NCCN Guidelines® Insights

Central Nervous System Cancers, Version 1.2017

Featured Updates to the NCCN Guidelines

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Abstract

For many years, the diagnosis and classification of gliomas have been based on histology. Although studies including large populations of patients demonstrated the prognostic value of histologic phenotype, variability in outcomes within histologic groups limited the utility of this system. Nonetheless, histology was the only proven and widely accessible tool available at the time, thus it was used for clinical trial entry criteria, and therefore determined the recommended treatment options. Research to identify molecular changes that underlie glioma progression has led to the discovery of molecular features that have greater diagnostic and prognostic value than histology. Analyses of these molecular markers across populations from randomized clinical trials have shown that some of these markers are also predictive of response to specific types of treatment, which has prompted significant changes to the recommended treatment options for grade III (anaplastic) gliomas.

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Central Nervous System Cancers
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Central Nervous System Cancers

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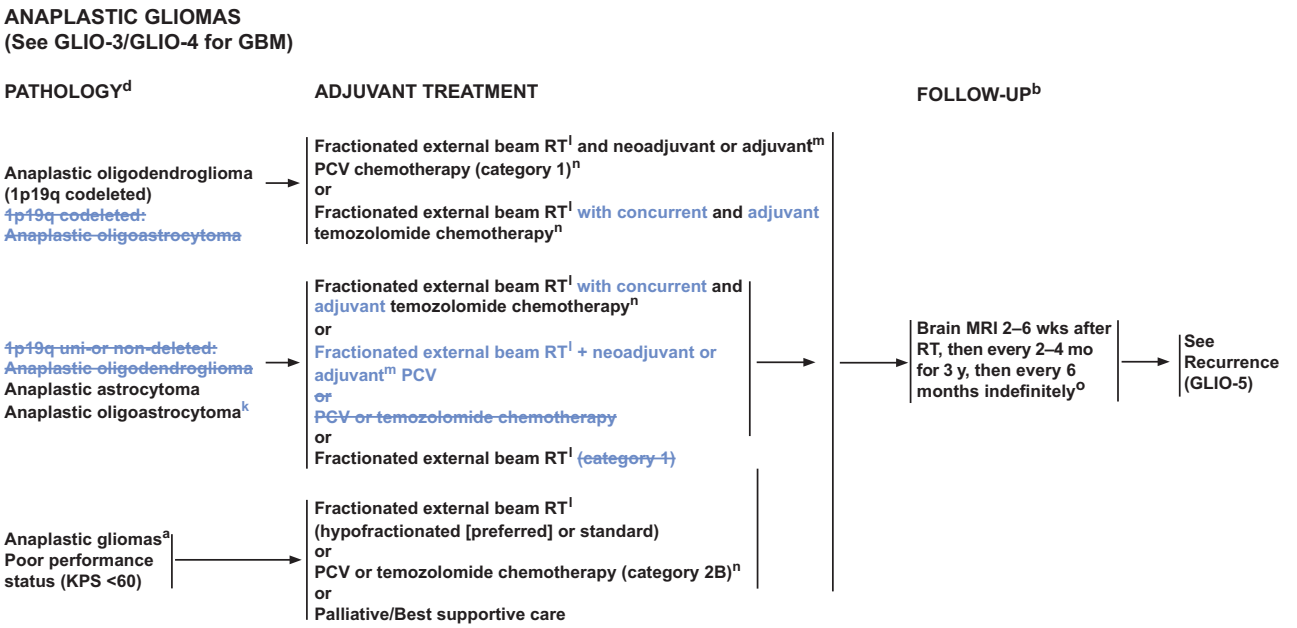


[a]This pathway includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[k]NOS WHO 2016 has deleted this category, although it may continue to be used for some patients.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[m]The panel recommends that PCV be administered after RT (as per EORTC 26951) since the intensive PCV regimen given prior to RT (RTOG 9402) was not tolerated as well.
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.

GLIO-2

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

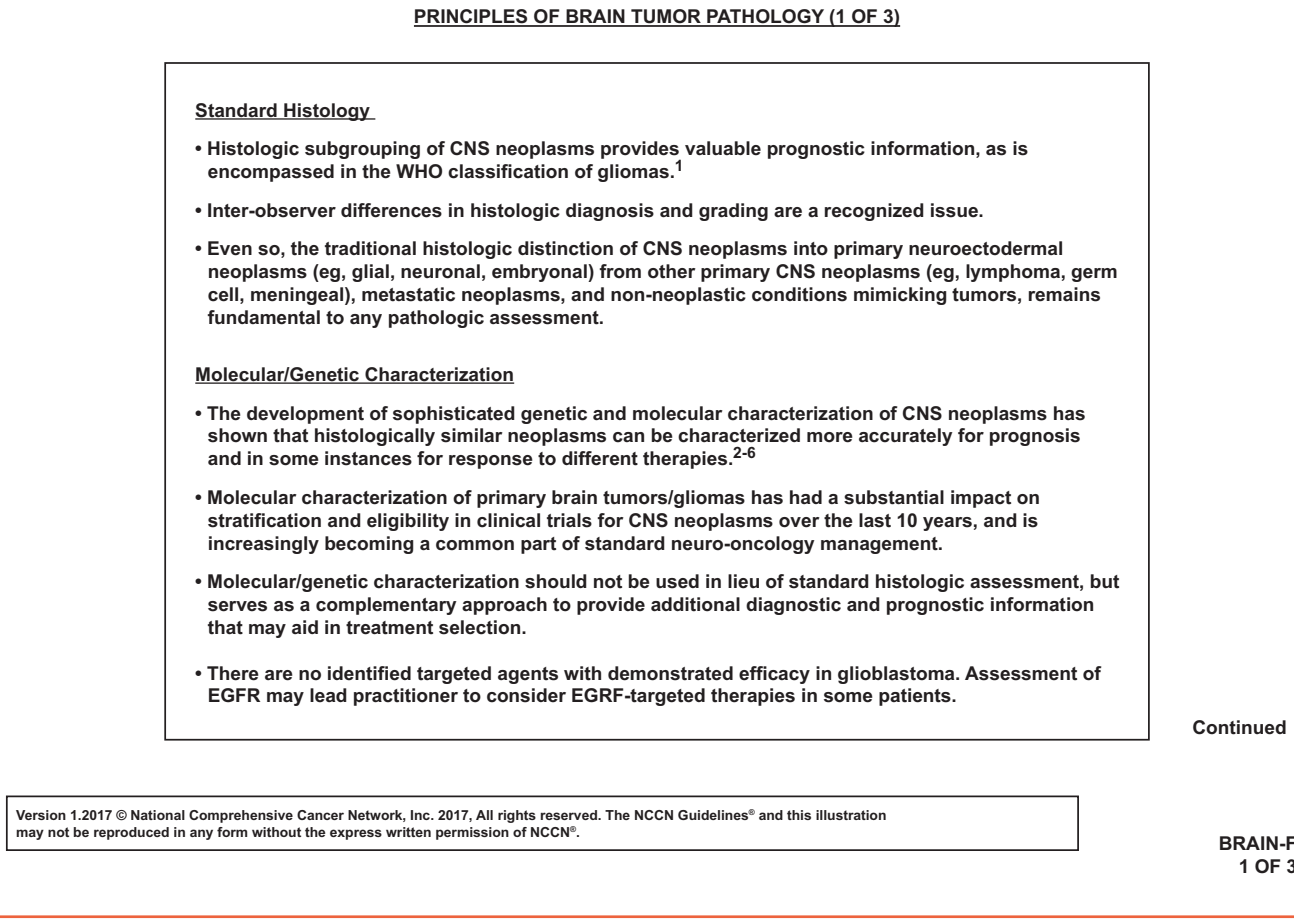
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Estimates based on recent population analyses indicate that nearly 24,000 people in the United States are diagnosed with primary malignant brain or other central nervous system (CNS) neoplasms each year.[1,2] In adults, the annual incidence of malignant primary brain and other CNS tumors is 8.7 per 100,000.[1] These cancers are a leading cause of death in adults, especially for those <40 years old, and are estimated to be responsible for 16,700 deaths in the United States in 2017.[1,2] High-grade gliomas are the most common type of brain cancer, accounting for more than half of all malignant primary tumors of the brain and CNS.[1] Although the prognosis for glioblastoma (grade IV glioma) is grim (5-year survival rates between 1% and 19%, depending on age), outcomes for anaplastic gliomas (grade III gliomas) are typically better, depending on the molecular features of the grade III glioma.[1] Clinicians are learning how to better predict survival and select treatments for patients with high-grade gliomas



based on the increasing amount of information obtained from molecular profiling of these tumors.

These NCCN Guidelines Insights focus on the molecular analyses of gliomas that prompted the addition of a section titled "Principles of Brain Tumor Pathology" (see BRAIN-F, pages 1334 and 1335) to provide background and recommendations for histologic characterization and molecular testing for gliomas. This article also describes data from clinical trials with available molecular information that have led to revisions or refinements in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommendations, particularly for the treatment of newly diagnosed anaplastic gliomas (see GLIO-2, page 1333).

Molecular Profiling for Glioma Classification

Classification of Gliomas Based on Histology

Although molecular tests for subtyping gliomas have been in use at some institutions since the late 1980s, histologic features, as observed by pathologists' review, have for many years been the primary basis for glioma grading and subtyping, and were the basis for the 2007 WHO classification system for gliomas.[3] Supplemental eTable 1 (available online with this article at JNCCN.org) shows the 2007 WHO categories of gliomas covered in the first 2 sections of the NCCN Guidelines for CNS cancers (see ASTR and GLIO pages in the full version of these guidelines at NCCN.org). In the 2007 WHO system, grade II and III gliomas were further categorized based on cell types; the most commonly observed histologic subtypes are astrocytoma, oligodendroglioma, and oligoastrocytoma.[3] Although the 2007 WHO system of grading and subtyping based on histology has been shown to provide some prognostic separation (for overall survival [OS] and progression-free survival [PFS]) in a few studies of larger populations (≥300 patients) with brain tumors,[4,5] results from other studies are less convincing and more variable.[6–13] Categorizing gliomas based solely on histology has also been

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PRINCIPLES OF BRAIN TUMOR PATHOLOGY (2 OF 3)
MOLECULAR MARKERS

The following molecular markers are often used by neuropathologists to facilitate characterization of gliomas and/or by neuro-oncologists to guide treatment decisions:

Codeletion of 1p and 19q
- **Description: This codeletion represents an unbalanced translocation (1;19)(q10;p10).**
- **Detection: The codeletion of 1p and 19q is detectable by FISH or PCR.**
- **Diagnostic value: It is strongly associated with oligodendroglial histology and helps confirm the oligodendroglial character of tumors with equivocal or mixed histologic features.[7]**
- **Prognostic value: The codeletion confers a favorable prognosis and is predictive of response to alkylating chemotherapy and combination therapy with radiation and alkylating chemotherapy.[8,9]**

Isocitrate Dehydrogenase 1 and 2 (IDH1 and IDH2) Mutation
- **Description: IDH1 and IDH2 are metabolic enzymes. Specific mutations of these enzymes are linked to the formation of D-2-hydroxyglutarate, an oncometabolite that causes epigenetic modifications.**
- **Detection: The most common IDH1 mutation (R132) is detectable by immunohistochemistry. Additional IDH1 as well as IDH2 mutations are detectable by PCR or pyrosequencing.**
- **Diagnostic value: Very common in grade II and III gliomas. Much less common in glioblastoma, but can help identify a glioblastoma as being a secondary glioblastoma (one that transformed from a lower grade glioma and generally does not behave as aggressively as a primary [de novo] glioblastoma).[10,11]**
- **Prognostic value:**
  - **IDH mutations are commonly associated with codeletion of 1p and 19q, and with MGMT promoter methylation.[4]**
  - **IDH1 or 2 mutations are associated with a favorable prognosis and are important in stratification for clinical trials.[12]**
  - **In grade II or III gliomas, wild-type IDH1 or 2 is associated with increased risk of aggressive disease.[4]**
  - **IDH1 or 2 mutations are associated with a survival benefit for patients treated with radiation or alkylator chemotherapy, but not for untreated patients.[13,14]**

MGMT Promoter Methylation
- **Description: MGMT (O^6-methylguanine-DNA methyltransferase) is a DNA repair enzyme that reverses the DNA damage caused by alkylating agents, resulting in tumor resistance to temozolomide and nitrosourea-based chemotherapy. Methylation of the MGMT promoter silences MGMT, making the tumor more sensitive to treatment with alkylating agents.[15]**
- **Detection: Methylation of the MGMT promoter is detectable by methylation-specific PCR[16] or pyrosequencing.[17]**
- **Prognostic value:**
  - **MGMT promoter methylation is strongly associated with IDH status and genome-wide epigenetic changes (G-CIMP phenotype).[4]**
  - **MGMT promoter methylation confers a survival advantage in glioblastoma and is used for risk stratification in clinical trials.[18]**
  - **MGMT promoter methylation is particularly useful in treatment decisions for elderly patients with high-grade gliomas (grades III-IV).[19,20]**
  - **Patients with glioblastoma that are not MGMT promoter methylated derive less benefit from treatment with temozolomide compared to those whose tumors are methylated.[18]**

References available online, in the full version of this guideline, at NCCN.org [BRAIN-F 3 of 3]

BRAIN-F 2 OF 3

shown to be limited by interobserver variability, especially for certain categories.[14–21] The variability in outcomes for oligoastrocytoma is likely related to the high interobserver variability (between pathologists) in assigning this particular category.[22–25] These challenges prompted searches for molecular characteristics to help better distinguish glioma subtypes and improve estimation of prognosis for patients with brain tumors.

Revised WHO Classification System for Gliomas

Findings from molecular analyses (described in more detail later) have prompted revision of the WHO classification system to incorporate molecular features that have been shown to have better prognostic value than standard pathology.[26] Supplemental eTable 1 shows the categorization of patients with grade II/III gliomas according to the WHO classification system versions 2007 and 2016.[3,26] Key changes for grade II/III gliomas are as follows: (1) oligodendrogliomas include only tumors with 1p19q codeletion (1p19q-codel) and *IDH* mutation (*IDH*-mut), unless molecular data are not available and cannot be obtained, in which case designation can be based on histology; (2) anaplastic gliomas are further subdivided according to *IDH* mutation status; and (3) oligoastrocytoma is no longer a valid designation unless molecular data (1p19q deletion and *IDH* mutation status) are not available and cannot be obtained, or there is phenotypic and genotypic evidence of spatially distinct oligodendroglioma (1p19q-codel) and astrocytoma (1p19q intact or deletion of only 1p or 19q) components in the same tumor.

Grade II/III Glioma: Search for Molecular Subgroups

Multiple independent studies on glioma tissue removed from the brain have conducted genome-wide analyses evaluating an array of molecular features (eg, mutations, DNA copy number, DNA methylation, mRNA, microRNA, protein expression) in large populations of patients with grade II–IV

disease.[5,9,27–29] Unsupervised clustering analyses, an unbiased method for identifying molecularly similar tumors, have been used to identify subgroups of gliomas with distinct molecular profiles.[5,9,27,29] Remarkably, further analysis showed that these molecular subgroups could be distinguished based on only a handful of molecular features, including mutation of *IDH1* or *IDH2* (*IDH*-mut) and 1p19q-codel, biomarkers independently verified by many studies as hallmarks for distinguishing molecular subgroups in grade II/III glioma.[4–7,9,13,28,30–39] Using these markers alone, most grade II/III tumors can be divided into 3 molecular subtypes: (1) mutation of either *IDH1* or *IDH2* with 1p19q codeleted (*IDH*-mut+1p19q-codel), (2) *IDH*-mut without deletion of 1p or 19q (1p19q intact) or with isolated deletion of 1p or 19q, and (3) no mutation of *IDH1* or *IDH2* (*IDH*-wt).[5] Multiple studies have shown that codeletion of 1p and 19q is strongly associated with *IDH*-mut, such that 1p19q codeletion in *IDH*-wt tumors is rare.[7,11,13,34,35]

Analyses of large molecular databases have also suggested a number of other molecular markers as being potential characteristic/prognostic features of specific molecular subgroups.[7,9,11,28,35,37,40] Molecular features suggested by more than one study as markers for subtyping grade II/III gliomas include (1) mutations in the *TERT* promoter, *NOTCH1*, *CIC*, *FUBP1*, *PIK3CA*; (2) mutation in or overexpression of *TP53*; (3) *PTEN* loss or promoter methylation; (4) loss/deletion of *ATRX* and *CDKN2A/B*; (5) amplification of *EGFR*; and (6) chromosome 7 gain, chromosome 10 loss.[5,9,27,28,34–37,40] Due to variability in results across studies, these molecular markers are not currently widely accepted as useful for classifying gliomas. Supplemental eTable 2 shows the molecular, phenotypic, and demographic characteristics associated with the 3 molecular subgroups of grade II/III gliomas defined by *IDH* and 1p19q status. It is important to note that the "associated molecular markers" listed in supplemental eTable 2 are not necessarily present in all tumors of a particular molecular subgroup and have not been fully validated as markers for assigning molecular subtype. Some of these markers can be found (not infrequently) in more than one molecular subgroup, but are merely more prevalent in one particular subgroup; other markers are found almost exclusively in one particular molecular subgroup.[5,11,28,35,37] It is important to note that correlations between the molecularly defined 2016 WHO categories and the histology-based 2007 WHO categories are limited and vary across studies.[5,7,34,37] Thus the change from 2007 WHO to 2016 WHO reclassifies a significant proportion of grade II–IV gliomas.

Grade II/III Glioma: Prognostic Relevance of Molecular Subgroups

Most importantly, the specific markers used to define molecular subgroups among grade II/III gliomas have been shown to have prognostic value. Numerous large studies of patients with brain tumors have shown that among grade II/III gliomas, 1p19q-codel is significantly correlated with improved PFS and OS.[4,6,7,9,10,13,30,32,41,42] Many of these studies used heterogenous populations treated with a variety of approaches, but a few showed statistically significant correlation between 1p19q-codel and outcome within a population of patients who received the same treatment. The independent prognostic value of 1p19q status was also confirmed through multivariate analyses from multiple studies in patients with grade II/III glioma.[4,7,13,41,42] For *IDH* mutation status, although a few analyses did not find a significant correlation with PFS,[7,32] many more studies found that *IDH*-mut was associated with improved PFS, including several multivariate analyses.[4,9,10,42,43] Numerous large studies, including many multivariate analyses, all found that *IDH*-mut is significantly associated with improved OS in patients with grade II/III glioma.[4,5,7,9–13,27,28,32,34,35,37,41,43,44] Analyses within single-treatment arms showed that the *IDH* status is prognostic for outcome across a variety of postoperative adjuvant options. For example, in the NOA-04 phase III randomized trial in newly diagnosed anaplastic gliomas, *IDH*-mut was associated with improved PFS, time to treatment failure, and OS in each of the 3 treatment arms: standard radiation therapy (RT; n=160); combination therapy with procarbazine, lomustine, and vincristine (PCV RT upon progression; n=78); and temozolomide (TMZ; RT upon progression; n=80).[10]

Multiple independent studies have shown that subdividing grade II/III gliomas by *IDH*- and 1p19q-based molecular subtype yields greater prognostic separation (for PFS and OS) than subdivision based on histology (as defined by WHO 2007).

These include very large studies covering multiple grades and histology-based subtypes of gliomas,[4,5,9,27] as well as smaller studies limited to 1 to 2 grades or histologic subtypes.[6–8,12,28] Multiple studies have also shown that among patients with grade II/III gliomas, the *IDH*-mut+1p19q-codel group has the best prognosis, with significantly better PFS and OS than the *IDH*-wt group, which has the worst prognosis of the 3; and outcomes for the group with *IDH*-mut and 1p19q intact or deletion of only 1p or 19q usually lie somewhere in between that of the *IDH*-mut+1p19q-codel and *IDH*-wt groups.[4,5,7,10,13,27,37,41] Analyses within single treatment arms have confirmed this trend in prognosis across a variety of postoperative adjuvant treatment options.[7,8,10,41] Table 1 shows a few examples of prospective phase II/III trials reporting outcomes for the 3 molecular subtypes within the following (postoperative) treatment arms: RT, TMZ, PCV or TMZ, and PCV then RT.

Molecular Features Relevant to Treatment Selection for Anaplastic Glioma

Supplemental eTable 1 shows the histologic and molecular features used to determine the recommended treatment pathway for grade III gliomas in the NCCN Guidelines (version 1.2017). Each pathway for anaplastic gliomas (grade III) has several recommended adjuvant treatment options (see GLIO-2, page 1333, and GLIO-5, available in the complete version of these guidelines at NCCN.org), and the recommended treatment pathway is also determined by performance status.[45] In addition, the "Principles of Brain Tumor Pathology" section was added to the NCCN Guidelines to provide guidance for the histologic and molecular characterization of gliomas (see BRAIN-F, pages 1334 and 1335). This section includes descriptions of how specific molecular markers (1p19-codel, *IDH1* and *IDH2* mutations,

Table 1. Prognosis for Three Molecularly Defined Subtypes of Grade II/III Gliomas

Study Phase, NCT, and Glioma Grade	Postoperative Treatment Arm	1p19q Status: / *IDH* Status:	Outcomes by Molecular Subgroup[a] Codel[b] Mut[d]	≤1 Deleted[c] Mut[d]	≤1 Deleted[c] WT[e]	
Phase II[8,f]	TMZ (n=120)	PFS	4.9	3.6	0.6	*P*=.01
NCT00313729		OS	9.7	11.2	1.8	*P*<.001
Grade II						
Phase III RCT[10,g]	PCV or TMZ (RT on progression) (n=158)	PFS	[h]	ND	ND	HR, 0.57; 95% CI, 0.34–0.97; *P*=.041
NOA-04		OS	[h]	ND	ND	HR, 0.41; 95% CI, 0.22–0.77; *P*=.006
NCT00717210		PFS	7.5	[h]	0.8	HR, 0.22; 95% CI, 0.12–0.41; *P*<.001
Grade III		OS	NR	[h]	3.1	HR, 0.24; 95% CI, 0.12–0.48; *P*<.001
	RT (n=160)	PFS	[h]	ND	ND	HR, 0.59; 95% CI, 0.34–1.0; *P*=.052
		OS	[h]	ND	ND	HR, 0.63; 95% CI, 0.33–1.2; *P*=.17
		PFS	8.7	[h]	0.8	HR, 0.25; 95% CI, 0.14–0.48; *P*<.001
		OS	NR	[h]	4.7	HR, 0.14; 95% CI, 0.06–0.36; *P*<.001
Phase III[41]	PCV then RT (n=148)	OS	14.7	5.5	1.0	*P*<.001
RTOG 9402	RT (n=143)	OS	6.8	3.3	1.3	*P*<.001
NCT00002569						
Grade III						

Abbreviations: HR, hazard ratio; ND, median PFS or OS are not reported, although statistics for the comparison are reported; NCT, National Clinical Trial; NR, not reached; OS, overall survival; PCV, procarbazine, lomustine, and vincristine; PFS, progression-free survival; RCT, randomized controlled trial; RT, radiation therapy; TMZ, temozolomide.
[a]Median PFS and OS, in years.
[b]1p and 19q are both deleted.
[c]1p and 19q both intact or only one of them is deleted.
[d]Mutation present in either *IDH1* or *IDH2*.
[e]*IDH1* and *IDH2* are wild-type.
[f]Only tested for *IDH1* mutation.
[g]Only reported 2-way comparisons between molecular subgroups. Cells with entries (ie, either data or "ND") show the subgroups being compared.
[h]Data omitted because not part of 2-way comparisons.

and *MGMT* promoter methylation) may be used to facilitate subtyping and treatment selection.

In the 2017 version of the NCCN Guidelines, "anaplastic oligodendroglioma" is limited to patients with 1p19q-codel tumors, and "anaplastic astrocytoma" to those with 1p19q intact or deletion of only 1p or 19q tumors. "Anaplastic oligoastrocytoma" corresponds to the 2016 WHO category "anaplastic oligoastrocytoma, NOS [not otherwise specified]" and should include only (1) patients with mixed histology and no available molecular data (ie, no tissue available for analysis) for determining whether to classify as oligodendroglioma versus astrocytoma, or (2) rare instances in which the tumor has regions with histologic features of oligoastrocytoma with 1p19q-codel, and distinct regions with histologic features of astrocytoma and no 1p19q-codel.[26]

Recent changes to the WHO system for classifying gliomas along with emerging trial data have prompted changes in the recommendations for postoperative treatment of anaplastic (grade III) gliomas (see GLIO-2, page 1333). For postoperative adjuvant treatment of anaplastic gliomas in patients with good performance status (Karnofsky performance score [KPS] ≥60), combination therapy with fractionated external-beam RT combined with PCV or TMZ, are among the recommended options in the NCCN Guidelines, shown in the top 2 pathways on GLIO-2.

Combination Therapy: RT Plus PCV

Addition of PCV to RT for treatment of anaplastic gliomas is supported by 2 phase III randomized trials, one testing RT plus adjuvant PCV (EORTC 26951[11,46,47]) and the other testing neoadjuvant PCV plus RT (RTOG 9402[41,48,49]). Both trials compared combination therapy with RT alone. Key data from these trials are summarized in Table 2.

RT With Neoadjuvant PCV: The RTOG 9402 trial showed that 4 cycles of a dose-intense PCV regimen followed by RT significantly improved OS compared with RT alone in a patient sample with histology-based anaplastic oligodendroglioma or anaplastic oligoastrocytoma (Table 2).[41,48,49] Based on this result, one option in the NCCN Guidelines is treatment with neoadjuvant PCV plus fractionated external-beam RT for all subtypes of anaplastic gliomas (see top 2 pathways on GLIO-2, page 1333) in patients with good performance status (KPS ≥60). Results showed significantly higher rates of discontinuation and acute toxicities in the neoadjuvant PCV plus RT arm compared with RT alone, with 2 early deaths attributed to PCV-induced neutropenia (Table 2),[48,49] supporting the notion that combination therapy with RT and chemotherapy is too toxic to be safely used in patients with poor performance status (KPS <60).

It is important to note that in RTOG 9402, the positive effect of neoadjuvant PCV on OS differed across molecular subgroups (Tables 2 and 3).[41,49] A significant benefit from the addition of PCV to RT was seen in patients with 1p19q-codel but not in those whose tumors did not have this molecular marker, taken as a group. Adding neoadjuvant PCV to RT significantly improved OS for patients with *IDH*-mut but not *IDH*-wt. For patients categorized using both 1p19q and *IDH* status, the addition of neoadjuvant PCV to RT significantly improved OS among patients with the *IDH*-mut+1p19q-codel tumor subtype, had a lesser effect on patients with *IDH*-mut and 1p19q intact or deletion of only 1p or 19q, and had no significant effect on patients with *IDH*-wt (1p19q intact or deletion of only 1p or 19q) tumors (Table 3).[41,49] Based on these results, neoadjuvant PCV plus RT is a category 1 recommendation for anaplastic oligodendroglioma (1p19q-codel; see top pathway on GLIO-2, page 1333), but a category 2A recommendation for anaplastic astrocytoma (1p19q intact or deletion of only 1p or 19q) and anaplastic oligoastrocytoma (NOS; see middle pathway on GLIO-2). In addition, these results support that external-beam RT alone is not listed as a recommended option for anaplastic oligodendroglioma (1p19q-codel) but is included as an option for anaplastic gliomas with 1p19q intact or deletion of only 1p or 19q, because the advantage of neoadjuvant PCV plus RT compared with RT alone is unclear or nonexistent in this group.

RT With Adjuvant PCV: The EORTC 26951 trial showed that RT followed by 6 cycles of PCV significantly improved PFS and OS compared with RT alone in a patient sample with histology-based anaplastic oligodendroglioma or anaplastic oligoastrocytoma (Table 2).[11,46,47] As in RTOG 9402, PCV was associated with higher rates of toxicity compared with RT alone. In EORTC 26951, PCV-associated

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Table 2. Key Randomized Trials Testing RT in Combination With PCV as Adjuvant Treatment for Anaplastic Glioma[a]

Trial	Patients Analyzed[a]	Adjuvant Treatment[b]	Efficacy Results[c]	Safety Results
RTOG 9402[41,48,49] Phase III RCT permuted block (ClinicalTrials.gov identifier: NCT00002569)	N=291 Age: median 43 y (range, 18–76 y) KPS ≥60 AA/AO/AOA: 0%/51%/49%	• PCV, then RT (n=148) • RT (n=143) Stratification: age, KPS, degree of anaplasia Follow-up: 11.3 y (range, 0.5–16.8 y)	PCV + RT improved outcome vs RT alone: • PFS: HR, 0.68; 95% CI, 0.53–0.88; *P*=.003 • OS: HR, 0.67; 95% CI, 0.50–0.91; *P*=.01 PCV improved OS in the following molecular subgroups: (see data in Table 3) • 1p19q-codel • *IDH*-mut • 1p19q-codel+*IDH*-mut	Failed to complete treatment: • PCV: 52% • RT: 10% vs 5%[d] Acute toxicities: • Grade 3/4 AEs during PCV vs during RT: 65% vs 7% Most PCV AEs were related to myelosuppression: • Grade 3/4 hematologic AEs during PCV vs during RT: 56% vs 2.2% Discontinuation due to toxicity, during PCV vs during RT: 20% vs 0%
EORTC 26951[11,46,47] Phase III RCT (ClinicalTrials.gov identifier: NCT00002840)	N=368 Age by arm: 49 vs 50 y (range, 19–69 y, for both) WHO ECOG PS: 0–2 AA/AO/AOA: 0%/72%/27%[e]	• RT + adjuvant PCV (n=185) • RT (n=183) Stratification: age, EOR, WHO ECOG PS, prior surgery for LGG Follow-up: 11.7 y	RT + adjuvant PCV improved outcome vs RT alone: • Median PFS: 24.3 vs 13.2 mo; HR, 0.66 (95% CI, 0.52–0.83); *P*=.0003 • Median OS: 42.3 vs 30.6 mo; HR, 0.75 (95% CI, 0.60–0.95); *P*=.018 Subgroups that tended to derive more benefit (OS, PFS) from PCV: (see data in Table 4) • *IDH*-mut (vs *IDH*-wt) • 1p19q-codel (vs 1p19q intact or only 1 deleted) • *MGMT* promotor methylated (vs unmethylated)	Failed to complete treatment: • PCV: 70% • RT: 5% PCV toxicities were primarily hematologic: • Grade 3 hematologic AEs: 32% • Grade 4 hematologic AEs: 14% PCV discontinuation due to toxicity: 38%
Medical Research Council Brain Tumor Working Party[50] RCT	N=113 Grade III[f] AA: all Age: median 53 y; 24% <45 y; 51% 45–59 y; 26% ≥60 to ≤70 y	• RT • RT then PCV Stratification: treatment center, age Follow-up: 3 y (1–8 y)	Nonsignificant trend toward PCV improving OS: HR, 0.86; 95% CI, 0.58–1.30	PCV toxicities were primarily hematologic

Abbreviations: 1p19q-codel, 1p and 19q codeleted; AA, anaplastic astrocytoma; AEs, adverse events; AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; EOR, extent of resection; HR, hazard ratio; GBM, glioblastoma; *IDH*-mut, mutation present in either *IDH1* or *IDH2*; *IDH*-wt, *IDH1* and *IDH2* are wild-type; KPS, Karnofsky performance status; LGG, low-grade glioma; OS, overall survival; PCV, procarbazine, lomustine, and vincristine; PFS, progression-free survival; PS, performance status; RCT, randomized controlled trial; RT, radiation therapy.

[a]Data are from patients with anaplastic glioma (grade III) unless otherwise noted. Subtype designation of AA, AO, and AOA are based on histology only (2007 WHO classification, not 2016 WHO). Percentage of patients with each of these subtypes is listed.

[b]Treatments listed were tested as postoperative adjuvant therapy. Separate treatment arms are listed as bullets. Stratification factors used for randomization are listed. Follow-up duration is reported as median (range).

[c]Unless otherwise noted, data are given for treatment arms in same order as bullets listed in the "Adjuvant Treatment" column.

[d]Percent of patients who started RT but failed to complete RT course, for PCV+RT arm vs RT arm.

[e]Histologic subtype missing in 1% of patients.

[f]This trial also included 449 patients with GBM and 32 patients with other grade III/IV tumors. Age and duration of follow-up are based on the total population (including patients with GBM). Efficacy data are from the 113 patients with AA.

Table 3. RTOG 9402: Benefit From Neoadjuvant PCV by Molecular Subtype[41]

		RT + Neoadjuvant PCV vs RT		
Molecular Markers	**Molecular Subtype**	**Median OS**	**HR (95% CI)**	***P* Value**
1p and 19q deletion	1p19q-codel	14.7 vs 7.3 y	0.59 (0.37–0.85)	.03
	1p19q intact or only 1p or 19q deleted	2.6 vs 2.7 y	0.85 (0.58–1.23)	.39
IDH mutation	*IDH*-mut	9.4 vs 5.7 y	0.59 (0.4–0.86)	.006
	IDH-wt	1.3 vs 1.8 y	1.14 (0.63–2.04)	.67
1p and 19q deletion and *IDH* mutation	1p19q-codel+*IDH*-mut	14.7 vs 6.8 y	0.49 (0.28–0.85)	.01
	1p19q intact or only 1p or 19q deleted + *IDH*-mut	5.5 vs 3.3 y	0.56 (0.32–0.99)	.045
	1p19q intact or only 1p or 19q deleted + *IDH*-wt	1.0 vs 1.3 y	0.99 (0.53–1.86)	.97

Abbreviations: 1p19q-codel, 1p and 19q codeleted; HR, hazard ratio; *IDH*-mut, mutation present in either *IDH1* or *IDH2*; *IDH*-wt, *IDH1* and *IDH2* are wild-type; OS, overall survival; PCV, procarbazine, lomustine, and vincristine; RT, radiation therapy.

toxicities led to discontinuation in 38% of all treated patients.[46] Based on the primary analysis of EORTC 26951, the NCCN Guidelines therefore recommend RT followed by PCV as a postoperative therapy option for any type of anaplastic glioma, provided that the patient has good performance status (KPS ≥60; see top 2 pathways on GLIO-2, page 1333). When selecting between neoadjuvant versus adjuvant PCV, many NCCN panel members prefer the latter because it appears to be better tolerated (there were 2 toxicity-related deaths among patients receiving the dose-intense schedule used for neoadjuvant PCV in RTOG 9402).

Analysis of outcomes for different molecularly defined subgroups in EORTC 26951 resulted in somewhat similar findings as for RTOG 9402, namely that benefit from adding PCV to RT was more pronounced in patients with 1p19q-codel (vs those with 1p19q intact or deletion of only 1p or 19q) and more common in cases with *IDH*-mut (vs wt) (Table 4).[11,47] In EORTC 26951, molecular subtype was responsible for statistically significant PCV-associated improvements in PFS, but the data for OS were less robust, particularly in the patient population with 1p19q intact or deletion of only 1p or 19q.

Both EORTC 26951 and RTOG 9402 only included patients with oligodendroglioma or oligoastrocytoma histology (≥25% oligodendroglioma component by histology).[46,48] Therefore, these trials did not include the bulk of grade III gliomas—those with pure astrocytoma histology. An older study conducted by the Medical Research Council Brain Tumour Working Party (MRC trial) is the only large randomized trial testing RT plus PCV (vs RT alone) in patients with anaplastic tumors that histologically appeared to be pure astrocytoma—tumors with mixed oligoastrocytoma histology were excluded from this trial (Table 2).[50] Analysis of the 113 patients with anaplastic astrocytoma showed a nonsignificant trend toward improved OS with RT plus PCV versus RT. Although analyses of molecular markers were not part of this trial, more recent data from studies of large populations suggest that anaplastic astrocytomas (so designated based on histology) nearly always have 1p19q intact or deletion of only 1p or 19q.[5,7,34,37] Therefore the mar-

Table 4. EORTC 26951: Benefit From Adjuvant PCV by Molecular Subtype[47]

		RT + Adjuvant PCV vs RT					
Molecular Markers	**Molecular Subtype**	**Median OS**	**HR (95% CI)**	***P* Value**	**Median PFS**	**HR (95% CI)**	***P* Value**
1p and 19q deletion	1p19q-codel	NR vs 111.8 mo	0.56 (0.31–1.03)	.059[a]	156.8 vs 49.9 mo	0.42 (0.24–0.74)	.002
	1p19q intact or only 1p or 19q deleted	25.0 vs 21.1 mo	0.83 (0.62–1.10)	.185[a]	14.8 vs 8.7 mo	0.73 (0.56–0.97)	.026
IDH mutation	*IDH*-mut	NR vs 64.8 mo	0.53 (0.30–0.95)		71.2 vs 36 mo	0.49 (0.29–0.84)	
	IDH-wt	19.0 vs 14.7 mo	0.78 (0.52–1.18)		10.0 vs 6.8 mo	0.56 (0.37–0.86)	

Abbreviations: 1p19q-codel, 1p and 19q codeleted; HR, hazard ratio; *IDH*-mut, mutation in either *IDH1* or *IDH2*; *IDH*-wt, *IDH1* and *IDH2* are wild-type; NR, not reached; OS, overall survival; PCV, procarbazine, lomustine, and vincristine; PFS, progression-free survival; RT, radiation therapy.
[a]Magnitude of improvement in OS from adding adjuvant PCV to RT was not significantly different for the group with 1p19q-codel vs the group with 1p19q intact or only 1p or 19q deleted.

ginal effect of adding adjuvant PCV to RT in this population of histology-based astrocytomas is consistent with the results from EORTC 26951 showing a small PCV effect with borderline significance in patients with 1p19q intact or deletion of only 1p or 19q (Table 4).

Taken together, these results support the following NCCN recommendations for patients with anaplastic glioma and good performance status (who can tolerate RT plus chemotherapy combinations): (1) for those with 1p19q-codel tumors (ie, oligodendrogliomas per 2016 WHO classification), RT plus adjuvant PCV is a category 1 recommendation, but RT alone is not recommended because it is associated with poorer outcomes; and (2) for those with tumors lacking 1p19q-codel (ie, astrocytomas per 2016 WHO classification), RT plus adjuvant PCV and RT alone are both category 2A recommended options. RT alone is no longer a category 1 option because results from RTOG 9402 and EORTC 26951 showed that in this subpopulation, RT alone did not result in better outcomes than combination RT plus PCV (Tables 3 and 4), and the MRC trial results suggest that this is true for tumors with 1p19q intact or deletion of only 1p or 19q, regardless of histologic phenotype.[50] In fact, data from all 3 trials show a small trend in favor of RT plus PCV in this subgroup previously thought to be insensitive to chemotherapy.

Combination Therapy: RT Plus TMZ

For treatment of anaplastic glioma in patients with good performance status (KPS ≥60), updates to the NCCN Guidelines have clarified the recommended regimen for combination therapy with RT plus TMZ as "fractionated external-beam RT *with concurrent* and *adjuvant* TMZ" (see top 2 pathways on GLIO-2, page 1333). This recommendation was largely based on extrapolation from results of the EORTC 26981-22981/NCIC CE3 multicenter international phase III randomized controlled trial in glioblastoma showing that RT with concurrent and adjuvant TMZ improved OS and PFS compared with RT alone,[51] because until very recently there were no data from randomized controlled trials evaluating whether addition of TMZ to RT provides any clinical benefit in anaplastic gliomas.

Table 5 summarizes the study design and recently reported results from phase III trials testing TMZ as part of postoperative adjuvant treatment for anaplastic gliomas. Three of these trials tested RT in combination with TMZ in patients with anaplastic glioma. The Nordic Clinical Brain Tumor Study Group (NCBTG) trial showed that for patients treated with RT with or without concurrent TMZ, the addition of neoadjuvant TMZ improved outcomes for anaplastic astrocytomas.[52] Although the sample size was small (N=41), the NCCN Panel considers these results supportive of the idea that adding TMZ to RT potentially provides clinical benefit for patients with anaplastic astrocytomas. Prospective trial data from a larger sample size of patients with anaplastic gliomas would be needed to support neoadjuvant TMZ plus RT as a recommended option in the NCCN Guidelines. RTOG 9813 showed that for patients with anaplastic astrocytomas, RT with concurrent TMZ results in similar outcomes as RT with concurrent nitrosourea, with perhaps slightly better PFS with TMZ.[43] As expected, the toxicity of nitrosourea was far worse than for TMZ, and resulted in higher rates of discontinuation due to toxicity. Because of increased toxicity and no improvement in outcomes (relative to RT plus TMZ), the RT plus nitrosourea regimen used in RTOG 9813 is not recommended in the NCCN Guidelines for treatment of anaplastic astrocytomas. The ongoing CATNON phase III randomized trial is testing RT alone and 3 different RT plus TMZ combination regimens (Table 5) in patients with anaplastic astrocytoma. A recently published interim analysis showed that adjuvant TMZ significantly improved PFS and OS.[53] Further follow-up is needed to determine whether TMZ concurrent with RT provides any clinical benefit, and which of the 3 RT plus TMZ combination regimens provides the best outcomes.

Monotherapy: RT, PCV, TMZ

For patients with anaplastic gliomas and poor performance status, treatment options recommended in the NCCN Guidelines are limited to single-modality therapies due to concerns about the ability of these patients to tolerate the toxicity associated with combination regimens. Table 5 summarizes the design and results from the NOA-04 phase III randomized trial comparing single-modality treatment options in patients with anaplastic glioma. Results from this trial showed no significant differences in outcomes for patients with anaplastic gliomas treated with

Table 5. Key Randomized Trials Testing TMZ in Adjuvant Treatment for Anaplastic Glioma[a]

Trial	Patients Analyzed[a]	Adj Treatment[b]	Efficacy Results[c]	Safety/HRQoL Results[c]
NOA-04[10,54] Phase III RCT, OL (ClinicalTrials.gov identifier: NCT00717210)	N=318; 274 in ITT AA/AO/AOA: 53%/33%/14% Age: 20–77 y KPS ≥70	• Standard RT (n=160); chemotherapy on progression • PCV (n=78); RT on progression • TMZ (n=80); RT on progression Follow-up: 9.5 y	RT vs PCV/TMZ: no effect on outcome (PFS, OS) • Median PFS: 2.5 vs 2.6 y • Median OS: 8 vs 6.5 y • No treatment-related differences in PFS or OS for any histologic or molecular subgroup (based on 1p19q deletion, *IDH* mutation, or *MGMT* promotor methylation) PCV vs TMZ: no effect on PFS except in *IDH*-mut+1p19q-codel subgroup • Median PFS: 2.52 vs 2.71 y (NS) ➤ *IDH*-mut+1p19q-codel: 9.4 vs 4.5 y (*P*=.0254) ➤ *IDH*-mut+1p19q intact or only 1p or 19q deleted, *IDH*-wt: difference NS between PCV and TMZ	• More toxicity with PCV/TMZ than RT: ➤ 39% vs 12% during first-line treatment ➤ 75% vs 45% during treatment for progression • More toxicity with PCV than TMZ
Nordic Clinical Brain Tumor Study Group[52] Phase III RCT ISRCTN45209900	N=41[d] Age: 27–60 y WHO PS 0–2 AA/AO/AOA: 100%/0%/0%	• Neoadjuvant TMZ followed by RT (n=21; 16 with concurrent TMZ) • RT only (n=20; 13 with concurrent TMZ) Stratification: center Follow-up: 20 mo	Neoadjuvant TMZ improves survival: Median OS: 95.1 vs 35.2 mo; HR, 0.41 (95% CI, 0.19–0.90); *P*=.022	Failed to complete treatment: • Neoadjuvant TMZ: 2 (10%) of 21 • RT: 0/21 vs 1/19[e]
NRG oncology/RTOG 9813[43] Phase III RCT Multicenter (ClinicalTrials.gov identifier: NCT00004259)	N=201; 196 ITT Age: 18–80 y KPS: ≥60 AA/AO/AOA: 97%/0%/3% AOA had ≤25% oligodendroglial component	• RT + concurrent TMZ (n=97) • RT + concurrent nitrosourea (carmustine or lomustine; n=99) Stratification: Age, KPS, extent surgery Follow-up: 10.1 y	Similar outcomes for TMZ vs nitrosourea: • Median OS: 3.9 vs 3.8 y (NS by UV or MV) • Median PFS: NS by UV but borderline significance by MV favoring TMZ: HR, 0.70 (95% CI, 0.5–0.98); *P*=.039	Failed to complete treatment: • TMZ vs nitrosourea: 40% vs 79% (*P*<.001) ➤ Due to toxicity: 0% vs 28% (*P*<.001) Grade ≥3 toxicity: 48% vs 76% (*P*<.001); mostly related to myelosuppression • Nonhematologic: 32% vs 34%
CATNON Intergroup trial (EORTC 26053-22054)[53] Phase III RCT, OL 2x2 factorial (ClinicalTrials.gov identifier: NCT00626990)	N=745 Age: 18–83 y WHO PS 0–2 AA/AO/AOA: 77%/0%/23% All 1p19q intact or only 1p or 19q deleted[f]	• RT alone (n=187) • RT + adj TMZ (n=185) • RT + concurrent TMZ (n=185) • RT + concurrent and adj TMZ (n=188) Stratification: institution, PS, age, 1p loss of heterozygosity, ODG elements on microscopy, *MGMT* methylation Follow-up: 27 mo	Adj TMZ (n=373) improved outcomes vs with no adj TMZ (n=372): • OS: ➤ Median: NR vs 41 mo ➤ 5-y: 56% vs 44% ➤ UV: HR, 0.67 (95% CI, 0.51–0.88) ➤ MV: HR, 0.65 (95% CI, 0.45–0.93); *P*=.0014 • PFS: ➤ Median: 43 vs 19 mo ➤ 5-y: 43% vs 24% ➤ UV: HR, 0.62 (95% CI, 0.5–0.76)	Failed to complete treatment: • RT (any arm): 16 (2%) of 733 • Adj TMZ: 106 (31%) of 343; reasons: ➤ PD/death: 56 (16%) ➤ Toxicity: 30 (9%) Grade 3/4 AEs with TMZ: 8%–12% of 549, mainly hematologic and reversible; thrombocytopenia the most frequent (7%–9%)

Abbreviations: 1p19q-codel, 1p and 19q codeleted; AA, anaplastic astrocytoma; adj, adjuvant; AEs, adverse events; AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; HR, hazard ratio; HRQoL, health-related quality of life; *IDH*-mut, *IDH1* or *IDH2* mutated; *IDH*-wt, *IDH1* and *IDH2* wildtype; ITT, intent-to-treat; KPS, Karnofsky performance status; MV, multivariate analysis (results); NR, not reached; NS, not statistically significant; OL, open-label; OS, overall survival; PCV, procarbazine, lomustine, and vincristine; PD, progressive disease; PFS, progression-free survival; PS, performance status; RCT, randomized controlled trial; RT, radiation therapy; TMZ, temozolomide; UV, univariate analysis (results).

[a]Data are from patients with anaplastic glioma (grade III) unless otherwise noted. Subtype designation of AA, AO, and AOA are based on histology only (ie, 2007 WHO, not 2016 WHO classification). Percentage of patients with each of these subtypes is listed.

[b]Treatments listed were tested as postoperative adj therapy. Separate treatment arms are listed as bullets. Stratification factors used for randomization are listed. Duration follow-up is reported as median.

[c]Unless otherwise noted, data is given for treatment arms in same order as bullets listed in the "Adj Treatment" column.

[d]This trial also enrolled 103 patients with glioblastoma. Data shown here are from the subanalysis of 41 patients with AA.

[e]Of patients who started RT, the number who did not finish the RT course, for the neoadjuvant TMZ+RT arm vs the RT only arm.

[f]All patients in the CATNON trial did not have 1p19q-codel, and therefore meet the 2016 WHO criteria for designation as astrocytoma.

PCV or TMZ or RT alone, both for the whole population and within various histologic and molecular subgroups.[10] The one exception was that PCV provided better PFS than TMZ in patients with *IDH*-mut+1p19q-codel. The application of this result to the recommendation for patients with poor performance status is limited by the fact that NOA-04 included KPS ≥70 as eligibility criteria.[54] Nonetheless, these results support that RT alone or TMZ or PCV are all reasonable options in terms of efficacy for patients opting for single-modality treatment. As expected, toxicity associated with chemotherapy was worse than that for RT, and adverse event rates were higher for PCV compared with TMZ. Because of the increased toxicity of chemotherapy compared with RT, chemotherapy alone (PCV or TMZ) is a category 2B option for patients with anaplastic gliomas and poor performance status (see bottom pathway on GLIO-2, page 1333), and this option was removed as a recommendation for patients with anaplastic astrocytoma/oligoastrocytoma and good performance status (middle pathway on GLIO-2).

Summary and Conclusions

Data emerging in the past few years have led to significant changes in the diagnosis, categorization, and treatment of anaplastic glioma brain tumors. Molecular markers have now been identified that provide diagnostic information as well as information about overall prognosis and responses to specific treatments. Data from randomized controlled trials have shown that the addition of PCV to RT improves outcomes in patients with anaplastic glioma and good performance status, particularly those whose tumors are 1p19q-codel. For tumors without 1p19q-codel (ie, anaplastic astrocytomas), data from an ongoing randomized controlled trial suggest that the addition of TMZ to RT improves outcomes, and longer follow-up may help discern the optimal protocol for this combination therapy. Data from randomized studies are needed to determine whether RT plus TMZ, which is generally better tolerated than PCV, will result in equivalent or improved outcomes compared with RT plus PCV in the treatment of grade II/III gliomas.

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Posttest Questions

1. A 60-year-old woman is diagnosed with an anaplastic glioma based on pathology after gross total resection. If she has good PS, what molecular tests are needed to determine her adjuvant treatment options (per the NCCN Guidelines)?
   a. 1p deletion status
   b. 1p and 19q deletion status
   c. 1p and 19q deletion status and *IDH1* and *IDH2* mutation status
   d. 1p and 19q deletion status, *IDH1* and *IDH2* mutation status, and *MGMT* promoter methylation status

2. True or False: Per the NCCN Guidelines recommendations, combination therapy with RT and chemotherapy is recommended for anaplastic gliomas, regardless of molecular phenotype, histologic phenotype, or patient PS.

3. For patients with anaplastic astrocytomas (per 2017 WHO classification) and good PS, which of the following postoperative adjuvant treatments are recommended?
   1. PCV alone
   2. TMZ alone
   3. Standard fractionated RT alone
   4. Standard fractionated RT + PCV
   5. Standard fractionated RT + neoadjuvant TMZ
   6. Standard Fractionated RT + concurrent and adjuvant TMZ

   There is only one correct answer:
   a. 1, 2, and 3
   b. 3, 5, and 6
   c. 3, 4, and 6
   d. 3, 4, 5, and 6