

**Kriterien zur Bestimmung der zweckmäßigen
Vergleichstherapie**

und

**Recherche und Synopse der Evidenz zur Bestimmung der
zweckmäßigen Vergleichstherapie nach § 35a SGB V**

und

**Schriftliche Beteiligung der wissenschaftlich-medizinischen
Fachgesellschaften und der Arzneimittelkommission der
deutschen Ärzteschaft (AkdÄ) zur Bestimmung der
zweckmäßigen Vergleichstherapie nach § 35a SGB V**

Vorgang: 2026-B-113 Vorasidenib

Stand: Juli 2026

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 Verfo G-BA

Vorasidenib

[zur Behandlung des Oligodendroglioms oder Astrozytoms nach Resektion]

Kriterien gemäß 5. Kapitel § 6 Verfo

Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.

Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.

Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.

- Chirurgische Resektion

Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen

Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:

- Vorasidenib (Beschluss am 07. Mai 2026)
- Dabrafenib in Kombination mit Trametinib (Beschlüsse am 17. Oktober 2024)

Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.

Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff ATC-Code Handelsname	Anwendungsgebiet (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Vorasidenib L01XX62 Vorango	<u>Zugelassenes Anwendungsgebiet:</u> Vorango als Monotherapie wird angewendet zur Behandlung von überwiegend nicht kontrastmittelanreichernden Grad 2 Astrozytomen oder Oligodendrogliomen mit einer IDH1-R132-Mutation oder einer IDH2-R172-Mutation bei erwachsenen und jugendlichen Patienten ab 12 Jahren und einem Gewicht von mindestens 40 kg, die nur chirurgische Intervention hatten und keine unmittelbare Strahlen- oder Chemotherapie benötigen
Dabrafenib L01EC02 Finlee	<u>Niedriggradig malignes Gliom</u> Finlee in Kombination mit Trametinib wird angewendet zur Behandlung von pädiatrischen Patienten ab einem Alter von 1 Jahr mit einem niedriggradig malignen Gliom (low-grade glioma, LGG) mit einer BRAF-V600E-Mutation, <u>die eine systemische Therapie benötigen.</u>
Trametinib L01EE01 Spexotras	<u>Niedriggradig malignes Gliom</u> Spexotras in Kombination mit Dabrafenib wird angewendet zur Behandlung von pädiatrischen Patienten ab einem Alter von 1 Jahr mit einem niedriggradig malignen Gliom (low-grade glioma, LGG) mit einer BRAF-V600E-Mutation, <u>die eine systemische Therapie benötigen.</u>

Quellen: AMLce-Datenbank, Fachinformationen

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2026-B-113 (Beratung nach § 35a SGB V)

Vorasidenib

Auftrag von: Abt. AM
Bearbeitet von: Abt. FB Med
Datum: 19. Juni 2026

Inhaltsverzeichnis

Abkürzungsverzeichnis	3
1 Indikation	4
2 Systematische Recherche	4
3 Ergebnisse	5
3.1 Cochrane Reviews	5
3.2 Systematische Reviews	5
3.3 Leitlinien	6
4 Detaillierte Darstellung der Recherchestrategie	20
Referenzen	23

Abkürzungsverzeichnis

AANS	American Association of Neurological Surgeons
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECRI	Emergency Care Research Institute
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
KPS	Karnofsky Performance Status
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall Survival
PCV	Procarbazin, Lomustin und Vincristin
PFS	Progression-Free Survival
RR	Relatives Risiko
RT	Radiotherapie
SIGN	Scottish Intercollegiate Guidelines Network
TMZ	Temozolomid
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von Astrozytomen oder Oligodendrogliomen Grad 2 mit einer IDH1-R132- oder IDH2-R172-Mutation bei erwachsenen und jugendlichen Patienten ab 12 Jahren und einem Körpergewicht von mindestens 40 kg, die ausschließlich chirurgisch behandelt wurden und keine unmittelbare Strahlen- oder Chemotherapie benötigen.

Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Astrozytome und Oligodendrogliome* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: *The Cochrane Library (Cochrane Database of Systematic Reviews)*, *PubMed*. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (<https://www.google.com/>) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 02.06.2026 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 1893 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Alle eingeschlossenen Referenzen wurden im Volltext beschafft. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen im Volltext gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet.

Basierend darauf wurden insgesamt 3 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine geeigneten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine geeigneten systematischen Reviews identifiziert.

3.3 Leitlinien

Platzhalter für dt. Leitlinien der AWMF:

Es liegt eine Anmeldung für eine S1-Leitlinie der AWMF zu Gliomen niedrigen Malignitätsgrades im Kindes- und Jugendalter vor (AWMF-Registernummer 025-024). Die geplante Fertigstellung ist auf den 30.06.2026 datiert. Zudem wurde eine S2k-Leitlinie der AWMF zu Gliomen identifiziert (AWMF-Registernummer 030-099), die am 31.12.2025 abgelaufen ist. Daher sind die Empfehlungen dieser Leitlinie als nicht mehr gültig einzustufen und werden entsprechend nicht in die vorliegende Evidenzsynopse einbezogen.

Mohile NA et al., 2022 [2, 3].

American Society of Clinical Oncology (ASCO) and Society for Neuro-Oncology (SNO)

Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults

Zielsetzung/Fragestellung

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

MethodikGrundlage der Leitlinie

- Repräsentatives Gremium mit Patientenvertretung sowie mit methodischer Expertise.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche (siehe *sonstige methodische Hinweise*), Auswahl und Bewertung der Evidenz.
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- PubMed published between January 1, 2001, and August 17, 2020
- 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
- ClinicalTrials.gov to identify ongoing and unpublished trials

LoE/GoR

- Randomized trial quality was assessed using methods based on the Cochrane Risk of Bias tool.
- The guideline recommendations were crafted, in part, using the Guidelines Into Decision Support methodology.

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.

Sonstige methodische Hinweise

- Die systematische Literaturrecherche erfolgte lediglich in einer Datenbank (PubMed). Dadurch könnte die Vollständigkeit der Literatur eingeschränkt sein.
- Es liegt ein Rapid Recommendation Update von April 2025 als Ergänzung zur Originalleitlinie von 2022 vor. Empfehlungen dieses Updates werden nachfolgend ebenfalls dargestellt und entsprechend gekennzeichnet.

Empfehlungen

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*).

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 ¹³

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*).

Updated Recommendation 1.2 (2025)

Within the group of people with oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 2, initial radiation therapy and chemotherapy (with PCV or temozolomide) may be deferred until radiographic or symptomatic progression in some people with favorable prognostic factors (eg, complete resection and younger age) or concerns about toxicity. See the Clinical Interpretation section (in the original publication) for more details (*Evidence quality: Low; Strength of recommendation: Conditional*).

New Recommendation 1.2.1 (2025)

Voridasenib may be offered to people with oligodendroglioma, IDH-mutant, 1p19q codeleted, CNS WHO grade 2, where, after one or more surgeries, further treatment with radiation and chemotherapy has been or can be deferred (*Evidence quality: High; Strength of recommendation: Conditional*).

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*).

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 ^[66]
	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 ^[65]

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*).

New Recommendation 1.5.1 (2005)

Voridasenib may be offered to people with astrocytoma, IDH-mutant, 1p19q non-codeleted, CNS WHO grade 2, where, after one or more surgeries, further treatment with radiation and chemotherapy has been or can be deferred (*Evidence quality: High; Strength of recommendation: Conditional*).

Hintergrundinformation:

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 al⁵⁵ 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 lowgrade 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 trial⁶⁷ and the NCCTG 86-72-51 trial⁵⁹ 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 trial⁷⁰ 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 trial⁷¹ and RTOG 9402 trial⁷² 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 trial⁷² 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 trial⁷¹ found a significant 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**.

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.

^aMedian OS data from 2013 paper and OS rate data from 2006 paper.

^bPFS data from 2006 article. The 2013 article indicates updated PFS data is online, but online appendix no longer available.

Temozolomide. The CATNON trial⁵³ (748 patients) and the smaller KNOG-1101 trial⁵⁷ (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 2017⁵³ 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 trial⁷⁵ 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 trial⁵⁴ 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 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.

Clinical interpretation (Recommendation 1.1 – 1.3). 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 IDHmutant, 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 trial⁵⁶ 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).

Clinical interpretation (Recommendation 1.4 – 1.6). 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 trial⁵³ 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.

Discussion Rapid Recommendation Update 2025. The new literature search identified 688 potential articles, of which 62 were reviewed in full text. Sixteen new publications for previously identified trials and 27 new publications of 26 previously unknown trials were located. Of these, only one trial was identified

that was relevant to the specific subpopulation addressed in this rapid update: the INDIGO trial.³ The remaining trials are briefly summarized in the Supplement. None of the other trials were considered to require a rapid recommendation update to the original guideline recommendations. [...]

The benefits in terms of PFS and time to next intervention with vorasidenib versus observation outweigh the increased frequency of adverse events for many patients. Regular monitoring for liver function is necessary every 2 weeks in the first 2 months of treatment and monthly thereafter. People who are seeking pregnancy as either father or mother and people who are pregnant or breast feeding should not be offered vorasidenib. The Panel notes that the FDA approval and the INDIGO trial itself included patients as young as age 12 years; the ASCO-SNO guideline and this update only address adult patients.

The regulatory approval of vorasidenib in the United States has several differences to the trial inclusion and exclusion criteria that warrant discussion.

- The trial required measurable disease assessed by magnetic resonance imaging (MRI) to determine the effect of vorasidenib on measurable tumor size; the approval allows patients to have had gross total resection. Patients without measurable tumor and their clinicians should carefully weigh the potential but uncertain benefits of beginning vorasidenib immediately versus continued observation until there is documented measurable tumor to allow for monitoring for response.
- The trial required patients to wait at least 1 year and no more than 5 years after surgery to determine the effect of vorasidenib on tumor growth rate before and then during treatment; the approval does not include this restriction. The panel believes this time window is arbitrary, and that it is reasonable to discuss vorasidenib at any time point after postoperative recovery.
- The trial only included patients with residual or recurrent disease who had received no previous nonsurgical therapy. This restriction on previous nonsurgical therapy is not mentioned in the approval. There are currently no randomized data from INDIGO or any other trial on the use of vorasidenib in patients who have received previous radiation and/or chemotherapy. The panel cannot make a recommendation about vorasidenib in those patients.
- The trial excluded patients based on criteria that may increase the patient's risk of progression or recurrence, such as measurable or nodular contrast enhancement on brain computed tomography and/or MRI, uncontrolled seizures, and brain-stem involvement. None of these factors are mentioned in the approval. There are currently inadequate data on the use of vorasidenib in these patients, and the panel cannot make a recommendation about vorasidenib in those patients. Patients with grade 3 or 4 disease are outside the scope of this rapid update and were not included in the INDIGO trial.

Referenzen

53. van den Bent MJ, Baumert B, Erridge SC, et al: Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: A phase 3, randomised, open-label intergroup study. *Lancet* 390:1645-1653, 2017
55. van den Bent MJ, Afra D, de Witte O, et al: Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: The EORTC 22845 randomised trial. *Lancet* 366:985-990, 2005
56. van den Bent MJ, Carpentier AF, Brandes AA, et al: Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: A randomized European Organisation for Research and Treatment of Cancer phase III trial. *J Clin Oncol* 24:2715-2722, 2006
57. Hwang K, Kim TM, Park CK, et al: Concurrent and adjuvant temozolomide for newly diagnosed grade III gliomas without 1p/19q co-deletion: A randomized, open-label, phase 2 study (KNOG-1101 study). *Cancer Res Treat* 52:505-515, 2020
58. Medical Research Council Brain Tumor Working Party: Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: A Medical Research Council trial. *J Clin Oncol* 19:509-518, 2001
59. Shaw E, Arusell R, Scheithauer B, et al: Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: Initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. *J Clin Oncol* 20: 2267-2276, 2002

60. Breen WG, Anderson SK, Carrero XW, et al: Final report from Intergroup NCCTG 86-72-51 (Alliance): A phase III randomized clinical trial of high-dose versus low-dose radiation for adult low-grade glioma. *Neuro Oncol* 22:830-837, 2020
61. Wick W, Hartmann C, Engel C, et al: NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. *J Clin Oncol* 27:5874-5880, 2009
62. Cairncross G, Berkey B, Shaw E, et al: Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. *J Clin Oncol* 24:2707-2714, 2006
63. Shaw EG, Wang M, Coons SW, et al: Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: Initial results of RTOG 9802. *J Clin Oncol* 30:3065-3070, 2012
64. van den Bent MJ, Klein M, Smits M, et al: Bevacizumab and temozolomide in patients with first recurrence of WHO grade II and III glioma, without 1p/19q codeletion (TAVAREC): A randomised controlled phase 2 EORTC trial. *Lancet Oncol* 19:1170-1179, 2018
65. Brada M, Stenning S, Gabe R, et al: Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. *J Clin Oncol* 28: 4601-4608, 2010
66. Wick W, Platten M, Meisner C, et al: Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: The NOA-08 randomised, phase 3 trial. *Lancet Oncol* 13:707-715, 2012
67. Ali AN, Zhang P, Yung WKA, et al: NRG oncology RTOG 9006: A phase III randomized trial of hyperfractionated radiotherapy (RT) and BCNU versus standard RT and BCNU for malignant glioma patients. *J Neurooncol* 137:39-47, 2018
68. Solomon MT, Selva JC, Figueredo J, et al: Radiotherapy plus nimotuzumab or placebo in the treatment of high grade glioma patients: Results from a randomized, double blind trial. *BMC Cancer* 13:299, 2013
69. Buckner JC, Shaw EG, Pugh SL, et al: Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med* 374:1344-1355, 2016
70. Bell EH, Zhang P, Shaw EG, et al: Comprehensive genomic analysis in NRG oncology/RTOG 9802: A phase III trial of radiation versus radiation plus procarbazine, lomustine (CCNU), and vincristine in high-risk low-grade glioma. *J Clin Oncol* 38:3407-3417, 2020
71. van den Bent MJ, Brandes AA, Taphoorn MJ, et al: Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: Long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol* 31:344-350, 2013
72. Cairncross G, Wang M, Shaw E, et al: Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: Long-term results of RTOG 9402. *J Clin Oncol* 31: 337-343, 2013
73. Dubbink HJ, Atmodimedjo PN, Kros JM, et al: Molecular classification of anaplastic oligodendroglioma using next-generation sequencing: A report of the prospective randomized EORTC Brain Tumor Group 26951 phase III trial. *Neuro Oncol* 18:388-400, 2016
74. van den Bent MJ, Tesileanu CMS, Wick W, et al: Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): Second interim analysis of a randomised, open-label, phase 3 study. *Lancet Oncol* 22:813-823, 2021
75. Jaeckle KA, Ballman KV, van den Bent M, et al: CODEL: Phase III study of RT, RT 1 Temozolomide (TMZ), or TMZ for newly-diagnosed 1p/19q Codeleted Oligodendroglioma. Analysis from the initial study design. *Neuro Oncol* 23:457-467, 2021

Alberta Health Services, 2026 [1].

IDH-mutant CNS WHO grade 2 and 3 gliomas

Zielsetzung/Fragestellung

- Is resection better than biopsy in the management of WHO grade 2 and grade 3 gliomas?
- What is the optimal radiation therapy plan for WHO grade 2 and grade 3 gliomas?
- What is the role of radiation and chemotherapy in the adjuvant treatment of WHO grade 2 and grade 3 gliomas?

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz, dem spezifischen Fokus auf IDH-mutierte, niedriggradige Gliome sowie der Aktualität der Leitlinie wird diese jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium mit methodischer Expertise, Patientenvertretung unklar.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche und Auswahl der Evidenz, systematische Bewertung der Evidenz unklar (siehe methodische Hinweise).
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- The PubMed database was searched for relevant studies, guidelines and consensus documents published up to December 2023.
- Online resources from oncology-based health organizations and guideline developers were also systematically searched and relevant guidelines from the following organizations were considered in the development of our recommendations: American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), Society for Neuro-Oncology (SNO) and the National Comprehensive Cancer Network (NCCN).

LoE/GoR

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Sonstige methodische Hinweise

- Aus der Tabelle zu den Levels of Evidence geht hervor, dass bei der Evidenzbewertung auch das Verzerrungspotenzial (Risk of Bias) berücksichtigt wurde. Es bleibt jedoch unklar, nach welcher Methodik die Bewertung des Verzerrungspotenzials bzw. der Vertrauenswürdigkeit der Evidenz erfolgte (z.B. mittels Cochrane RoB-2-Tool, GRADE oder vergleichbarer Methoden). Damit ist eine ausreichend umfassende und systematische Qualitätsbewertung möglicherweise nicht sichergestellt.
- Die Literaturrecherche erfolgte in lediglich einer Datenbank (PubMed). Dadurch könnte die Vollständigkeit der Literatur eingeschränkt sein.

Empfehlungen

Treatment: IDH-mutant, CNS WHO Grade 2 Astrocytoma^{4,5}

Surgical Intervention: *(Level of evidence: I, Strength of recommendation: A)^{5,7}*

4. Surgery is recommended as the first-line treatment for presumed gliomas, encompassing tumour diagnosis, biopsy or resection for symptom relief, and tissue collection (including tumour banking) for research.

5. Maximal safe resection of the tumour is recommended. Repeat surgery may be necessary following an initial biopsy for a resectable lesion. For patients with WHO grade 2 astrocytoma and a gross total resection, surveillance after maximal safe resection may be appropriate if no high-risk factors are present.

Radiation Therapy (RT):^{4,6} *(Level of evidence: II, Strength of recommendation: B)⁸⁻¹⁰*

6. Based on extrapolation from CATNON, RT with sequential chemotherapy is recommended for high-risk WHO grade 2 astrocytomas.⁸

- High-risk prognostic factors include Subtotal resection, age ≥ 40 , tumour size ≥ 4 -6 cm, tumour crosses midline, refractory seizures or presurgical neurologic symptoms from tumour.
- Treatment planning – A dose of 50.4 to 54 Gy delivered in 28 to 30 fractions is recommended.
- A referral for proton beam radiation therapy can be considered after consulting the proton beam referral guidelines if the patient is eligible.

Chemotherapy: *(Level of evidence: II, Strength of recommendation: B)^{8,11,12}*

7. Approximately 1 month after the completion of radiation therapy, adjuvant chemotherapy with temozolomide (150-200 mg/m²) given orally once daily for 5 days every 4 weeks for twelve cycles is recommended.

8. Alternatively, PCV may be used instead of temozolomide for adjuvant chemotherapy (procarbazine 60 mg/m² orally once daily on days 8 to 21, lomustine 110 mg/m² orally once daily on day 1, and vincristine 1.4 mg/m² IV once daily on days 8 and 29 every six to eight weeks for a total of six cycles).⁵

9. Vorasidenib may be offered to patients with non-enhancing astrocytoma, IDH-mutant, 1p19q non-codeleted, CNS WHO grade 2, where, after one or more surgeries, further treatment with radiation and chemotherapy has been or can be deferred.⁵ *This drug is not currently covered on the Alberta Outpatient Cancer Drug Benefit Program.*

IDH-mutant, CNS WHO Grade 2 Oligodendroglioma

(Level of evidence: II, Strength of recommendation: B)^{8-10,13}

14. For patients with oligodendroglioma, IDH-mutant, WHO grade 2 with high-risk features, radiation therapy followed by adjuvant PCV is recommended. The CCTG CEC6 clinical trial was designed to address this question of adjuvant PCV vs TMZ, but the trial is closed, and data has not been presented yet. In that study, TMZ was given concurrently with radiation therapy followed by adjuvant TMZ.

15. TMZ is a reasonable alternative to PCV when toxicity is a concern.

16. High-risk prognostic factors include: subtotal resection, age ≥ 40 , tumour size ≥ 4 -6 cm, tumor crosses midline, refractory seizures or presurgical neurologic symptoms from tumour. For patients with WHO grade 2 oligodendroglioma who are under the age of 40, have had a gross total resection, and/or have low-risk prognostic factors as defined above, adjuvant therapy may be deferred post-resection until radiographic or symptomatic progression.

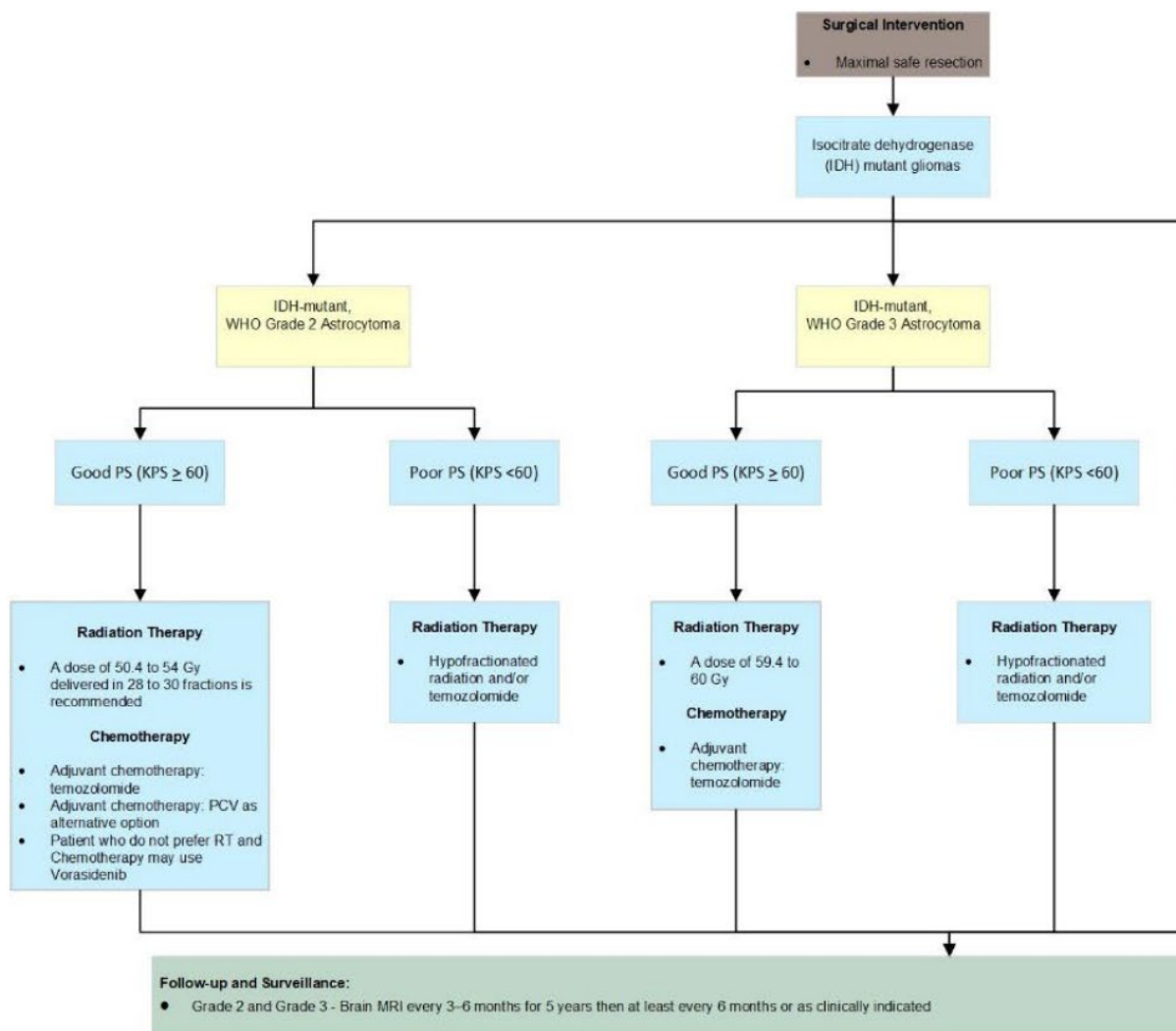
17. Vorasidenib may be offered to patients with non-enhancing CNS WHO grade 2, IDH-mutant, 1p/19q codeleted oligodendroglioma, where, after one or more surgeries, further treatment with radiation and chemotherapy has been or can be deferred.¹³ This drug is not currently covered on the Alberta Outpatient Cancer Drug Benefit Program.

18. A referral for proton beam radiation therapy can be considered after consulting the proton beam referral guidelines if the patient is eligible. Proton Beam Radiation Therapy Guideline

Follow-up and Surveillance

21. The following schedule should be considered to manage complications related to treatment, to detect disease recurrence and/or the development of new disease:

- *WHO grade 2 and WHO grade 3 IDH-mutant glioma* - Brain MRI every 3–6 months for 5 years then at least every 6 months or as clinically indicated.⁶
- *WHO Grade 4, IDH-mutant glioma* - Brain MRI 4–8 weeks after standard radiation therapy, then every 2–4 months for 3 years, then every 3–6 months indefinitely.⁶



Hintergrundinformation:

Based on the most recent WHO classification, IDH-mutant astrocytomas do not have a 1p/19q codeletion and are subdivided into WHO grade 2 (formerly diffuse astrocytoma), WHO grade 3 (formerly anaplastic astrocytoma), and CNS WHO grade 4 (previously known as IDH-mutant glioblastoma).^{3,14,15} Oligodendrogliomas have a 1p/19q codeletion which is subdivided into WHO grade 2 and WHO grade 3. Younger age and better performance status at diagnosis are major therapy-independent prognostic factors associated with favourable outcomes in adults with glioma.¹⁶

Surgery. Surgery is the first step in the treatment of gliomas and maximum safe resection is the preferred surgical approach. The majority of observational studies demonstrate an association between a higher extent of resection and prolonged tumor control and survival.¹⁷ The study by Jakola et al. also suggested that early surgical resection resulted in a clinically relevant survival benefit.⁷

Radiotherapy. The goal of radiotherapy (RT) is to improve overall survival without inducing neurotoxicity. The timing, dosing and scheduling of RT depends on disease subtype and prognostic factors, including age, size, patients' functional status and residual tumour volume. RT should start within 3–5 weeks after surgery⁹ and is commonly administered at 50.4–60 Gy in 1.8–2 Gy daily fractions for both grade 2 and grade 3 glioma. There is no evidence to support the use of higher doses of radiation in patients with WHO grade 2 gliomas¹⁰ and, for those with higher WHO grade tumours, data from randomized studies do not support the use of doses >60 Gy.¹⁸ The Phase III trial by Galanis et al. suggested that there is no benefit of

high-dose over low-dose radiation (high dose, 15.2% vs low dose, 9.5%; $P = 0.7142$) for low grade astrocytoma.

The RTOG9006 trial¹⁹ and the NCCTG 86-72-51 trial¹⁰ both investigated the alternative doses of RT for low grade astrocytoma and oligodendroglioma patients but found no significant difference in OS or PFS between their arms. The study by Green et al. randomized (1:1) the low-grade gliomas patients with 50.4 Gy in 28 fractions versus 64.8 Gy in 36 fractions after resection. High-dose radiation did not improve 15-year OS vs low-dose (22.4% vs 24.9%) or PFS (high dose, 15.2% vs low dose, 9.5%; $P = 0.7142$). The trial addressed the role of RT only, and data supported the role of RT as a backbone of therapy for diffuse astrocytoma (grade 2, low-grade gliomas).

Temozolomide. Based on results from the CATNON clinical trial, RT with sequential chemotherapy is recommended for WHO grade 3 astrocytomas.⁸ The phase III trial investigated the addition of concurrent, adjuvant, and both current and adjuvant temozolomide to RT in adults with newly diagnosed 1p/19q non-codeleted grade 3 gliomas.⁸ Patients were randomly assigned to treatment either with RT alone (59.4 Gy in 33 fractions; three-dimensional conformal RT or intensity-modulated RT), RT with concurrent oral temozolomide (75 mg/m² per day), RT with adjuvant oral temozolomide (12 4-week cycles of 150–200 mg/m² temozolomide given on days 1–5), or RT with both concurrent and adjuvant temozolomide. The study showed that adjuvant temozolomide improves overall survival compared with no adjuvant temozolomide (median OS 82.3 months vs 46.9 months [37.9–56.9]; HR 0.64 [95% CI 0.52–0.79], $p < 0.0001$). The study concluded that adjuvant temozolomide chemotherapy, but not concurrent temozolomide chemotherapy, was associated with a survival benefit in patients with 1p/19q non-codeleted grade 3 gliomas.

Procarbazine, Lomustine, and Vincristine. Many trials investigated the role of PCV versus no PCV in patients with low-grade gliomas. The RTOG 9802 trial evaluated the role of chemotherapy in high-risk low-grade gliomas and included patients with oligodendroglioma and astrocytoma. The trial showed 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.¹¹ EORTC26951 trial also investigated the role of PCV in patients who were classified as anaplastic oligodendroglioma based on histological criteria. The trial showed significant increase in OS (42.3 vs 30.6 months) for RT/PCV treatment as compared to RT only.²⁰ Based on these studies, it is recommended to use PCV for patients with astrocytoma and oligodendroglioma. Buckner et al. also investigated the role of PCV in low grade gliomas who were 40 years of age or older and had undergone biopsy or resection of any of the tumour. Patients who received radiation therapy plus chemotherapy had longer median OS than did those who received radiation therapy alone (13.3 vs. 7.8 years; hazard ratio for death, 0.59; $P = 0.003$).¹²

Chemotherapy Alone. Clinical trials have also investigated the role of chemotherapy as monotherapy for low-grade (WHO grade 2) and anaplastic (WHO grade 3) astrocytoma. The EORTC 22033-26033 trial patients were randomly assigned (1:1) to receive either conformal RT (up to 50.4 Gy; 28 doses of 1.8 Gy once daily, 5 days per week for up to 6–7 weeks) or dose-dense oral temozolomide (75 mg/m² once daily for 21 days, repeated every 28 days [one cycle], for a maximum of 12 cycles) to determine the overall survival.²¹ 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) between the patients treated with radiation vs chemotherapy.²¹

Referenzen aus Leitlinien

3. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.* Aug 02 2021;23(8):1231-1251. doi:10.1093/neuonc/noab106
4. Halasz LM, Attia A, Bradfield L, et al. Radiation Therapy for IDH-Mutant Grade 2 and Grade 3 Diffuse Glioma: An ASTRO Clinical Practice Guideline. *Pract Radiat Oncol.* 2022;12(5):370-386. doi:10.1016/j.prro.2022.05.004
5. Mohile NA, Messersmith H, Gatson NT, et al. Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO Guideline. *J Clin Oncol.* Feb 01 2022;40(4):403-426. doi:10.1200/JCO.21.02036
6. Central Nervous System Cancers: NCCN Guidelines Version 4.2024
Central Nervous System Cancers - Guidelines Detail.
7. Jakola AS, Skjulsvik AJ, Myrnes KS, et al. Surgical resection versus watchful waiting in low-grade gliomas. *Ann Oncol.* Aug 01 2017;28(8):1942-1948. doi:10.1093/annonc/mdx230
8. van den Bent MJ, Tesson CMS, Wick W, et al. Adjuvant and concurrent temozolomide for 1p/19q non-codeleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. *Lancet Oncol.* Jun 2021;22(6):813-823. doi:10.1016/S1473-2045(21)00090-5

9. Press RH, Shafer SL, Jiang R, et al. Optimal timing of chemoradiotherapy after surgical resection of glioblastoma: Stratification by validated prognostic classification. *Cancer*. Jul 15 2020;126(14):3255-3264. doi:10.1002/cncr.32797
10. Breen WG, Anderson SK, Carrero XW, et al. Final report from Intergroup NCCTG 86-72-51 (Alliance): a phase III randomized clinical trial of high-dose versus low-dose radiation for adult low-grade glioma. *Neuro Oncol*. Jun 09 2020;22(6):830-837. doi:10.1093/neuonc/noaa021
11. Shaw EG, Wang M, Coons SW, et al. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802. *J Clin Oncol*. Sep 01 2012;30(25):3065-70. doi:10.1200/JCO.2011.35.8598
12. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. *N Engl J Med*. Apr 07 2016;374(14):1344-55. doi:10.1056/NEJMoa1500925
13. Pan Z, Bao J, Wei S. Vorasidenib for IDH-mutant grade 2 gliomas: clinical advances and future directions. *Front Oncol*. 2025;15:1628195. doi:10.3389/fonc.2025.1628195
14. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat Rev Clin Oncol*. Mar 2021;18(3):170-186. doi:10.1038/s41571-020-00447-z
15. Torp SH, Solheim O, Skjulsvik AJ. The WHO 2021 Classification of Central Nervous System tumours: a practical update on what neurosurgeons need to know-a minireview. *Acta Neurochir (Wien)*. Sep 2022;164(9):2453-2464. doi:10.1007/s00701-022-05301-y
16. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. *Neuro Oncol*. Nov 01 2019;21(Suppl 5):v1-v100. doi:10.1093/neuonc/noz150
17. Bond KM, Hughes JD, Porter AL, Orina J, Fang S, Parney IF. Adult Pilocytic Astrocytoma: An Institutional Series and Systematic Literature Review for Extent of Resection and Recurrence. *World Neurosurg*. Feb 2018;110:276-283. doi:10.1016/j.wneu.2017.11.102
18. Khan L, Soliman H, Sahgal A, Perry J, Xu W, Tsao MN. External beam radiation dose escalation for high grade glioma. *Cochrane Database Syst Rev*. Aug 19 2016;(8):CD011475. doi:10.1002/14651858.CD011475.pub2
19. Ali AN, Zhang P, Yung WKA, et al. NRG oncology RTOG 9006: a phase III randomized trial of hyperfractionated radiotherapy (RT) and BCNU versus standard RT and BCNU for malignant glioma patients. *J Neurooncol*. Mar 2018;137(1):39-47. doi:10.1007/s11060-017-2558-x
20. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol*. Jan 20 2013;31(3):344-50. doi:10.1200/JCO.2012.43.2229
21. Baumert BG, Hegi ME, van den Bent MJ, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol*. Nov 2016;17(11):1521-1532. doi:10.1016/S1470-2045(16)30313-8

4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 06 of 12, June 2026)
am 01.06.2026**

#	Suchschritt
1	MeSH descriptor: [Astrocytoma] explode all trees
2	MeSH descriptor: [Gliosarcoma] explode all trees
3	(astrocytoma* OR oligoastrocytoma* OR xanthoastrocytoma* OR astroglioma* OR glioblastoma* OR gliosarcoma*):ti,ab,kw
4	MeSH descriptor: [Oligodendroglioma] explode all trees
5	(oligodendroglioma*):ti,ab,kw
6	((astrocytic OR oligodendroglial) AND (tumor* OR tumour* OR neoplas* OR cancer* OR carcinoma*)):ti
7	MeSH descriptor: [Glioma] this term only
8	(glioma*):ti,ab,kw
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	#9 with Cochrane Library publication date from Jun 2021 to present, in Cochrane Reviews
11	#10 with Cochrane Library publication date from Jun 2024 to present
12	#10 NOT #11

Leitlinien und systematische Reviews in PubMed am 01.06.2026

verwendete Suchfilter für Leitlinien:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 20.03.2026

verwendeter Suchfilter für systematische Reviews:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 01.01.2026.

#	Suchschritt
	Leitlinien
1	astrocytoma[mh]
2	gliosarcoma[mh]
3	astrocytoma*[tiab] OR oligoastrocytoma*[tiab] OR xanthoastrocytoma*[tiab] OR astroglioma*[tiab] OR glioblastoma*[tiab] OR gliosarcoma*[tiab]
4	oligodendroglioma[mh]
5	oligodendroglioma*[tiab]
6	(astrocytic[ti] OR oligodendroglial[ti]) AND (tumor[ti] OR tumors[ti] OR tumour*[ti] OR neoplas*[ti] OR cancer*[ti] OR carcinoma*[ti])
7	glioma[mh:noexp]

#	Suchschritt
8	glioma*[tiab]
9	brain neoplasms[majr:noexp]
10	(intracranial[ti] OR brain[ti] OR cerebral[ti] OR central nervous system[ti] OR CNS[ti]) AND (tumor[ti] OR tumors[ti] OR tumour*[ti] OR neoplas*[ti] OR cancer*[ti] OR carcinoma*[ti])
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12	(#11) AND (Guideline[pt] OR Practice Guideline[pt] OR Consensus Statement [pt] OR Consensus Development Conference, NIH[pt] OR guideline*[ti] OR recommendation*[ti] OR ((consensus[ti] OR position[ti]) AND (expert[ti] OR delphi[ti] OR statement*[ti] OR paper*[ti] OR document*[ti] OR report*[ti])))
13	(#12) AND ("2021/06/01"[PDAT] : "3000"[PDAT])
14	(#13) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "preprint"[pt])
	systematische Reviews
15	(astrocytic[tiab] OR oligodendroglial[tiab]) AND glioma*[tiab]
16	("Glioma/drug therapy"[Mesh:NoExp] OR "Glioma/radiotherapy"[Mesh:NoExp] OR "Glioma/surgery"[Mesh:NoExp] OR "Glioma/therapy"[Mesh:NoExp])
17	(glioma*[ti]) AND (treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #15 OR #16 OR #17
19	(#18) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR (((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebSCO[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR

#	Suchschritt
	proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
20	(#19) AND ("2021/06/01"[PDAT] : "3000"[PDAT])
21	(#20) NOT "The Cochrane database of systematic reviews"[Journal]
22	(#21) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
23	#22 NOT #14
24	(#23) AND ("2024/06/01"[PDAT] : "3000"[PDAT])
25	#23 NOT #24

Iterative Handsuche nach grauer Literatur, abgeschlossen am 02.06.2026

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- American Society of Clinical Oncology (ASCO)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- ECRI Guidelines Trust (ECRI)
- Dynamed/EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Alberta Health Services (AHS).** IDH-mutant CNS WHO grade 2 and 3 gliomas [online]. Edmonton (CAN): AHS; 2026. [Zugriff: 01.06.2026]. (Clinical Practice Guideline CNS-015). URL: <https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-cns015-idh-mutant-gliomas.pdf>.
2. **Blakeley J, Mohile NA, Messersmith H, Lassman AB, Schiff D, Therapy for Diffuse Astrocytic Oligodendroglial Tumors in Adults Guideline Expert Panel.** Therapy for diffuse astrocytic and oligodendroglial tumors in adults: ASCO-SNO guideline rapid recommendation update. J Clin Oncol 2025;43(18):2129-2133. <https://dx.doi.org/10.1200/JCO-25-00250>.
3. **Mohile NA, Messersmith H, Gatson NT, Hottinger AF, Lassman A, Morton J, et al.** Therapy for diffuse astrocytic and oligodendroglial tumors in adults: ASCO-SNO guideline. J Clin Oncol 2022;40(4):403-426. <https://dx.doi.org/10.1200/JCO.21.02036>.

-
- [A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. <https://doi.org/10.1186/s13643-020-01542-z>
- [B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. <https://doi.org/10.1016/j.jclinepi.2016.01.021>

**Schriftliche Beteiligung der wissenschaftlich-medizinischen
Fachgesellschaften und der Arzneimittelkommission der
deutschen Ärzteschaft (AkdÄ) zur Bestimmung der
zweckmäßigen Vergleichstherapie nach § 35a SGB V**

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO