing studies that either did not meet other inclusion criteria or results that would not influence recommendations. Randomized trials that only investigated the effect of surgery were excluded as the target patient population was patients who had already received appropriate surgery.
- Letters, comments, and editorials were excluded.

Randomized trial quality was assessed using methods based on the Cochrane Risk of Bias tool.[6] The guideline recommendations were crafted, in part, using the Guidelines Into Decision Support methodology.[7] In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

In addition, a search for conference abstracts published in 2019 or 2020 at the ASCO, European Society for Medical Oncology, SNO, European Association of Neuro-Oncology, and American Academy of Neurology annual meetings was conducted in order to identify randomized trials that may not have yet been published in the peer-reviewed literature. These abstracts were not used as the basis of any recommendation but provide context regarding developments that may occur in the future. Also, a search of ClinicalTrials.gov to identify ongoing and unpublished trials was conducted for a similar purpose, and also to assess the possibility of publication bias.

Just prior to public release of the guidelines, the summary of the 2021 WHO Classification of Tumors of the Central Nervous System[4] was released, and appropriate edits were made to include this up-to-date classification schema. The ASCO Multi-Site Guideline Advisory Group and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO and SNO will jointly determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at

http://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A total of 92 randomized trials published in peer-reviewed journals met eligibility criteria. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of the search process can be found in the Data Supplement (online only). Of these, 33 trials were considered by the Panel to be immaterial for the development of recommendations because the experimental therapy had only been tested in one or two trials found in the systematic review and no statistically significant benefits were found or the trial design was flawed by an inappropriate control arm, or patients in both arms received an unproven therapy. These trials are summarized in the Data Supplement (Table 8) and are not discussed further. The remaining 59 trials form the evidence base of this guideline: 30 trials in newly diagnosed glioblastoma,[8-30] 14 trials in recurrent glioblastoma,[31-52] 11 trials of nonglioblastoma,[53-64] and four trials of mixed glioblastoma and nonglioblastoma.[65-68]

Study design aspects related to individual study quality, evidence quality, strength of recommendations, and risk of bias were assessed. Refer to the Data Supplement for more information and for definitions of ratings for overall potential risk of bias. Full details of these trials, including quality assessment, patient eligibility, outcome data, and subgroup analyses can be found in the Data Supplement (Tables 1-7). Articles that present secondary analyses of these trials but were not considered relevant to recommendations development are listed in the Data Supplement (Table 9).

Several trials that have only been published to date in the form of conference abstracts were identified in a search for conference abstracts. These trials are summarized in the Data Supplement (Table 10). These trials are mentioned within the text where they provide important context or suggest future potential treatment options, but they are not used as the basis of recommendations. A search of the US and European trial registries found registered trials that are either ongoing, completed but not yet published, or otherwise had no peer-reviewed publication that could be located and were not published as conference abstracts. These trials are listed in the Data Supplement (Table 11).

RECOMMENDATIONS

Organization of the Recommendations

While the clinical questions that drove development of this guideline can be found in the Clinical Questions section, the Expert Panel has organized the recommendations for gliomas based on IDH-mutation status and the diagnostic categories in the WHO 2016 and 2021 classification systems for tumors of the CNS,[4,5] as noted in the Introduction. The effect of *MGMT* promoter methylation status on treatment decisions and recommendations for other subgroups of importance (eg, older patients, poor performance status) is considered within each of these sections as appropriate.

The majority of the trials meeting criteria for inclusion in this guideline are based on eligibility criteria that predate the 2016 and 2021 WHO CNS classification systems. Every effort to synergize the patient populations in the foundational clinical trials and the most up-to-date diagnostic criteria was made by the Expert Panel. However, discrepancies between patient populations in the published trials and the current diagnostic classification criteria could not be entirely avoided. For example, although the guideline recommendations are organized based on IDH mutation status, consistent with modern diagnostic criteria, the population of patients for a given trial is defined based on the published criteria for that study. In each section, the Panel has carefully interpreted the data from clinical trials that were designed based on historic nomenclature and developed recommendations that are organized based on what one would expect to see in a contemporary pathology report.

An important omission is oligoastrocytoma. This tumor classification was technically included within the scope of this guideline and is included in the 2016 WHO classification schema, however, is no longer acknowledged in the 2021 classification. It was the consensus of the Expert Panel that because the classification of IDH-mutant oligodendrogliomas is entirely dependent on 1p19q status and because oligoastrocytoma is a rare entity diagnosed only in cases where molecular diagnostics are unavailable (or inconclusive), no formal recommendations for the management of oligoastrocytoma were made.

SECTION 1: IDH-MUTANT ASTROCYTIC AND OLIGODENDROGLIAL TUMORS

Section Introduction

For oligodendrogliomas, genomic alterations guide the nomenclature and the understanding of prognosis and decisions about treatment. In the 2016 and 2021 WHO CNS classifications, oligodenrogliomas are defined by the presence of a 1p19q codeletions. The 1p19q codeletion is a diagnostic biomarker and a requirement for the pathologic diagnosis of oligodendroglial tumors, and it represents a key branch point among IDH-mutant gliomas

(oligodendroglioma *v* astrocytoma). Oligodendrogliomas are subdivided into oligodendroglioma, CNS WHO grade 2, and CNS WHO grade 3 (formerly anaplastic oligodendroglioma). Histologically, oligodendrogliomas are characterized by infiltrative tumor cells with monomorphic rounded nuclei with artifactual clear perinuclear halos on paraffin-processed tissues (fried-egg pattern), delicate capillary vascular networks (chicken-wire vessels), and focal microcalcifications with no or very few mitoses. Oligodendrogliomas, IDH-mutant, 1p19q-codeleted, CNS WHO grade 3 (formerly anaplastic) have high mitotic activity, microvascular proliferation, and, frequently, necrosis.

IDH-mutant astrocytomas do not have a 1p19q codeletion and are subdivided into astrocytoma, CNS WHO grade 2 consistent with low-grade astrocytoma (formerly diffuse astrocytoma), CNS WHO grade 3 (formerly anaplastic astrocytoma), and CNS WHO grade 4 (previously known as IDH-mutant glioblastoma). Grade 2 astrocytomas show an infiltrative diffuse growth pattern (perineuronal and/or perivascular satellitosis, subpial spread), have a variable degree of nuclear atypia and pleomorphism, and no or very few mitoses. Grade 3 astrocytomas (formerly anaplastic) have increased cellularity and mitotic activity. Necrosis and microvascular proliferation are absent. Astrocytoma, IDH-mutant, CNS WHO grade 4 (formerly IDH-mutant glioblastoma or secondary glioblastoma) and glioblastoma, IDH-wildtype, CNS WHO grade 4 (formerly primary glioblastoma) are diffuse glioma of astrocytic morphology with increased cellularity, mitotic activity, microvascular proliferation, and/or necrosis. Increasingly, pathologists and neuro-oncologists view IDH-mutant astrocytomas as a single biologic entity, with histologic grading representing a potentially artificial separation. This approach has important implications for treatment decision making as clinicians parse out patient populations within clinical trials.

Combined Literature Review and Analysis: IDH-Mutant Astrocytic and Oligodendroglial Tumors

As the evidence around these tumors is highly redundant across the various recommendations in this section, the literature review and analysis were combined for all recommendations in Section 1, IDH-Mutant Astrocytic and Oligodendroglial Tumors.

Radiation therapy. The EORTC 22845 trial, also known as the MRC BR04 trial, reported by van den Bent et al[55] in 2005 compared immediate RT to observation in patients with histologically confirmed low-grade glioma (both astrocytoma and oligodendroglioma) per the classification system in use at that time. There was no observed difference in OS (hazard ratio [HR], 0.97; 95% CI, 0.71 to 1.34), but there was a significant improvement in PFS (HR, 0.59; 95% CI, 0.45 to 0.77) with RT. It is important to note that approximately two thirds of patients received RT at time of progression, suggesting that RT likely improves OS for low-grade gliomas, but the optimal timing of treatment initiation remains uncertain. Although this trial addressed the role of RT only, it is included here because the data support the role of RT as a backbone of therapy for diffuse astrocytomas (grade 2, low-grade gliomas). The RTOG 9006 trial[67] and the NCCTG 86-72-51 trial[59] both investigated alternate schedules and doses of RT in patients with low-grade astrocytomas and oligodendrogliomas, but found no significant differences in OS or PFS between their arms (see Table 2 for recommended schedules and doses).

Procarbazine, lomustine, and vincristine. Three trials have investigated the value of PCV versus no PCV in patients with low-grade and anaplastic gliomas.

The RTOG 9802 trial[63,69] evaluated the role of chemotherapy in high-risk, low-grade gliomas and included patients with oligodendroglioma, astrocytoma, and what was then described as oligoastrocytoma (omitted from the 2021 WHO CNS classification), based on histologic criteria alone. Patients with low-risk (complete resection and under age 40 years) were excluded. The trial found a significant improvement in OS (median 13.3 years *v* 7.8 years) in patients who received RT and PCV when compared to patients who received RT alone. In addition to including all low-grade glioma histologies, this trial also included patients with IDH-wildtype tumors because it predated awareness and testing for IDH mutation status. A secondary analysis of the RTOG 9802 trial[70] published outside of the search window and identified by the Panel found survival benefit in all IDH-mutant subgroups, but no improvement in survival in IDH-wildtype patients (OS HR, 0.96; $P = .94$). There were OS benefits for PCV versus no PCV in adults with 1p19q codeleted tumors (HR, 0.21; $P = .029$) and non-codeleted tumors (HR, 0.38; $P = .013$).

The EORTC 26951 trial[71] and RTOG 9402 trial[72] investigated adjuvant PCV versus no PCV in patients who were then classified as having anaplastic oligodendrogliomas based on histologic criteria (1p19q codeletion was not required for enrollment). Both studies demonstrated an improvement in PFS with the addition of PCV to RT, but only the EORTC 26951 study demonstrated an improvement in OS.

Trial results consistently demonstrated that lower histologic grade, IDH mutation, and 1p19q codeletion confer better prognosis, individually and in combination across all treatment arms. In a subgroup analysis of the EORTC 26951 trial,[73] patients with IDH-mutant and 1p19q codeleted tumors had a median OS of 9.53 years compared to 3.07 years for those with non-codeleted tumors and 1.13 years for those with IDH-wildtype tumors. All patients with IDH-mutant tumors derived benefit in the RTOG 9402 trial[72] with adjuvant PCV (OS HR, 0.59; 95% CI, 0.40 to 0.86), whereas patients with IDH-wildtype tumors did not. Subgroup analyses in both studies found that patients with 1p19q codeletion had survival benefits from the addition of PCV to RT. The EORTC 26951 trial[71] found a significant

TABLE 2. Reasonable Doses and Schedules by Recommendation

IDH-Mutant Glioma

Recommendation	Therapy	Dose and Schedule	Source
Recommendation 1.1 (IDH-mutant, 1p19q codeleted oligodendroglioma [grade 2]) and 1.4 (IDH-mutant, 1p19q non-codeleted diffuse astrocytoma [grade 2])	Radiation	54 Gy in 30 fractions over 6 weeks	As used in the RTOG 9802 trial[63]
	Adjuvant PCV	Procarbazine 60 mg/m^2 orally once per day days 8 through 21, lomustine 110 mg/m^2 orally once on day 1, and vincristine 1.4 mg/m^2 IV once daily on days 8 and 29 in 8 week cycle for a total of six cycles	As used in the RTOG 9802 trial[63] and As used in the EORTC 26951 trial[56]
	Adjuvant TMZ	150-200 mg/m^2 adjuvant TMZ given once daily on days 1-5 every 4 weeks for a maximum of 12 months	As used in the CATNON trial[53]
Recommendation 1.3 (IDH-mutant, 1p19q codeleted, anaplastic oligodendroglioma [grade 3])	Radiation	59.4 Gy in 33 fractions at five fractions per week	As used in the EORTC 26951 trial[56]
	Adjuvant PCV	As in 1.1 and 1.4	
	Adjuvant TMZ	As in 1.1 and 1.4	
Recommendation 1.6 (IDH-mutant, 1p19q non-codeleted anaplastic astrocytoma [grade 3])	Radiation	59.4 Gy given in 33 fractions of 1.8 Gy	As used in the CATNON trial[53]
	Adjuvant TMZ	As in 1.1 and 1.4	As used in the CATNON trial[53]

IDH-Wildtype Glioma

Recommendation	Therapy	Dose and Schedule	Source
Recommendation 2.2 and 2.3 (newly diagnosed glioblastoma)	Radiation	60 Gy in 2 Gy fractions 5 fractions a week	As used in the EORTC 26981-22981 trial[16]
	Concurrent TMZ	75 mg/m^2 once daily TMZ during RT	As used in the EORTC 26981-22981 trial[16]
	Adjuvant TMZ	150-200 mg/m^2 once daily for five out of 28 consecutive days for a maximum of 6 months	As used in the EORTC 26981-22981 trial[16]
Recommendation 2.4 (newly diagnosed supratentorial GBM who have completed chemoradiation therapy)	Alternating electric field therapy	Daily use, > 18 hours per day, until second progression	See EF-14 trial protocol[14] for details on therapy
Recommendation 2.6 (patients where the expected survival benefits of a 6-week radiation course combined with TMZ may not outweigh the harms)	Hypofractionated radiation	40.05 Gy in 15 fractions over 3 weeks	As used in Perry et al[30]
	Concurrent TMZ	75 mg/m^2 once daily for 21 days	As used in Perry et al[30]
	Adjuvant TMZ	150-200 mg/m^2 once daily for five of 28 consecutive days for a maximum of 12 months	As used in Perry et al[30]
Recommendation 2.7 (patients with older age, poor performance status, or with concerns about toxicity or prognosis)	Hypofractionated radiation alone	40 Gy in 15 fractions over 3 weeks	As used in Roa et al[46]
	TMZ alone	100 mg/m^2 once daily on days 1-7 of every 2 weeks until progression. OR 200 mg/m^2 once daily on days 1-5 of every 28 days for up to six cycles	As used in NOA-08 trial[66] As used in Nordic trial[26]

NOTE. Only recommendations with recommended therapy are listed.

Abbreviations: GBM, glioblastoma multiforme; IDH, isocitrate dehydrogenase; IV, intravenous; PCV, procarbazine, lomustine, vincristine; RT, radiation therapy; TMZ, temozolomide.

improvement in PFS in people with 1p19q codeleted tumors (HR, 0.42; 95% CI, 0.24 to 0.74) while the RTOG 9402 trial showed improvement in OS as well (HR, 0.59; 95% CI, 0.37 to 0.95). Notably, in RTOG 9402, there was not a significant benefit in PFS for patients with 1p19q non-codeleted tumors (HR, 0.81; 95% CI, 0.56 to 1.16). The specific inclusion criteria and outcome data from each of these trials can be found in Table 3.

Temozolomide. The CATNON trial[53] (748 patients) and the smaller KNOG-1101 trial[57] (84 patients) both investigated TMZ in addition to RT for 1p19q non-codeleted anaplastic glioma (anaplastic astrocytoma grade III). The KNOG-1101 trial reported improved PFS for patients who received both concurrent and adjuvant TMZ with RT but did not demonstrate improvement in OS versus RT alone. The CATNON trial was multifactorial and included random assignment to concurrent TMZ as well as adjuvant TMZ.[53] The first interim analysis of this trial published in 2017[53] found significant improvement in OS (HR, 0.65; 95% CI, 0.45 to 0.93) and PFS (HR, 0.62; 95% CI, 0.50 to 0.76) with the addition of adjuvant TMZ after RT in all patients, regardless of IDH-mutation status. Immediately prior to submission of this guideline, the second interim analysis of the trial was published.[74] This provided results for all patients including the IDH-mutated and IDH-wildtype subgroups. These data are reported here because of their importance despite the fact that they were published outside the search window. Across all patients, no significant difference in OS was found for concurrent TMZ (HR, 0.93; 95% CI, 0.75 to 1.14), while the difference in OS with adjuvant TMZ was similar to that in the interim analysis (HR, 0.67; 95% CI, 0.55 to 0.83). In the subgroup of 444 patients with IDH-mutated tumors, concurrent TMZ was not associated with improved OS with an HR of 0.80 (95% CI, 0.58 to 1.10) while adjuvant TMZ showed an OS HR of 0.48 (95% CI, 0.35 to 0.67). The ongoing CODEL trial[75] specifically includes patients with newly diagnosed, 1p19q codeleted low-grade, and anaplastic oligodendroglioma to assess RT plus PCV versus RT plus TMZ. Outcome data are pending.

Chemotherapy alone. Two trials have investigated chemotherapy as monotherapy for low-grade (grade 2) and anaplastic (grade 3) astrocytomas and oligodendrogliomas. The EORTC 22033-26033 trial[54] investigated TMZ versus RT for low-grade astrocytoma and oligodendroglioma (grade II). However, as of the 2016 publication, the OS data were not considered mature and no significant difference in PFS was found (HR, 1.16; 95% CI, 0.9 to 1.5). Subgroup analysis shows that those with non-codeleted tumors may

TABLE 3. Key Trials of PCV Versus No PCV in Adults With Astrocytic and Oligodendroglial Gliomas

Study: Author Year Arms (No. of patients)	OS	PFS	Inclusion Criteria With Histology Breakdown
EORTC 26951: van den Bent et al 2006[56] and 2013[71] PCV (185) versus no PCV (183)	Median OS 42.3 months versus 30.6 months, HR 0.75 (95% CI, 0.60 to 0.95) 5 year OS rate 43.4% versus 37.0%	Median PFS 24.3 months versus 13.2 months, HR 0.66 (95% CI, 0.52 to 0.83) 5 year PFS rate 37.5% versus 22%	Patients age ≥ 16 and ≤ 70 years with newly diagnosed anaplastic oligodendroglioma or anaplastic mixed oligoastrocytoma with at least 25% oligodendroglial elements; had at least three of five anaplastic characteristics.
RTOG 9402: Cairncross et al 2013[72] and Cairncross et al 2006[62] PCV (148) versus no PCV (143)	Median OS 4.6 years versus 4.7 years, HR 0.79 (95% CI, 0.60 to 1.04; $P = .1$) 24 month OS rate 70% versus 74%[a]	Median PFS 2.6 years versus 1.7 years, HR 0.69 (95% CI, 0.52 to 0.91; $P = .004$)[b] 12 month PFS rate 57% versus 46%	Patients age ≥ 18 years with newly diagnosed anaplastic oligodendroglioma or anaplastic oligoastrocytoma. Proportion of patients with noted histology in PCV/no PCV arms Anaplastic oligodendroglioma 52%/51% Anaplastic oligoastrocytoma, oligodendroma dominant 19%/26% Anaplastic oligoastrocytoma, no dominance 16%/11% Anaplastic oligoastrocytoma, astrocytoma dominant 13%/13%
RTOG 9802: Shaw et al 2012[63] and Buckner et al 2016[69] PCV (125) versus no PCV (126)	Median OS not reached versus 7.5 years, HR 0.72 (95% CI, 0.47 to 1.10; $P = .33$) 2 year OS rate 85% versus 87% 5 year OS rate 72% versus 63% At final analysis HR 1.00 (95% CI, 0.74 to 1.36)	Median PFS NR, no significant difference in PFS PFS rates NR At final analysis HR 0.96 (95% CI, 0.70 to 1.27)	Patients age ≥ 18 years with histologically proven uni- or multifocal WHO grade 2 astrocytoma, oligodendroglioma, or mixed oligoastrocytoma. Patients age < 40 must have subtotal resection or biopsy. Proportion of patients with noted histology in PCV/no PCV arms Astrocytoma 29%/23% Oligodendroglioma 40%/45% Mixed 31%/32%

Abbreviations: HR, hazard ratio; NR, no response; OS, overall survival; PCV, procarbazine, lomustine, vincristine; PFS, progression-free survival.

[a]Median OS data from 2013 paper and OS rate data from 2006 paper.

[b]PFS data from 2006 article. The 2013 article indicates updated PFS data is online, but online appendix no longer available.

be less likely to benefit from TMZ alone with inferior PFS compared to RT (HR, 1.86; 95% CI, 1.21 to 2.87). The NOA-04 trial[61,76] studied anaplastic gliomas and involved two random assignments: a random assignment to either chemotherapy or RT postoperatively and then within the chemotherapy arm a random assignment to either TMZ or PCV with a primary end point of time to progression. At the time of progression or unacceptable toxicity, participants were crossed over to either RT or chemotherapy. There was no difference in time to progression between the arms. In the 2016 long-term follow-up publication,[76] no change to the primary outcome was reported.

General Clinical Interpretation: IDH-Mutant Astrocytic and Oligodendroglial Tumors

Prospective trials have yet to specifically study these molecularly defined groups based on the modern WHO 2016 and 2021 integrated diagnostic criteria. All available data on IDH mutation and 1p19q codeletion status are either indirect or from subgroup analyses that incorporated post hoc categorization of patients. While some subgroup analyses have found significant predictive effects for either IDH mutation or 1p19q codeletion status, these analyses are known to be at risk of bias because of many factors (eg, lack of statistical correction for multiple comparisons). Even those analyses that have not found significant differences are affected by low statistical power, and the confidence intervals of the outcome data often include the possibility of both clinical benefit and harm. However, on the basis of the available data, the following recommendations can be made:

Recommendation 1.1. People with oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 2 should be offered radiation 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).

Recommendation 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 (eg, complete resection and younger age) or concerns about toxicity. See the Clinical Interpretation section for more details (Type: informal consensus; Evidence quality: low, Strength of recommendation: weak).

Recommendation 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).

Clinical interpretation. The consensus of the Expert Panel was that the preponderance of the evidence is in favor of offering both chemotherapy and RT to patients with IDH-mutant, 1p19q codeleted oligodendroglioma and anaplastic oligodendroglioma. RTOG 9802 supports the use of PCV in all low-grade gliomas; subgroup analyses support trends that people with 1p19q codeletion may, in fact, be the patients who derive the most benefit from chemotherapy. Even though these studies incorporated both RT and chemotherapy at time of diagnosis, the optimal timing of therapy remains unclear based on the EORTC 22845 study. Physicians and patients must balance when to start therapy by assessing the neurologic risks of RT versus the neurologic risk of progressive disease. In the case of low-grade oligodendroglioma, where patients can survive decades and clinical progression may not occur for many years, balancing the benefits of therapy with potential harms is critical. RTOG 9802 excluded patients defined as low-risk low-grade glioma (age under 40 years and complete resection), and in these patients in particular, observation with deferral of therapy is an appropriate option. The evidence from the EORTC 26951 trial[56] and RTOG 9402 demonstrates activity of PCV and improvement in survival outcomes in people with newly diagnosed anaplastic oligodendrogliomas. In the latter trial, a substantial percentage of patients in the RT arm received chemotherapy at recurrence, confounding the assessment of impact of PCV on OS in this population. A reasonable interpretation of the data is that PCV has activity against newly diagnosed anaplastic oligodendroglioma, but optimal timing of therapy remains uncertain. Analyses enriched for 1p19q codeleted patients in both studies demonstrated benefit from PCV, and collectively, data support the use of PCV in addition to RT in patients with 1p19q codeleted anaplastic oligodendrogliomas.

PCV is a multiagent chemotherapy regimen and can result in significant nausea, fatigue, peripheral neuropathy, and bone marrow toxicity. Because of these concerns and the ever-growing data supporting the use of TMZ across all gliomas, the Expert Panel agreed that TMZ could be considered in circumstances where toxicity or intolerability were concerns. The CODEL trial (NCT00887146)[75] is assessing RT plus PCV versus RT plus TMZ in people with newly diagnosed 1p19q codeleted low-grade and anaplastic oligodendroglioma. This trial is scheduled to be completed in 2025 and will hopefully provide a clearer picture of the best chemotherapy option for these patients. There are also clinical trials specifically for IDH-mutant gliomas (NCT03749187).

Recommendation 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).

Recommendation 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 (eg, complete resection, younger age) or concerns about short- and long-term toxicity given the natural history of the disease. See the Clinical Interpretation section for more details (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 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).

Clinical interpretation. Given the available data, the consensus of the Expert Panel was that the preponderance of the evidence favors RT and chemotherapy for patients with IDH-mutant, 1p19q non-codeleted diffuse astrocytoma (grade 2, low-grade glioma and anaplastic astrocytoma [grade 3]).

The use of PCV as an adjuvant to RT for diffuse astrocytoma is supported by RTOG 9802 and confirmed by the subgroup analysis of patients with 1p19q non-codeleted tumors.[70] Here, as with 1p19q codeleted oligodendrogliomas, the timing of therapy remains uncertain and the decision needs to be made with careful attention to prognostic factors and potential risks of toxicity. Low-risk, low-grade glioma is a poorly defined entity, but clinical trials (ie, RTOG 9802) include patients under age 40 years who have undergone surgical gross total resection. In these patients, observation has historically been favored, excluding them from all of the discussed clinical trials. The consensus of the panel was that patients with IDH-mutant, 1p19q non-codeleted diffuse astrocytoma should be offered both chemotherapy and RT, but that timing of this could be deferred in patients with favorable prognosis until radiographic or symptomatic progression. The use of TMZ is supported indirectly by the results of the CATNON trial[53] and by the growing understanding that IDH-mutant, 1p19q non-codeleted tumors are one biologic entity that likely exists across a continuum rather than in discrete cohorts of grade. In fact, the Panel contemplated grouping these recommendations by 1p19q status rather than by grade. Based on the CATNON data, evolution regarding understanding about IDH-mutant, 1p19q non-codeleted tumors, significant toxicity with PCV, and ever-growing data for TMZ across glioma subtypes, the Expert Panel agreed that TMZ is a reasonable treatment option for these tumors.

Therefore, for 1p19q non-codeleted, grade 3, anaplastic astrocytoma, the available evidence supports RT plus adjuvant TMZ based on the recent interim analysis of the CATNON trial, obviating concurrent TMZ as a reasonable option. In these tumors, deferral of therapy is not considered appropriate in most cases.

See Table 2 for doses and schedules of both RT and chemotherapy considered by the Panel as reasonable in this population.

Recommendation 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: informal consensus; Evidence quality: very low; Strength of recommendation: weak).

Literature review and analysis. No randomized trials were identified in this setting.

Clinical interpretation. There is no available randomized evidence specifically in patients with IDH-mutant grade 4 astrocytoma, but it is important to note that survival in this population is nearly double that of IDH-wildtype glioblastoma.[77] It was the consensus of the Panel in the absence of other evidence that patients would benefit from RT with adjuvant TMZ as is recommended for IDH-mutant anaplastic astrocytoma (grade 3) or RT with concurrent and adjuvant TMZ as in IDH-wildtype glioblastoma.

See Table 2 for reasonable doses and schedules of RT and chemotherapy.

SECTION 2: GLIOBLASTOMA AND OTHER IDH-WILDTYPE DIFFUSE GLIOMA

Recommendation 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).

Literature review and analysis. No randomized trials in this setting were identified in the systematic review. However, immediately prior to the submission of this guideline, the second interim analysis of the CATNON trial was published.[74] This trial included 216 patients with newly diagnosed 1p19q non-codeleted anaplastic glioma, regardless of IDH-mutation status, and therefore included a subgroup of patients with IDH-wildtype tumors. In this subgroup, neither concurrent TMZ (OS HR, 1.03; 95% CI, 0.77 to 1.38) nor adjuvant TMZ (OS HR, 1.00; 95% CI, 0.75 to 1.33) was associated with OS. No association for TMZ was found when this subgroup was further broken down into *MGMT* promoter methylation status subgroups.

Clinical interpretation. Perhaps the biggest change in the WHO 2016 and WHO 2021 classification schemes is the recognition that IDH-wildtype lower-grade astrocytomas are distinct from their IDH-mutant counterparts. In

IDH-wildtype tumors, the molecular alteration eclipses traditional grading criteria when it comes to prognosis and, consequently, therapeutic decision making such that IDH-wildtype tumors appear to behave phenotypically like glioblastoma regardless of grade[78] and, therefore, are increasingly treated as such. In WHO 2021 nomenclatures,[4] these tumors are called glioblastoma and further defined by molecular criteria, including *EGFR* amplification, chromosome 7 gain and loss of chromosome 10 (+7 and –10), and *TERT* promoter mutation. Homozygous *CDKN2A* or *CDKN2B* deletions are commonly associated with this genotype, but by itself, it is not a marker for tumors that behave like glioblastoma.[79] Across all the subgroup analyses in the trials discussed in Section 1, no significant benefits for any therapeutic strategy were identified in patients with IDH-wildtype glioma, and they consistently demonstrated a worse prognosis than their IDH-mutant counterparts. The consensus of the Expert Panel was that people with IDH-wildtype, 1p19q non-codeleted gliomas of any grade may be treated in the same manner as patients with glioblastoma.

Recommendation 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 of older age or poor performance status, no prospective, randomized evidence provides a sufficient basis to guide decision-making based on *MGMT* promoter methylation status.

Recommendation 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).

Literature review and analysis. Clinical trials that specifically enrolled older (defined in some trials as anywhere from ≥ 60 to ≥ 70 years) or frail patients with the goal of identifying an attenuated therapeutic regimen are discussed separately in the Literature Review and Analysis section for recommendations 2.5 and 2.6. No trials were identified that compared RT alone to chemotherapy alone in patients that were not categorized as older or frail.

Prior to 2005, fractionated RT was considered the standard of care for the treatment of glioblastoma.[80] TMZ given concurrently with RT followed by adjuvant TMZ versus RT alone has been studied in two randomized trials: the EORTC 26981-22981 trial reported by Stupp et al in 2005[16] and 2009[81] and the trial reported by Athanassiou et al[9] in 2005. The EORTC 26981-22981 trial used 60 Gy in 2 Gy fractions at five fractions a week in both arms. Stupp et al[16,81] reported statistically significant differences in OS (median OS 14.6 months *v* 12.1 months; HR, 0.63; 95% CI, 0.53 to 0.75; $P < .0001$) and PFS (median PFS 6.9 months *v* 5.0 months; HR, 0.56; 95% CI, 0.47 to 0.66; $P < .0001$) in favor of the addition of TMZ. Improvements in OS were retained with long-term follow-up, demonstrating benefits in both 2-year and 5-year survival. Grade 3 or worse adverse events were only reported with TMZ, and no persistent health-related quality of life (HRQOL) differences were reported. *MGMT* promoter methylation status was known in 206 out of 573 (36%) patients in this study and was associated with longer survival.[82] Although patients with *MGMT* promoter methylated glioblastoma appeared to derive more benefit from TMZ than those with *MGMT* promoter unmethylated tumors, the study was not prospectively powered to detect this difference and the analysis was limited to a subset of patients. Athanassiou et al[9] reported an OS benefit (median 13.4 months *v* 7.7 months, $P < .0001$) in a trial similar but smaller than EORTC 26981-22981. The CeTeG/NOA-09 trial reported by Herrlinger et al[11] in 2019 specifically enrolled patients with glioblastoma and evidence of *MGMT* promoter methylation. Patients were randomly assigned to a control arm (RT with concurrent and adjuvant TMZ as defined by Stupp et al[16]) or 6-week cycles combining lomustine and TMZ that began during RT. The study reported significantly improved OS but not PFS for the lomustine arm. At this time, the results from the CeTeG/NOA-09 trial are too immature, and the trial is too small (141 total patients) for the development of a recommendation regarding combination treatment with TMZ and lomustine for people with newly diagnosed glioblastoma and *MGMT* promoter methylation. The consensus of the Expert Panel was to interpret these data cautiously, particularly because the OS benefit reflected differences in a small group of patients that could be susceptible to confounding factors.

In order to provide clarity on optimal dosing during the adjuvant phase of therapy, the RTOG 0525 trial[47] compared a dose-dense schedule of TMZ to the EORTC 26981-22981 schedule of 5 out of 28 days and did not find significant differences in OS or disease-free survival. This trial also evaluated the value of a 6-month versus 12-month duration of TMZ in each arm and found no significant differences in OS or PFS. This is supported by results of the GEINO 14-01 study reported by Balana et al[17] in 2020, where patients with newly diagnosed glioblastoma who had not progressed after six cycles of adjuvant TMZ were allocated to no further therapy until progression compared to an additional six cycles of therapy. No significant differences in OS or PFS were reported, regardless of tumor *MGMT* promoter methylation status. Hence, adjuvant treatment with TMZ is recommended as a five out of every 28 day dosing schedule and not recommended for more than six cycles for people with newly diagnosed glioblastoma.

Clinical interpretation. The EORTC 26981-22981 trial demonstrated that RT with concurrent and adjuvant TMZ should be considered the standard of care for patients age ≥ 18 and ≤ 70 years (the upper limit of the age of enrollment in EORTC 26981-22981) with Karnofsky Performance Status (KPS) ≥ 70. The combination provides clinically meaningful benefits to both OS and PFS with a manageable increase in toxicity and no meaningful difference in HRQOL. Therapy was initiated within 6 weeks of diagnosis. There are currently no data to further specify optimal timing. It is important to note that adjuvant TMZ is considered an integral part of the upfront therapy for newly diagnosed glioblastoma and should only be discontinued in the setting of progressive disease or toxicity. Given the possibility of pseudoprogression, a determination of progressive disease at the initiation of or during the first 2 months of adjuvant TMZ can only be made in the presence of new enhancement outside the RT field or pathologic evidence of viable tumor as described in the most recent Response Assessment in Neuro-Oncology criteria.[83] The presence of increased enhancement, the growth of measurable lesions, or an increase in cerebral edema within the first 3 months after chemoradiotherapy may or may not constitute pseudoprogression, and patients should continue with first-line therapy until definitive glioblastoma progression can be proven.

There is no evidence from any randomized trial to suggest that more than 6 months of adjuvant TMZ is beneficial. Rather, available data[17] indicate that extending adjuvant TMZ does not provide additional benefit and may increase rates of toxicity. Although the randomized trial that assessed this question did not show any difference in OS or PFS regardless of *MGMT* promoter methylation status, the number of patients per treatment arm with either methylated or unmethylated *MGMT* promoter status was relatively low. Alternate dosing regimens of TMZ were not superior to that in the EORTC 26981 trial. See Table 2 for doses and schedules of RT and TMZ thought reasonable by the Panel.

Although patients with *MGMT* promoter methylated tumors live longer and are likely to derive more benefit from the addition of an alkylating chemotherapy such as TMZ, there are insufficient data to recommend for or against a treatment plan based on a tumor's *MGMT* promoter methylation status in people age ≥ 18 and ≤ 70 years and with KPS ≥ 70 based on the studies in this analysis. Specifically, the studies that met criteria for inclusion lacked adequate sample sizes of patients with known *MGMT* promoter methylation status or lacked a significant test for intervention between treatment and *MGMT* status. Based on this state of the data related to *MGMT* promoter methylation status and treatment intervention, no statement about the consideration of *MGMT* promoter methylation status is made.

Recommendation 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).

Literature review and analysis. The EF-14 trial reported by Stupp et al[14] in 2017 randomly assigned patients after chemoradiation therapy to either adjuvant TMZ alone or adjuvant TMZ combined with alternating electric field therapy. Significant improvements in OS (median OS 20.9 months *v* 16.0 months; HR, 0.63; 95% CI, 0.53 to 0.76) and PFS (median PFS 6.7 months *v* 4.0 months; HR, 0.63; 95% CI, 0.52 to 0.76; $P < .001$) were reported. No clinically meaningful differences in toxicity or QOL were reported.

Clinical interpretation. At face value, the EF-14 trial provides evidence for the addition of alternating electric field therapy to adjuvant TMZ. However, this trial has limitations that must be considered. The intervention in this study began following chemoradiotherapy and excluded patients with evidence of progression or pseudoprogression at 1 month after chemoradiation therapy, limiting generalizability. Biological mechanisms underlying alternating electric field therapy remain poorly understood, and to date, to our knowledge no other randomized phase III study has demonstrated biological activity of this intervention. Finally, the EF-14 trial was stopped early as a result of a planned interim analysis. There is evidence that trials that have been stopped early with fewer than 500 events are at substantial risk of bias for overestimating the magnitude—although not the direction—of effect, and that preplanned stopping rules do not reduce this risk.[84] Given these concerns, the consensus of the Expert Panel was that only a weak recommendation in favor of tumor treatment fields could be made based on existing data.

Recommendation 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).

Literature review and analysis. Three trials were identified that investigated bevacizumab in patients with newly diagnosed glioblastoma. The GENOM 009 trial reported by Balana et al[18] in 2016 was small (93 total patients) and investigated neoadjuvant bevacizumab plus TMZ. It did find a significant improvement in OS (HR, 0.68; 95% CI, 0.44 to 1.04; $P = .007$), but not in PFS. The AVAglio trial reported by Chinot et al[10] in 2014 and the RTOG 0825 trial reported by Gilbert et al[48] in 2014 were similar in patient population and used similar radiation, TMZ, and bevacizumab dosing and schedule. The OS, PFS, and toxicity and QOL data from these two trials are summarized in Table 4.

TABLE 4. Trials of Bevacizumab Versus No Bevacizumab in Newly Diagnosed Glioblastoma

Study: Author Year Arms (No. of patients)	OS	PFS	Toxicity and QOL
AVAglio: Chinot et al 2014[10] Bevacizumab (458) versus placebo (463)	Median OS 16.8 months versus 16.7 months, HR 0.88 (95% CI, 0.76 to 1.02; $P = .10$)	Median PFS 10.6 months versus 6.2 months, HR 0.64 (95% CI, 0.55 to 0.74; $P < .001$)	Serious adverse events more frequent with bevacizumab (38.8% *v* 25.5%). Grade 3 or worse events more frequent with bevacizumab (66.8% *v* 51.3%). Global health status deterioration-free survival longer with bevacizumab (HR 0.64; 95% CI, 0.56 to 0.74; $P < .001$)
RTOG 0825: Gilbert et al 2014[48] Bevacizumab (320) versus placebo (317)	Median OS 15.7 months versus 16.1 months, HR 1.13 (95% CI, 0.93 to 1.37; $P = .21$)	Median PFS 10.7 months versus 7.3 months, HR 0.79 (95% CI, 0.66 to 0.94; $P = .007$)[a]	Serious adverse events more prevalent with bevacizumab than placebo Significant worsened QLQ-C30 and QLQ-BN20 scores with bevacizumab

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; QLQ-BN20, Quality of Life Questionnaire–Brain; QLQ-C30, Quality of Life Questionnaire–Cancer; QOL, quality of life.

[a]Given the trial design, the authors set the threshold for statistical significant for PFS at 0.004; therefore, this result is not considered statistically significant per the protocol.

Clinical interpretation. Although the AVAglio trial reported a significant improvement in PFS with the addition of bevacizumab to RT and TMZ, the RTOG 0825 trial did not (see footnote a in Table 4 for reasons) and neither trial reported evidence of improvement in OS. In the case of RTOG 0825, the potential for clinically meaningful reduction in OS with bevacizumab cannot be ruled out. Bevacizumab was associated with increased toxicity in both trials. It was associated with improvement in QOL in AVAGlio and reduction in QOL with RTOG 0825. Given the absence of demonstrated improvement in OS, limited evidence of improvement in PFS, and the increased harms because of toxicity, the consensus of the Expert Panel was that bevacizumab not be recommended for routine use in patients with newly diagnosed glioblastoma.

Carmustine Wafers

Literature review and analysis. The trial reported by Westphal et al[52] in 2003 allocated patients with an intraoperative diagnosis of malignant glioma to the implantation of either up to eight carmustine wafers or placebo wafers. A significant benefit was seen in OS (median OS 13.9 months *v* 11.6 months; HR, 0.71; 95% CI, 0.52 to 0.96), but not in PFS (median PFS 5.9 months *v* 5.9 months; $P = .90$).

A trial reported by Brem et al[85] in 1995 was published prior to the search window for the systematic review but remains relevant. In this trial, patients with recurrent glioma (approximately 65% of these patients had glioblastoma) were randomly assigned to carmustine wafer or placebo wafer. Among patients with glioblastoma, a significant benefit in OS was reported (adjusted HR, 0.67; 95% CI, 0.48 to 0.95; $P = .02$).

Clinical interpretation. There are several limitations to the data regarding carmustine wafers: These trials predate the widespread adoption of concurrent and adjuvant TMZ; there is no randomized prospective evidence that the addition of carmustine wafers to RT and TMZ provides additional benefits. Also, implementation of carmustine wafer implantation has favored centers with experience with the agent and is limited to patients with excellent performance status who are eligible for complete resection. These factors limit generalizability to the larger population. Given that this therapy is approved for this indication by the US Food and Drug Administration, but in light of the limitations stated, the consensus of the Panel was to make no statement with respect to carmustine wafers within these guidelines.

Recommendation 2.6

In people with glioblastoma, IDH-wildtype, CNS WHO grade 4 where the expected survival benefits of a 6-week radiation course combined with TMZ may not outweigh the harms, hypofractionated RT combined with TMZ is a reasonable alternative. See the Clinical Interpretation section for further explanation (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: weak).

Recommendation 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 unmethylated tumors) or TMZ alone (for *MGMT* promoter methylated tumors) are reasonable options. See the Clinical Interpretation section for further explanation (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Literature review and analysis. Keime-Guibert et al[24] reported on a small RCT (81 total patients) that allocated older patients (age ≥ 70 years and with KPS ≥ 70) to either RT or no RT and best supportive care therapy. The trial showed significant improvements in OS (median OS: 29.1 weeks *v* 16.9 weeks; HR, 0.47; 95% CI, 0.29 to 0.79; $P = .002$) and PFS (median PFS 14.9 weeks *v* 5.4 weeks; HR, 0.28; 95% CI, 0.17 to 0.47; $P < .001$) with RT.

Roa et al[46] in 2004 demonstrated that when patients were randomly assigned to hypofractionated RT in a 40-Gy regimen over 3 weeks OS was equivalent to a traditional

6-week course. The IAEA trial reported by Roa et al[23] in 2015 took this a step further and investigated a 1-week short course RT schedule versus a standard RT schedule. The 2015 trial was designed as a noninferiority trial and reported the 1-week short course RT schedule was noninferior in terms of both OS and PFS.

The trial reported by Perry et al[30] in 2017 included older patients (age ≥ 65 years) who were not considered suitable for 60 Gy RT. All patients received 40 Gy in 15 fractions over 3 weeks and were then allocated to either concurrent and adjuvant TMZ or no TMZ. Significant improvements in OS (median OS 9.3 months *v* 7.6 months; HR, 0.67; 95% CI, 0.56 to 0.80; $P < .001$) and PFS (median PFS 5.3 months *v* 3.9 months; HR, 0.50; 95% CI, 0.41 to 0.60; $P < .001$) with more frequent grade 3 or worse adverse events were reported in the TMZ arm.

The NOA-08 trial reported by Wick et al[66] in 2012 as well as a trial reported by Malmstrom et al[26] in 2012, commonly referred to as the Nordic trial, compared RT alone to TMZ alone. The NOA-08 trial was a noninferiority trial of patients age ≥ 65 years and KPS ≥ 60; TMZ alone was reported as noninferior to RT alone for both OS ($P = .033$) and PFS ($P = .043$). The Nordic trial found significantly improved OS with TMZ alone compared to a 6-week course of RT alone (HR, 0.70; 95% CI, 0.52 to 0.93; $P = .01$) in patients age ≥ 65 years and deemed unfit (defined by investigator) to receive combination therapy. The Nordic trial also included a hypofractionated RT alone arm, and OS in this arm was not significantly different from either RT alone or TMZ alone.

In the NOA-08 trial,[66] longer-term follow-up data reported by Wick et al[86] and published after the search window but identified by the Expert Panel, *MGMT* status and the effect of TMZ were strongly correlated. In patients with *MGMT* promoter unmethylated tumors, PFS was longer in patients who received RT versus TMZ (HR, 1.86; 95% CI, 1.32 to 2.62), while in patients with *MGMT* promoter methylated tumors both OS (HR, 0.44; 95% CI, 0.27 to 0.70) and PFS (HR, 0.46; 95% CI, 0.29 to 0.73) were longer in patients who received TMZ. A similar correlation was observed in the Nordic trial[26] although the OS difference was not statistically significant in either group.

Clinical interpretation. The intention in writing recommendations 2.6 and 2.7 is to offer guidance in patients with newly diagnosed glioblastoma for whom, for a variety of reasons, a 6-week course of RT with concurrent and adjuvant TMZ may not be appropriate. The Expert Panel agreed that this population could not be discretely defined, but might include older patients, frail patients, patients in whom the toxicity of therapy may outweigh the benefit, or patients in whom expected survival is so limited that enduring a 6-week course would not be practical. Specific criteria such as an absolute age or performance status cutoff, as used in clinical trials, are not endorsed in practice. Some patients age ≥ 70 years may be candidates for a full dose regimen, while some age ≤ 70 years may require an attenuated regimen. Performance status is a crude measure and, in older patients, may underestimate the risk of toxicity and geriatric syndromes.[87] The Panel recommends that patients and providers discuss the balance of risks and benefits in the context of prognosis for survival, potential for toxicity, and goals related to HRQOL.

The trials by Roa et al in 2004[46] and 2015[23] support the use of hypofractionated regimens as equivalent in survival to a 6-week course. A 3-week, 40-Gy regimen served as the control arm in the Perry et al[30] trial, and this trial demonstrated that the addition of concurrent and adjuvant TMZ resulted in improved survival in all patients. Although the benefit was greater in patients with *MGMT* promoter methylated tumors in these studies, unmethylated patients also had improved survival. Together, these studies support the backbone of a hypofractionated regimen with concurrent and adjuvant TMZ in patients for whom a 6-week course is not reasonable.

Risk of toxicity can be further minimized with monotherapy. Several studies support the use of hypofractionated RT alone or TMZ alone as options that improve survival yet have manageable toxicity. The Panel agrees that decision making regarding these two options should be based on *MGMT* promoter methylation status. The rationale for this is that *MGMT* status was specifically evaluated for interaction with treatment in NOA-08[66] and the Perry et al[30] trial. Specifically, in NOA-08, PFS was longer in people with newly diagnosed glioblastoma with *MGMT* promoter unmethylated tumors when treated with RT monotherapy versus TMZ monotherapy, and there was both OS and PFS advantage with TMZ monotherapy in people with *MGMT* promoter methylated newly diagnosed glioblastoma multiforme (GBM).

As the recommended choice of monotherapy in this setting is contingent on *MGMT* status, timely and accurate ascertainment of that status is essential.

In patients who are particularly frail or have very poor prognosis, the harms of any therapy may exceed the likely benefits; in those patients, supportive care alone is reasonable. While Keime-Guibert et al[24] demonstrated a survival benefit with RT, it was modest while requiring patients with only a few months to live to go through a 6-week course of RT. Individual considerations about risk and benefit are necessary to make decisions about the value of therapy for the patient.

Additional discussion regarding newly diagnosed glioblastoma. Randomized trials of a number of other interventions have been conducted and can be found in the Data Supplement, including stereotactic radiosurgery,[88] irinotecan,[19,22] topotecan,[20] and cilengitide.[13,15] None of these trials found any significant differences between their arms and are not further discussed.

Recommendation 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 the 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).

Literature review and analysis. Numerous randomized trials have investigated the value of bevacizumab in patients with recurrent glioblastoma: BELOB,[31] Checkmate 143,[35] EORTC 26101,[37] TAMIGA,[43] and Weathers et al.[44] Only the EORTC 26101 trial[37] reported any significant benefit for bevacizumab; PFS was improved (median PFS: 4.2 months *v* 1.5 months; HR, 0.49; 95% CI, 0.39 to 0.61; $P < .001$), but not OS for the combination of bevacizumab and lomustine versus lomustine alone. The other trials reported no significant improvement in OS or PFS with bevacizumab alone or in combination with other therapies.

The randomized phase II REGOMA trial reported by Lombardi et al[41] in 2019 compared regorafenib to lomustine in patients with recurrent glioblastoma. It found significant benefit for regorafenib in OS (median 7.5 months *v* 5.6 months; HR, 0.50; 95% CI, 0.33 to 0.75; $P = .0009$) and PFS (median 2.0 months *v* 1.9 months; HR, 0.65; 95% CI, 0.45 to 0.95; $P = .022$). However, the objective response rates were only 5% for regorafenib versus 2% with lomustine, and median PFS on both arms was 2 months or less. For comparison, the median OS for lomustine in the EORTC 26101 trial (bevacizumab plus lomustine *v* lomustine alone for first recurrence glioblastoma) was 8.6 months.[37]

Many other interventions have been studied in randomized trials in patients with recurrent glioblastoma including cediranib,[40] irinotecan,[42] alternating electric field therapy,[36] nivolumab,[35] carboplatin,[33,34] and nimotuzumab,[38] among others. No significant improvements in OS or PFS were reported in any of these trials.

Clinical interpretation. Options for treating patients with recurrent glioblastoma are limited, and no therapy has clearly demonstrated superior activity over others in the recurrent setting. Surgery is potentially useful in patients who might benefit from palliation of neurologic symptoms from the tumor or cerebral edema or evaluation of tumor tissue to determine eligibility for molecularly targeted clinical trials. Retreatment with TMZ—depending on the interval of time between the stopping of adjuvant TMZ and development of tumor progression—may be reasonable, although this strategy has not been studied in a randomized trial. Additionally, treatment with a nitrosourea (lomustine or carmustine) may be reasonable as it was the control arm in several studies where no significant improvements of the alternative therapy were found, suggesting that the therapy appropriate as control was still appropriate. Although bevacizumab has been approved by the US Food and Drug Administration in the United States for treatment of recurrent glioblastoma on the basis of the PFS benefit found in the EORTC 26101 trial,[37] no study of bevacizumab has demonstrated an improvement in OS. Furthermore, interpretation of imaging (the basis for determination of PFS) is complicated with antiangiogenic agents as they are known to decrease contrast enhancement and cerebral edema without necessarily having direct antiglial effects. Because of its steroid-sparing effect, treatment with bevacizumab can meaningfully improve a patient's QOL and it retains a potentially important role in supportive care management of recurrent gliomas. Reirradiation is also an option, although data showing improvement in OS are lacking. The REGOMA trial[41] demonstrated that regorafenib may improve outcomes in recurrent GBM compared to lomustine. However, the outcome of patients included in the control arm of this trial was exceptionally poor, indicating that larger efficacy studies are required.

Next-generation sequencing may help identify a subset of patients with particular molecular features that may be targeted specifically and offer a reasonable chance of response. In particular, there have been case reports of glioblastomas with BRAF V600E mutations (1%-2% of all glioblastomas) that respond to BRAF inhibitors, with or without MEK inhibitors (ie, dabrafenib with trametinib).[89,90] Similarly, there are some data from nonrandomized studies that report that pan–tyrosine receptor kinase inhibitors such as entrectinib may induce radiological responses in patients with glioblastoma that harbored *NTRK* fusion genes (1%-2% of all glioblastomas).[91] These pan–tyrosine receptor kinase inhibitor compounds have been approved independently of cancer type based on the identification of the respective molecular pathway in the tumor and on the basis of nonrandomized data.

In summary, at first recurrence and especially in later lines of therapy, there is no clearly effective treatment strategy, and decisions about treatment options should take into account a patient's preferences and goals in the context of poor prognosis and little evidence of benefit. The only definitive recommendation the Panel can make for the treatment of patients with recurrent GBM is that, in light of the limited efficacy of current available treatment options, wherever possible these patients should be offered participation in well-designed clinical trials.

Recommendation 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).

Literature review and analysis. No randomized trials of adults with diffuse midline glioma were identified.

Clinical interpretation. Diffuse midline glioma in adults is a relatively new entity, defined by the H3K27M mutation and most commonly found in midline CNS structures. These tumors are rare in adults and, because of location where biopsy is sometimes difficult, tissue and genetic analysis is not always feasible. Because of these factors, no randomized studies in adults inform therapeutic decision making. Given the aggressive nature of these tumors, radiotherapy is the most commonly used option in attempts to delay progression. Treatment approach should be based on factors such as mitotic rate, concurrent mutations, KPS, and grade. It was the consensus of the Expert Panel that whenever possible, patients should be enrolled in clinical trials. The goals of clinical trials in diffuse midline glioma are to better understand biology, natural history, and develop therapeutics.

DISCUSSION

Accumulating evidence supporting the use of systemic and device therapies in the treatment of adult diffuse astrocytic and oligodendroglial tumors prompted ASCO and SNO to jointly develop the recommendations in this guideline.[16,30,53,56,63,66] The timing of this process, in the midst of a reorganization of pathologic classification of CNS tumors,[5] obliged the Expert Panel to integrate published outcomes that are largely based on histology and a modern classification system that is organized based on molecular genetics. Most clinical trials with positive and potentially practice-changing conclusions included molecularly heterogeneous populations of gliomas, in categories that are in many cases no longer consistent with contemporary understanding of tumor biology. Considering this, the Expert Panel carefully interpreted the reported outcomes and subgroup analyses of key randomized studies to make the best possible recommendations that are consistent with contemporary pathologic nomenclature.

Studies with IDH-mutant tumors inevitably included patients with IDH-wildtype tumors and few studies prospectively collected data regarding 1p19q codeletion. The trials that did so were focused on rare tumor subtypes that have a natural history of long OS time ranges with and without treatment, some spanning more than a decade from conception to publication.[56,62,63] Hence, reinventing such studies in the short term is not possible and in the long term may be limited by lack of equipoise, especially in the United States. Two ongoing international intergroup trials, the CODEL study[75] in patients with IDH-mutant 1p19q codeletion and the CATNON trial[53] in patients with IDH-mutant, 1p19q non-codeletion, were designed to evaluate patients based on WHO 2016 criteria and are the first large randomized trials to group patients by molecular status rather than traditional histology. Both studies are ambitiously designed to ask specific questions regarding the type of chemotherapy (RT plus PCV *v* RT plus TMZ in people with codeleted gliomas) and the optimal regimen (concurrent TMZ *v* adjuvant TMZ *v* concurrent and adjuvant TMZ in people with non-codeleted gliomas) and will provide more data driven clarity to these recommendations in the coming years. Results from one arm of the CATNON study are published and included in this guideline, resulting in an unambiguous recommendation for IDH-mutant, 1p19q non-codeleted anaplastic astrocytomas (recommendation 1.4), a harbinger for potential future molecularly driven updates.

Recommendations for IDH-wildtype tumors were less influenced by the changes in WHO 2016 and 2021 CNS classification systems as only a minority of newly diagnosed patients in a glioblastoma trial are expected to have an IDH-mutant tumor.[3] The landmark EORTC trial comparing RT to RT with concurrent and adjuvant TMZ[16] continues to define the standard therapy in this population. The addition of alternating electric field therapy to the regimen may add benefit but is limited by positive results in only one trial. The recommendation for use in very distinct circumstances reflects the uncertainty of antitumor activity of this approach and concerns about cost and burden, but also recognition of safety.[14] Vaccine therapies for malignant gliomas represent an emerging field of therapeutics, but remain experimental and inaccessible outside of clinical trials. For these reasons, the Expert Panel agreed that analysis of these studies did not fit within the scope of a practical clinical guideline.[92-94] Older patients or those with poor performance status require special attention and judicious decision making in order to provide care that is most appropriate for the individual. Performance status in older patients can underestimate a patient's frailty, risk of geriatric syndromes, and toxicity. Geriatric assessment is currently a recommendation for patients over age 65 years in an ASCO guideline in order to better predict medical vulnerabilities, estimate toxicity to chemotherapy, and to guide decisions for the use of attenuated regimens.[87] Patients with gliomas have not been well represented in geriatric oncology studies, and future work that prospectively evaluates the role of a geriatric assessment and its impact on decision making may clarify its effectiveness and its potential role in prospective clinical trials for older patients with glioblastoma.

Older patients or those with poor performance status are the rare population of people for whom there is evidence that *MGMT* promoter methylation status is associated with treatment outcome. Specifically, in NOA-08, the evidence supports RT monotherapy for people with newly diagnosed *MGMT* promoter unmethylated glioblastoma and TMZ monotherapy for people with newly diagnosed *MGMT* promoter methylated glioblastoma. No other studies had sufficient data to justify a treatment recommendation based on *MGMT* promoter methylation status. The progress that has been made in the treatment of IDH-mutant tumors, and even in newly diagnosed IDH-wildtype glioblastoma, is offset by the absence of proven therapies in recurrent

glioblastoma and diffuse midline glioma. In the case of recurrent glioblastoma, many trials met the criteria but included unproven therapies in both arms of the study, were randomly assigned to an unconventional control arm, or included other modalities that made assessment of activity difficult. OS in these studies ranged from 3 to 22 months. Patients enrolled in trials for recurrent glioblastoma are most certainly a heterogeneous group with molecular features that are not well described as many patients will not have tissue analysis at time of recurrence, will have mixed prognostic factors, and, possibly, important confounding factors that are not well understood. In the end, a PFS or OS result in a single-arm prospective study is nearly impossible to interpret and, in a randomized trial, populations should be well delineated according to known biomarkers and prognostic factors. When this has been done thus far, there have been some studies showing improvement in PFS, but none meeting the OS study goal. The challenges for diffuse midline glioma are even greater as these tumors are only recently defined by the H3K27M mutation, often are in locations inaccessible for biopsy (or small amounts of tissue are available from biopsy), and are rare in adults, and the field is still learning about the relationship between this mutation, histology, and natural history.[95,96] For both recurrent glioblastoma and H3K27M-mutant midline glioma in adults, the Panel agreed that patients are currently best served by prioritizing enrollment into a clinical trial and in situations where a local trial may not be available, referral to a regional brain tumor program is indicated. The Expert Panel hopes that the clinical research community in neurooncology along with patient advocacy groups will work to improve geographic and financial access to clinical trials and streamline the processes to reduce the burden on patients and their families to enhance trial participation.

There is no algorithm that helps clinicians balance potential benefits, which in some cases may be marginal, with potential risks and patient preferences. Despite evaluating HRQOL and toxicity in 59 RCTs (Data Supplement [Table 5]), the recommendations presented are principally based on survival outcomes. Greater toxicity was reported with chemotherapy regimens, especially PCV, leading the Panel to allow substitution with TMZ in cases where the physician or patient has concerns. No clear narrative could be gleaned from QOL data and it did not directly influence any of the recommendations. Often, no clear differences were observed between arms and, in one case, two similarly designed trials evaluating bevacizumab in newly diagnosed glioblastoma used different tools to reach opposite conclusions.[10,48] However, many of the studies included HRQOL end points and these can be referenced (Data Supplement [Table 5]) when discussing the relative merits of a treatment plan.

The Expert Panel sought to clearly articulate recommendations born from the fusion of modern diagnostic criteria and the highest quality available therapeutic outcome data to inform practical treatment decisions in adults with gliomas. Simultaneously, the Panel sought to explain circumstances where latitude on decision making is warranted. Practice-changing trials and advances in cancer genomics are a cause for optimism in neurooncology; however, the reality is that molecular diagnostics have only recently been included as stratifying criteria for clinical trials for gliomas. Hence, creating contemporary recommendations for diffuse astrocytic and oligodendroglial tumors in adults required meticulous review of inclusion criteria and outcomes data from existing trials as well as rigorous discussion that engaged the viewpoints of the various experts on the Panel who practice and receive care in diverse settings. As the data from studies like CODEL and CATNON mature, increasing data that prospectively integrate modern classification schemas and efficacy and tolerability data will further support specific treatment recommendations for the full range of adult gliomas. As the data continue to accumulate and provide greater clarity about treatment outcomes for distinct subtypes of adult gliomas, new recommendations should continue to place the patient at the center of decision making, focusing on applying the best available data to their specific tumor subtype and treatment goals. In coming to consensus on these recommendations, the Expert Panel establishes the standard for treatment of diffuse astrocytic and oligodendroglial tumors in adults based on the best available evidence today, and sets the footing for the next generation of evidence-based guidelines for these tumors.

PATIENT AND CLINICIAN COMMUNICATION

With all cancers, clinician expertise when informing patients about their disease, their diagnosis, and their treatments, and when educating patients regarding clinical trials, is vital. Information given to the patient should allow the patient to feel enabled to make an informed choice that is best for their priorities. A patient that finds agency with the information they receive is likely more motivated, more proactive, more adherent, and better able to cope with their diagnosis.

Gliomas are complex, with multiple factors that contribute to diagnosis and prognosis. Patients with glioma need resources and time with their oncologists to understand the details of their condition and what it may mean for them. Patients need tools to understand the terminology around their disease (eg, IDH mutation status).

The recommendations in this guideline allow for customization of treatment based on the specific context of the patient (eg, frailty, age). Providers should ensure that patients are fully informed about the benefits and harms they may experience with each potential strategy. Also, given the substantial difference in prognosis between the different forms of glioma described in this guideline, providers should exercise care to be precise about the molecular and histologic considerations. As with all cancers, providers need to recognize the emotional toll that the wait for information around prognosis, and the prognosis itself, can have on patients.

Patients' access to information on and opportunities to enroll in clinical trials may vary substantially depending on whether the patient is receiving care in a community versus academic center setting.[97-99] Clinicians should work to inform themselves of relevant clinical trials. Clinicians may also encourage patients to seek out local, regional, and national patient support organizations. ASCO's Cancer.Net online resource provides information on such organizations in the United States, and SNO (https://www.soc-neuro-onc.org/) provides a list of resources more closely targeted to neurooncological patients. Patients are not experimental subjects, they are individuals; providers should avoid making patients feel as though they are a part of an academic lab study. As enrollment in a clinical trial remains the recommended course of action for many glioma subtypes in adults, efforts are required to help patients and their families navigate these opportunities and make them feasible.

For recommendations and strategies to optimize patient-clinician communication, see "Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline."[100]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care and/or receive fragmented care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving fragmented care or poor quality care than other Americans.[101,102] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[103] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[104,105]

Discussion of cost can be an important part of shared decision making.[106] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[106]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[106]

Estimating the costs associated with RT, all of the systemic therapies assessed for glioma, and regional therapies such as alternating electric field therapy or carmustine wafers is beyond the scope of this guideline and will likely vary widely depending on the geographic and institutional context. The costs of the systemic therapy options recommended in this guideline have been estimated as more than $1,500 US dollars (USD) a month for PCV[107] and at least $500 USD and as much as $2,000 USD a month for TMZ depending on whether a generic or brand drug is used, with costs increased after the first month.[108] There are also costs associated with participating in clinical trials including copays for all evaluations billed to a third-party payer as standard of care, travel, and missed work time.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from December 14, 2020, through January 5, 2021. Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. See comments" were captured for every proposed recommendation with 15 responses received. Of the 16 recommendations, six were met with agreement or agreement with modifications by all respondents. Of the remaining 10 recommendations, no more than three of the 15 respondents (21%) disagreed with that recommendation. The cochairs reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes to the recommendations were incorporated prior to Clinical Practice Guideline Committee and SNO review and approval.

The draft was submitted to two external reviewers with content expertise. It was rated as high quality, and it was agreed it would be useful in practice. Review comments were reviewed by the Expert Panel and integrated into the final manuscript before approval by the Clinical Practice Guideline Committee.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the

community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/neurooncology-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care Into Standard Oncology Care[109] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[100] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy[87] (https://ascopubs.org/doi/full/10.1200/JCO.2018.78.8687)

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EDITOR'S NOTE

This joint ASCO and Society for Neuro-Oncology (SNO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/neurooncology-guidelines.

DISCLAIMER

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the National Cancer Institute, HIV/AIDS or cancer registries, or their contractors.

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N.M. and J.B. were Expert Panel Cochairs.

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Expert Panel members are listed in Appendix Table A1 (online only).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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APPENDIX

TABLE A1. Therapy for Diffuse Astrocytic and Oligodendroglial Tumors Expert Panel

Name	Affiliation/Institution	Role/Area of Expertise
Jaishri Blakeley, MD (Cochair)	Johns Hopkins University School of Medicine, Baltimore, MD	Neurooncology
Nimish A. Mohile, MD (Cochair)	Department of Neurology and Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY	Neurooncology
Na Tosha Gatson, MD, PhD	Banner MD Anderson Cancer Center, Phoenix, AZ and Geisinger Neuroscience Institute, Danville, PA	Neurooncology
Andreas F. Hottinger, MD, PhD	Departments of Clinical Neurosciences and Oncology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland	Neurooncology
Andrew Lassman, MD	Columbia University Medical Center, New York, NY	Neurooncology, SNO represenative
Jordan Morton, MD	Mercy Hospital, Oklahoma City, OK	PGIN representative
Douglas Ney, MD	University of Colorado School of Medicine, Aurora, CO	Neurooncology
Phioanh Leia Nghiemphu, MD	UCLA David Geffen School of Medicine, Los Angeles, CA	Neurooncology
Adriana Olar, MD	Nomix Laboratories, Denver, CO	Neuropathology/Molecular Pathology
Jeffrey Olson, MD	Emory University, Atlanta, GA	Neurosurgical Oncology
James Perry, MD	Sunnybrook Health Sciences Center, Toronto, Ontario, Canada	Neurooncology
Jana Portnow, MD	City of Hope National Medical Center, Duarte, CA	Medical Oncology
David Schiff, MD	University of Virginia Medical Center, Charlottesville, VA	Neurooncology, SNO representative
Anne Shannon		Patient representative
Helen A. Shih, MD, MS	Massachusetts General Hospital, Boston, MA	Radiation Oncology
Roy Strowd, MD, MEd	Wake Forest Baptist Health Medical Center, Winston-Salem, NC	Neurooncology
Martin Van Den Bent, MD, PhD	The Brain Tumor Center at Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands	Neurology
Mateo Ziu, MD, MBA	INOVA Neurosciences and Inova Schar Cancer Institute, Falls Church, VA	Neurosurgical Oncology, AANS/CNS representative
Hans Messersmith, MPH	American Society of Clinical Oncology, Alexandria, VA	ASCO Practice Guideline staff (Health Research Methods)

Abbreviations: AANS, American Association of Neurological Surgeons; CNS, Congress of Neurological Surgeons; PGIN, Practice Guideline Implementation Network; SNO, Society for Neuro-Oncology.

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of Evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Strength of Recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects.
	In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects.
	All or almost all informed people would make the recommended choice for or against an intervention.
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists.
	In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists.
	Most informed people would choose the recommended course of action, but a substantial number would not.