brain sciences

MDPI

Systematic Review

Postoperative Radiotherapy and Chemotherapy for Grade 2 Glioma in the Vorasidenib Era: A Systematic Review of Historical Randomized Trials with INDIGO as Context

Simon G. Ammanuel, Brady F. Lundin, Christopher R. Trujillo, Daniel T. Hernandez, Jack M. Shireman, Sudarshawn Damodharan and Mahua Dey *

Department of Neurological Surgery, School of Medicine & Public Health, University of Wisconsin, Madison, WI 53792, USA; sammanuel@uwhealth.org (S.G.A.); crtrujillo@wisc.edu (C.R.T.); tinocohernan@wisc.edu (D.T.H.); jshireman@wisc.edu (J.M.S.); sdamodha@uchicago.edu (S.D.)
* Correspondence: dey@neurosurgery.wisc.edu; Tel.: 608-262-7303; Fax: 608-263-1728

Highlights

What are the main findings?

- Four historical randomized controlled trials on the effects of radiotherapy and chemotherapy on low-grade glioma patients were identified during this review. Early radiotherapy and radiotherapy with chemotherapy extended progression-free survival (PFS).
- The INDIGO trial differs from the historical trials in its definition of progression and molecular characterization. In INDIGO, vorasidenib prolonged PFS compared with placebo in patients with grade 2 IDH-mutant glioma who could defer radiotherapy and chemotherapy.

What are the implications of the main findings?

- PFS definitions differed between the historical trials and the vorasidenib trial, making direct comparison difficult. INDIGO supports vorasidenib as an option for patients who can defer radiotherapy and chemotherapy.
- Head-to-head trials comparing IDH inhibitors with radiotherapy and chemotherapy, with harmonized imaging and molecular and progression definitions, should be conducted.

Abstract

Background: In grade 2 IDH-mutant glioma, postoperative radiotherapy (RT) and chemotherapy improve disease control but cause toxicity, including late neurocognitive effects, prompting interest in mutant-IDH inhibitors such as vorasidenib. We reviewed randomized trials of postoperative RT and chemotherapy to summarize progression-free survival (PFS) and toxicity and to assess their applicability to the population eligible for the INDIGO trial. **Methods**: We searched PubMed/MEDLINE, Embase, and Cochrane CENTRAL (January 2000–April 2026) for randomized phase II/III trials of postoperative RT or chemotherapy in grade 2 glioma. Comparisons were limited to randomized arms within each trial. Risk of bias was assessed with RoB 2, and results were summarized by treatment strategy following SWiM guidance. The review was not registered. **Results**: Four randomized phase III trials contributed 1242 patients; INDIGO randomized 331. The trials compared early versus deferred RT, two RT doses, RT with or without procarbazine, lomustine, and vincristine (PCV), and RT versus temozolomide; none required an IDH

Academic Editor: Paolo Tini

Received: 11 November 2026
Revised: 24 November 2026
Accepted: 27 November 2026
Published: 28 November 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

mutation. Within-trial PFS was longer with early RT and with RT plus PCV. These trials differed from INDIGO in population, randomization timing, molecular definition, and progression assessment. In INDIGO, vorasidenib prolonged PFS and time to next intervention compared with placebo. **Conclusions**: Vorasidenib is an option for patients in whom RT and chemotherapy can be deferred. Because the trials studied different populations, no conclusions about comparative efficacy can be drawn; head-to-head trials are needed to determine whether IDH inhibitors should replace or complement the current standard of care.

Keywords: IDH-mutant glioma; astrocytoma; oligodendroglioma; CNS WHO grade 2; vorasidenib; radiotherapy; chemotherapy; progression-free survival

1. Introduction

Diffuse gliomas are the most common primary malignant brain tumors in adults (accounting for 80–85% of cases) [1]. Progress in our understanding of glioma biology has led to improved classification and the development of therapies targeting specific molecular alterations. The 2021 5th edition of the WHO classification of central nervous system (CNS) tumors incorporates these advances, with tumor types now defined by a combination of histopathological and molecular features [2]. Mutations in isocitrate dehydrogenase 1 and 2 (IDH1/2) are early events in gliomagenesis and alter enzyme function, resulting in the production of the oncometabolite D-2-hydroxyglutarate, which in turn leads to epigenetic dysregulation and a distinct biological pathway of glioma development [3–5]. IDH-mutant and IDH-wildtype gliomas are thus two very different entities with significant differences in their biology, clinical behavior, and prognosis [4–6]. The WHO classification now recognizes three adult-type diffuse gliomas: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype [2]. Many of the earlier clinical trials, however, predate the current molecular classification and enrolled patients with what was then a histologically defined ‘low-grade glioma’. On subsequent molecular testing of the available tissue, it has been shown that these cohorts included a significant number of IDH-wildtype tumors [7,8].

Management of CNS WHO grade 2 IDH-mutant glioma begins with maximal safe resection [9,10]. After resection, further treatment is individualized based on the amount of residual disease, molecular subtype, patient age and performance status, evidence of growth or progression, neurological symptoms, and the likely benefits and risks of further therapy [9,11,12]. Some patients will be managed with surveillance by serial MRI; others at high risk of progression will generally be offered radiotherapy (RT) followed by chemotherapy [9,11,13]. Historical trials did not define high risk consistently, as they used clinical criteria before the era of routine molecular classification [7,14]. For grade 2 oligodendroglioma (IDH-mutant and 1p/19q-codeleted), the ASCO-SNO guideline recommends RT with PCV (procarbazine, lomustine, vincristine), with temozolomide as an alternative if toxicity is a concern [11]. For grade 2 astrocytoma (IDH-mutant), the guideline recommends RT with adjuvant temozolomide or PCV [11]. These treatments will extend the period of disease control, but chemotherapy toxicity and the potential for delayed neurocognitive effects from RT are important considerations, particularly in patients with long expected survival [15,16].

Vorasidenib is an oral, brain-penetrant inhibitor of mutant IDH1 and IDH2 that reduces production of the oncometabolite D-2-hydroxyglutarate [17]. In the double-blind, placebo-controlled phase III INDIGO trial, 331 patients with residual or recurrent CNS WHO grade 2 IDH-mutant astrocytoma or oligodendroglioma were randomized to

vorasidenib or placebo. To be included in the trial, patients had to have had surgery as their only prior treatment, and the most recent surgery had to have been between 1 and 5 years prior to randomization. Patients had to have measurable non-enhancing disease and were not deemed to require immediate radiotherapy or chemotherapy [17]. In the initial INDIGO analysis, vorasidenib significantly improved imaging-based progression-free survival and delayed the need for the next intervention. An updated double-blind analysis confirmed the PFS and time-to-next-intervention findings [18].

The 2025 ASCO-SNO rapid recommendation update states that vorasidenib may be offered after surgery in adults with grade 2 IDH-mutant astrocytoma or oligodendroglioma when radiotherapy and chemotherapy can be deferred [13]. INDIGO demonstrated the benefit of vorasidenib over placebo in the appropriate population for deferral, but it did not compare vorasidenib to RT or chemotherapy [17,18]. Historical trials of RT and chemotherapy remain valuable, but they differ from INDIGO in the patient population, treatment decisions, molecular classification, and how progression was defined. Because of these differences, PFS estimates across the trials cannot be compared to determine the relative efficacy of vorasidenib versus historical treatment strategies. We therefore undertook a systematic review of randomized trials of postoperative RT and chemotherapy to summarize PFS and toxicity and to assess the relevance of the historical data to the INDIGO population.

2. Methods

2.1. Protocol, Registration, and Reporting

This review adhered to the PRISMA 2020 statement [19] (Supplementary Table S1) and the Synthesis Without Meta-analysis (SWiM) reporting guideline [20] (Supplementary Table S2). It was not prospectively registered. Following peer review, we modified the review question and inclusion criteria, grouped the trials by treatment strategy, and updated the risk of bias assessment.

2.2. Review Question

We used the PICOS (Population, Intervention, Comparison, Outcomes and Study) framework to formulate the review question (Table 1). We looked at PFS and toxicity following surgery in the historical trials of RT and chemotherapy for histologically defined low-grade glioma. The treatment comparisons were restricted to the randomized arms within each trial. We also undertook a comparison of the historical trials with INDIGO in terms of patient population, indication for treatment, molecular profile, and the definition and assessment of PFS. INDIGO [17,18] was treated separately as it was the trial that prompted the review and formed the reference trial.

Table 1. Eligibility criteria, structured by PICOS domain.

Domain	Inclusion Criteria	Exclusion Criteria
Population	Pathologically confirmed grade 2 (low-grade) diffuse glioma (astrocytoma, oligodendroglioma, or mixed oligoastrocytoma) after biopsy or resection; predominantly adult population (minimum enrollment age ≥16 years); no other neurological diseases	Efficacy population including WHO grade 3 or 4 glioma; pediatric populations; patients with other neurological diseases
Molecular status	IDH-defined eligibility not required, because most trials preceded the discovery of IDH mutations; IDH and 1p/19q status extracted where available	—
Intervention	At least one arm receiving a postoperative RT- and/or chemotherapy-based strategy	No RT- or chemotherapy-based arm

Comparator	Any control arm within the same randomized trial	No within-trial randomized comparator
Outcome	PFS reported for each randomized arm or as a within-trial HR	PFS not reported
Study design	Randomized controlled trial, phase II or III, with ≥2 randomized arms	Single-arm trials; post hoc analyses of non-randomized cohorts; reviews; case reports; case series
Publication	Full-text, peer-reviewed article in English; human subjects; report published from 1 January 2000 through 30 April 2026, regardless of when enrollment began	Conference abstracts and other non-peer-reviewed reports; non-English; non-human; published before 1 January 2000

2.3. Eligibility Criteria

Eligibility criteria are set out in Table 1. We included randomized phase II or III trials with at least two treatment arms, enrolling patients with pathologically confirmed grade 2 diffuse glioma (following biopsy or resection). At least one arm had to receive post-operative radiotherapy and/or chemotherapy and the trial had to report PFS. For the historical trials, we used the histological diagnosis and classification at the time of the trial to determine the grade of the tumor. As most of the trials were conducted prior to the era of routine molecular classification, we did not require patients to have a confirmed IDH mutation. Where available IDH status was extracted and taken into account in the assessment of applicability. We restricted eligibility to trials which enrolled predominantly adults, although EORTC 22845 included patients aged 16–65 years [21].

We excluded single-arm trials, post hoc analyses of non-randomized cohorts and trials which enrolled patients with known grade 3 or 4 glioma at baseline. We also excluded reviews, case reports and series, conference abstracts and other non-peer reviewed reports; non-English publications; non-human studies and reports published prior to 1 January 2000. Where multiple reports from the same trial were available, we used the one with the most mature PFS follow-up as our source. We chose January 2000 to focus on reports published during an era of more contemporary trial reporting and increasing use of MRI for follow-up. The cutoff applied to publication date, so trials that began enrolling before 2000 were eligible if their most mature PFS report was published within the review period.

2.4. Information Sources and Search Strategy

We searched PubMed/MEDLINE, the Cochrane Library (Cochrane Central Register of Controlled Trials) and Embase for reports published from 1 January 2000 to 30 April 2026. In PubMed and Embase, we combined three concept groups using Boolean logic: (1) tumor terms such as (“oligodendroglioma” OR “astrocytoma” OR “low grade glioma” OR “grade 2 glioma” OR “grade II glioma” OR “IDH mutant”); (2) treatment terms such as (“radiotherapy” OR “radiation” OR “chemotherapy” OR “chemoradiotherapy” OR “radio-chemotherapy” OR “temozolomide” OR “procarbazine” OR “lomustine” OR “vincristine”); and (3) trial design terms or database filters for randomized controlled trials and phase II and III clinical trials. In CENTRAL, we used the glioma and treatment terms without a separate trial-design filter. Our full search strategy for each database is shown in Supplementary Table S3.

Figure 1 shows how we identified and selected the historical trials. We limited our database search to trials of radiotherapy and chemotherapy rather than IDH inhibitors. As the first INDIGO paper was the catalyst for this review, we treated it separately from the historical trials. The original INDIGO report was used to describe the trial design and the patient population [17]. The later double-blind report provided updated PFS and time to next intervention data, along with data on health-related quality of life and

neurocognition [18]. We also included the secondary and exploratory outcomes from both reports to add further context [17,18].

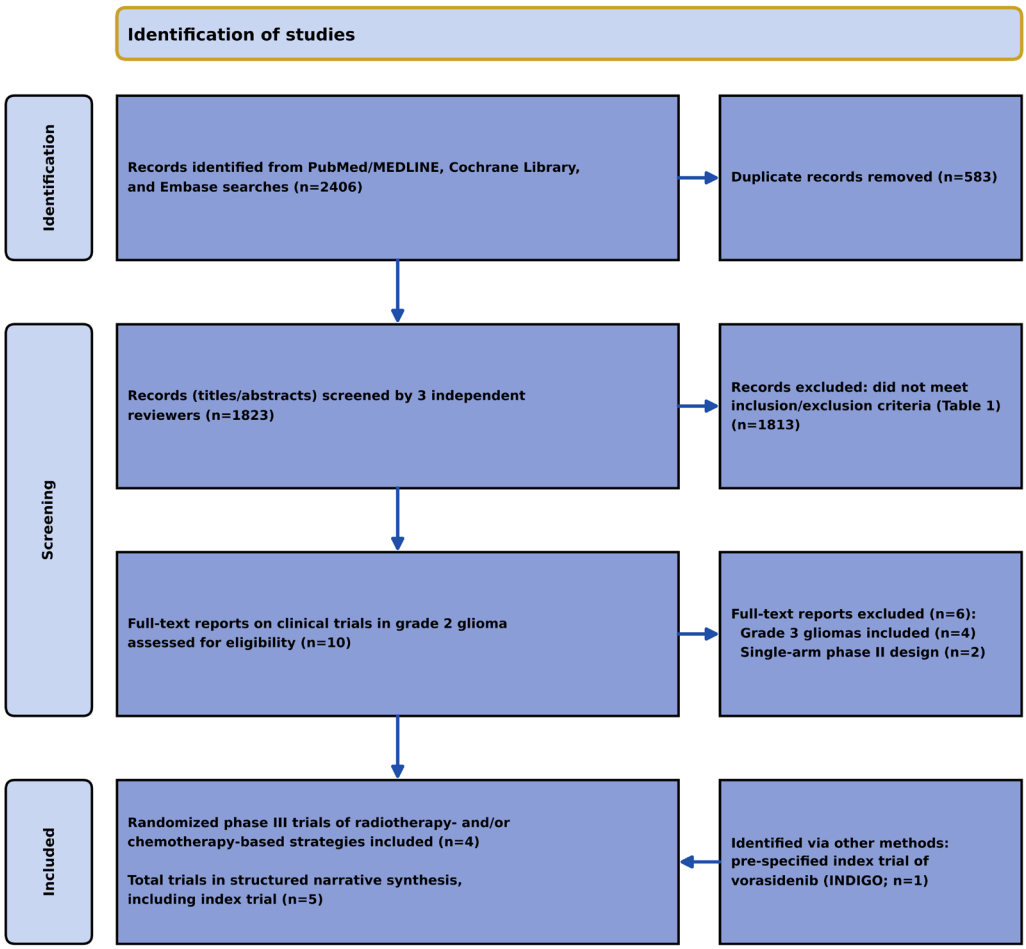

Figure 1. PRISMA 2020 flow diagram of study identification and selection. Records were identified through searches of PubMed/MEDLINE, the Cochrane Library, and Embase.

2.5. Selection Process

Three reviewers (S.G.A., B.L., and S.D.) independently screened the titles and abstracts and then reviewed the full-text reports for eligibility. Disagreements were resolved by discussion and, when necessary, by consultation with the senior author (M.D.). All ten full-text reports were then reassessed by us against the eligibility criteria in Table 1. Two single-arm phase II studies of temozolomide were identified (one of which was a post hoc analysis). Neither study had at least two randomized treatment arms, so both were excluded [22,23].

2.6. Data Collection Process and Data Items

All data were independently extracted by the three reviewers using a standardized form, and all reviewers agreed on the final values. Data were taken from the main text, tables, figures, and Supplementary Material of the included articles. For each trial, we extracted the trial identifier, study design and phase, the period of enrollment, the number of patients randomized and analyzed in each arm, and the treatment regimens. Patient characteristics included age, extent of resection, high-risk criteria, time of randomization relative to surgery, prior treatment, whether treatment could be deferred, histological

classification, and, where available, how the IDH and 1p/19q status was determined. We also extracted the PFS definitions, imaging methods and schedules, who assessed progression (investigators or blinded independent central reviewers), the median PFS and 95% CIs for each arm, the within-trial HR for PFS, the median follow-up, the IDH-defined subgroup results, and grade ≥3 and late toxicity. All durations reported in years were converted to months. Following peer review, the extracted values were checked against the original publications. S.G.A. then carried out the data extraction again and corrected any errors identified during the search update. The trial investigators were not contacted.

2.7. Outcomes

The primary outcome was progression-free survival (PFS), defined by each trial. Table 2 summarizes the trial-specific definitions of PFS, the method of assessment, and the analysis population as reported in the published papers. PFS definitions were not harmonized across trials. Results from the IDH-defined subgroups were considered exploratory. The secondary outcome was grade ≥3 acute and late toxicity, as reported in each trial. Overall survival and time to next intervention were also reported where available. Findings on health-related quality of life and neurocognition from the subsequent INDIGO report were included for context [18].

Table 2. Progression-free survival, definitions of progression, and toxicity in the included trials. Values are reported as published and are not comparable across trials.

Trial	Arm	Median PFS, Months (95% CI)	Within-Trial Effect Estimates (HR, 95% CI)	PFS Definition and Assessment	Median Follow-Up	IDH-Defined Subgroup Findings	Grade ≥3 and Late Toxicity
EORTC 22845 [21]	Early RT	63.6 (55.2–75.6)	Early vs. deferred RT [21]. PFS HR 0.59 (0.45–0.77), $p < 0.0001$. Median OS 7.4 vs. 7.2 years; HR 0.97 (0.71–1.34)	Clinical and/or radiological (CT or MRI) progression; investigator-assessed; open-label	7.8 years	Not available	6 patients discontinued RT for acute toxicity; seizure control at 1 year better with early RT
	Deferred RT	40.8 (34.8–52.8)					
NCCTG 86-72-51 [24]	50.4 Gy	67.2 (51.6–86.4)	64.8 vs. 50.4 Gy [24]. PFS HR 0.95 (0.70–1.27); $p = 0.71$ Overall median PFS 62.4 months (95% CI 51.6–79.2) and median OS 8.4 years	≥25% increase in product of perpendicular diameters or clear increase in tumor size; CT or MRI every 4 months (years 1–2), every 6 months (years 3–5), then annually; investigator-assessed; open-label	17.2 years (surviving patients)	Not available	Late grade ≥3 toxicity among 5-year survivors: 2 (50.4 Gy) vs. 3 (64.8 Gy)
	64.8 Gy	62.4 (43.2–97.2)					
RTOG 9802 [14]	RT alone	48.0 (37.2–66.0)	RT followed by PCV vs. RT alone [14]. PFS HR 0.50 (0.36–0.68), $p < 0.001$. Median OS 13.3 vs. 7.8 years, HR 0.59 (0.42–0.83), $p = 0.003$.	Clinical or radiological (CT/MRI) progression; investigator-assessed; open-label	11.9 years	R132H staining: 71/113 positive [14]. Genomic classification: 106/251 [8]. See table note.	More grade 3–4 neutropenia with RT + PCV; not reported by molecular subgroup
	RT + PCV	124.8 (73.2–NR)					

	RT	46 (40–56)					
EORTC 22033-26033 [7]	TMZ	39 (35–44)	PFS HR 1.16 (0.9–1.5) for TMZ vs. RT; $p = 0.22$ OS immature	Protocol-defined MRI-based progression; investigator-assessed; open-label	48 months	IDH-mutant non-codeleted: TMZ vs. RT, median PFS 36 vs. 55 months. HR 1.86 (95% CI 1.21–2.87), $p = 0.004$ [7].	Grade 3–4 hematological: 14% (TMZ) vs. <1% (RT); grade 3–4 infection: 3% vs. 1%
	Placebo	11.1 (11.0–13.7)					
INDIGO [17,18]	Vorasidenib	27.7 (17.0–NE)	Vorasidenib vs. placebo [17]. PFS HR 0.39 (0.27–0.56); $p < 0.001$. TTNI HR 0.26 (0.15–0.43). Updated HRs [18] in table note.	Imaging-based progression by blinded independent central review; modified RANO-LGG; MRI approximately every 12 weeks; double-blind	≈14 months (primary); 20.1 months (updated)	All patients IDH-mutant (eligibility criterion)	Grade ≥3 AEs: 22.8% vs. 13.5%; grade ≥3 ALT increase 9.6%; No between-group difference in exploratory neurocognitive measures during double-blind follow-up [18].

RTOG 9802 molecular subgroups. For RT followed by PCV versus RT alone, the PFS HR amongst the 71 of 113 evaluable IDH1 R132H-positive (by IHC) tumours was 0.32 (95% CI 0.17 to 0.62) [14]. The integrated analysis encompassed IHC, IDH1/2 sequencing and 1p/19q arrays to classify 106 of 251 patients [8]. The PFS HRs (95% CIs) were 0.32 (0.15 to 0.69) for the IDH-mutant, non-codeleted group ($n = 43$), 0.13 (0.04 to 0.44) for the IDH-mutant, codeleted group ($n = 37$) and 0.70 (0.31 to 1.61) for the IDH-wildtype group ($n = 26$). In EORTC 22033-26033 the molecular analysis included 318 patients and there was no significant difference in PFS between the codeleted and IDH-wildtype groups [7]. Analysis time points were March 2004 (EORTC 22845) [21], the 4 February 2019 database freeze (NCCTG 86-72-51) [24], the long-term analysis with a median follow-up of 11.9 years among survivors (RTOG 9802) [14] and the 7 August 2013 database lock (EORTC 22033-26033) [7]. The later RTOG genomic analysis had a median follow-up of 9.0 years overall [8]. Neither of the RTOG 9802 papers specified an exact data cut-off date [8,14]. The INDIGO estimates in the table body are from the second interim analysis on 6 September 2022 [17]. At the 7 March 2023 double-blind update the PFS HR for vorasidenib versus placebo was 0.35 (95% CI 0.25 to 0.49) and the TTNI HR was 0.25 (95% CI 0.16 to 0.40) [18]. The medians reported in years have been converted to months (x12). AE = adverse event; ALT = alanine aminotransferase; CT = computed tomography; HR = hazard ratio; MRI = magnetic resonance imaging; NE = not estimable; NR = not reached; OS = overall survival; RANO-LGG = Response Assessment in Neuro-Oncology criteria for low-grade glioma; TTNI = time to next intervention.

2.8. Risk of Bias

We assessed the risk of bias for PFS using the Cochrane risk of bias tool for randomized trials (RoB 2) [25], with a focus on the effect of assignment to the intervention. The five domains assessed were: bias due to the randomization process; bias due to deviations from the intended intervention; bias due to missing outcome data; bias in the measurement of the outcome; and bias in the selection of the reported result. For each domain and the overall risk of bias, we assigned a rating of low risk, some concerns, or high risk. Table

3 shows the judgment for each trial and the rationale for each judgment. S.G.A. and C.R.T. independently assessed each trial, with any disagreements resolved by consensus.

Table 3. Risk of bias in the progression-free survival result of each trial (RoB 2) [25].

Trial	D1 Randomization Process	D2 Deviations from Intended Interventions	D3 Missing Outcome Data	D4 Measurement of the Outcome	D5 Selection of the Reported Result	Overall	Rationale
EORTC 22845 [21]	Some concerns	Low	Low	Some concerns	Low	Some concerns	D1: allocation concealment not described. D4: open-label trial; investigator-assessed progression that included clinical criteria (CT/MRI era).
NCCTG 86-72-51 [24]	Low	Low	Low	Some concerns	Some concerns	Some concerns	D4: open-label trial; investigator-assessed progression. D5: final report >25 years after enrollment; prespecified analysis plan not accessible. Total of 8 of 211 randomized patients (ineligible or refused treatment) not analyzed; judged unlikely to bias the result.
RTOG 9802 [14]	Low	Low	Low	Some concerns	Low	Some concerns	D4: open-label trial; investigator-assessed progression. Total of 3 of 254 enrolled patients ineligible and not analyzed; judged unlikely to bias the result. IDH1 subgroup analyses post hoc with incomplete tissue.
EORTC 22033-26033 [7]	Low	Low	Low	Some concerns	Low	Some concerns	D4: open-label trial; investigator-assessed MRI progression. PFS was the prespecified primary end point. Molecular subgroup analyses exploratory (67% with tissue).
INDIGO [17]	Low	Low	Low	Low	Low	Low	Double-blind; blinded independent central review of PFS; prespecified interim analysis. Unblinding after an interim analysis for efficacy may overestimate the effect size [26].

We did not assign separate RoB 2 assessments to the IDH-defined subgroup results because these were exploratory analyses restricted to patients with available tumor tissue. We therefore regarded them as hypothesis-generating. Relevance to the INDIGO population was assessed separately from risk of bias, with consideration of clinical indication, time to randomization, prior treatment, molecular classification, PFS definitions and how PFS was assessed, treatment era, and follow-up.

2.9. Synthesis Methods

We conducted a structured narrative synthesis in accordance with the SWiM reporting guideline [20]. Trials were grouped by the treatment question they addressed (timing of RT, RT dose, RT + chemotherapy vs. RT alone, chemotherapy vs. RT, IDH inhibitor vs. placebo). Within-trial HRs for PFS were used as the primary effect measures because they reflect the randomized comparison within each trial. Table 2 identifies the intervention and reference arm for each HR and gives the source report and analysis time point. An

HR below 1 favors the first-listed treatment for the time-to-event outcome. Median PFS values for each treatment arm were reported descriptively and are shown in Figure 2.

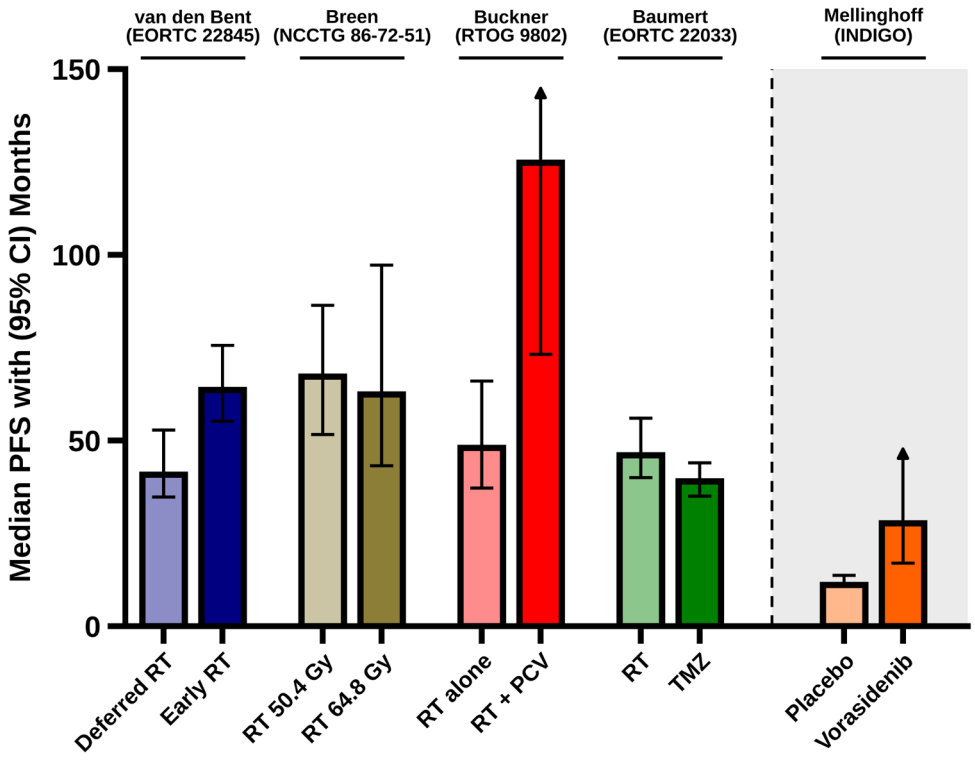

Figure 2. Median progression-free survival (PFS) with 95% confidence intervals for the randomized arms of each included trial, shown separately by trial. The bars show descriptive estimates for individual treatment arms. Differences in median PFS across trials cannot establish relative treatment efficacy. The arrows represented the unbounded upper bound of 95% confidence interval. INDIGO values are from the primary analysis [17]. The shaded area is to show as context of the INDIGO trial of IDH inhibitors while non shaded area shows the different radiotherapy/chemotherapy trials given the trials' different protocols which makes it difficult to make a comparison

We assessed treatment effects within each trial because the patient populations enrolled in the various studies were clinically very different, and there were no studies that directly compared vorasidenib with radiotherapy or chemotherapy. We therefore did not carry out any indirect comparisons, did not pool results, did not count studies according to the direction of the findings, did not rank the treatments, and did not use the differences in median PFS across the trials to infer relative efficacy. We did not formally assess bias across studies. For each treatment comparison and outcome, we assessed confidence qualitatively, considering risk of bias, completeness of outcome reporting, relevance to the clinical question, and precision. We examined whether confidence intervals allowed clinically important benefit or harm. For toxicity, we also considered event counts and duration of follow-up. We did not assign formal GRADE ratings.

3. Results

3.1. Study Selection

The database search identified 2406 records. A total of 583 were duplicates and were removed, leaving 1823 records to be screened. Of these 1823, 1813 were excluded. Ten full-text reports were assessed for eligibility, and six were excluded. Four were excluded because their efficacy populations were patients with WHO grade 3 glioma, and two were

excluded because they were single-arm phase II studies [22,23]. Four randomized phase III trials met all eligibility criteria [7,14,21,24]. With INDIGO [17] included as the contextual index trial, the narrative synthesis therefore covered five trials.

3.2. Characteristics of Included Trials

The four historical trials were multicenter, open-label, randomized phase III trials that enrolled patients between 1986 and 2012, with 1242 patients included in the efficacy analyses. These were EORTC 22845 (n = 311; 1986–1997) [21], NCCTG 86-72-51 (203 of 211 randomized analyzed; 1986–1994) [24], RTOG 9802 (n = 251; 1998–2002) [14], and EORTC 22033-26033 (n = 477; 2005–2012) [7]. INDIGO randomized 331 patients between Jan 2020 and Feb 2022 [17]. In total, the five trials comprised 1573 patients.

EORTC 22845 and NCCTG 86-72-51 enrolled patients after surgery without selecting for high-risk features [21,24]. RTOG 9802 defined high risk as age ≥40 years or, for patients aged 18–39 years, and subtotal resection or biopsy [14]. EORTC 22033-26033 required at least one high-risk feature (age >40 years, radiographic progression, tumor diameter >5 cm, tumor crossing the midline, or neurological symptoms) [7]. All patients in the four historical trials were randomized to a postoperative treatment strategy with no prior radiotherapy or chemotherapy. INDIGO, by contrast, enrolled patients aged ≥12 years with residual or recurrent measurable non-enhancing disease, an IDH1 or IDH2 mutation, no prior radiotherapy or chemotherapy, and no immediate need for further treatment. The most recent surgery had to have been performed 1–5 years prior to randomization [17].

EORTC 22845 and NCCTG 86-72-51 used histopathological classification without molecular eligibility criteria, and EORTC 22845 also permitted patients with incompletely resected pilocytic astrocytomas. On central review, 52 of the 232 tumors assessed in EORTC 22845 were reclassified as grade III or IV, even though patients had originally been entered into the trial based on their local diagnosis [27]. RTOG 9802 assessed IDH1 R132H status by immunohistochemistry and submitted tumor tissue for 117 patients. Of these, 113 were deemed suitable for analysis, and 71 had IDH1 R132H-mutant tumors [14]. In EORTC 22033-26033, IDH and 1p/19q status was available for 318 of the 477 patients (67%). Of these, 104 had IDH-mutant, 1p/19q-codeleted tumors (32.7%), 165 had IDH-mutant, non-codeleted tumors (51.9%), and 49 had IDH-wildtype tumors (15.4%) [7]. None of the historical trials required an IDH mutation for entry, in contrast to INDIGO, which required central confirmation of an IDH1 R132 or IDH2 R172 mutation [17].

PFS definitions and assessment methodologies differed across the trials (Table 2). In the four historical trials, progression was assessed using CT or MRI with trial-specific clinical and radiological criteria and surveillance schedules [7,14,21,24]. For instance, in NCCTG 86-72-51, progression was defined as a ≥25% increase in the product of the perpendicular tumor diameters or a clear increase in tumor size. Imaging was performed every 4 months for the first 2 years, every 6 months in years 3 to 5, and then annually thereafter [24]. INDIGO, on the other hand, used blinded, independent central review to assess imaging-based progression according to modified RANO-LGG criteria, with MRI approximately every 12 weeks [17,28].

3.3. Findings by Treatment Strategy

3.3.1. Timing of RT: Early vs. Deferred RT (EORTC 22845)

EORTC 22845 had 311 patients (aged 16–65 years) in the efficacy analysis. A total of 154 were randomized to early postoperative RT (54 Gy in 1.8-Gy fractions) and 157 to deferred RT at progression [21]. Median PFS was 5.3 years (63.6 months; 95% CI 55.2–75.6) with early RT compared to 3.4 years (40.8 months; 95% CI 34.8–52.8) with deferred RT (HR 0.59, 95% CI 0.45–0.77; $p < 0.0001$). Median OS was 7.4 years with early RT and 7.2 years with deferred RT (HR 0.97, 95% CI 0.71–1.34). Of the patients in the deferred RT

group, 73 received RT at progression. Seizure control at 1 year was superior with early RT. RT was stopped in 6 patients due to acute reactions.

3.3.2. Dose of RT: 50.4 Gy vs. 64.8 Gy (NCCTG 86-72-51).

NCCTG 86-72-51 randomized 211 patients after surgical resection to receive either 50.4 Gy in 28 fractions or 64.8 Gy in 36 fractions. Of these, 203 were eligible and treated (101 in the low-dose group and 102 in the high-dose group) [24]. PFS did not differ significantly between the groups (HR 0.95, 95% CI 0.70–1.27; $p = 0.71$). Median PFS was 67.2 months (95% CI 51.6–86.4) with 50.4 Gy and 62.4 months (95% CI 43.2–97.2) with 64.8 Gy. The overall median PFS was 5.2 years (62.4 months; 95% CI 51.6–79.2), and median overall survival was 8.4 years. Of the patients alive at 5 years, 2 had late grade ≥3 toxicity with 50.4 Gy and 3 with 64.8 Gy.

3.3.3. RT Plus Chemotherapy Versus RT Alone (RTOG 9802)

RTOG 9802 randomized 254 high-risk patients, 251 of whom were eligible for the efficacy analysis. A total of 126 received RT alone (54 Gy in 30 fractions), and 125 received RT followed by 6 cycles of PCV [14]. At a median follow-up of 11.9 years, the median PFS was 10.4 years (124.8 months; 95% CI 73.2 months to not reached) with RT + PCV compared with 4.0 years (48.0 months; 95% CI 37.2–66.0) with RT alone (HR 0.50, 95% CI 0.36–0.68, $p < 0.001$). Median OS was 13.3 years vs. 7.8 years (HR 0.59, 95% CI 0.42–0.83, $p = 0.003$).

In the earlier analysis, 71 of 113 evaluable tumors stained positive for IDH1 R132H. Within this subgroup, PFS was longer with RT followed by PCV than with RT alone (HR 0.32, 95% CI 0.17–0.62) [14]. Bell et al. subsequently used IDH1 R132H immunohistochemistry, targeted IDH1/2 sequencing, and array-based assessment of 1p/19q codeletion to classify 106 of 251 eligible patients [8]. For RT followed by PCV versus RT alone, the PFS HR was 0.32 (95% CI 0.15–0.69) in the IDH-mutant, non-codeleted group ($n = 43$), 0.13 (95% CI 0.04–0.44) in the IDH-mutant, codeleted group ($n = 37$), and 0.70 (95% CI 0.31–1.61) in the IDH-wildtype group ($n = 26$) [8]. The small tissue-defined subgroups limit the precision of these estimates, particularly for IDH-wildtype tumors. Grade 3–4 neutropenia was more common with RT + PCV, though no toxicity was reported by molecular subgroup. RTOG 9802 was the only trial in the analysis to look at RT in combination with chemotherapy.

3.3.4. Chemotherapy Alone vs. RT (EORTC 22033-26033)

EORTC 22033-26033 randomized 477 patients with at least one high-risk feature to either conformal radiotherapy (50.4 Gy in 28 fractions; $n = 240$) or dose-dense temozolomide (75 mg/m^2 daily for 21 of 28 days for up to 12 cycles; $n = 237$) [7]. At a median follow-up of 48 months, median PFS was 46 months (95% CI 40–56) with RT versus 39 months (95% CI 35–44) with temozolomide (HR for TMZ vs. RT 1.16, 95% CI 0.90–1.50, $p = 0.22$). Of the 318 patients in the exploratory molecular analysis, those with IDH-mutant, 1p/19q non-codeleted tumors had significantly longer PFS with RT than with temozolomide (median 55 vs. 36 months for RT vs. TMZ, HR for TMZ vs. RT 1.86, 95% CI 1.21–2.87, $p = 0.004$). There was no significant difference in PFS between the two treatment arms in the IDH-mutant codeleted or IDH-wildtype subgroups. Grade 3–4 hematologic toxicity was seen in 14% of patients on temozolomide compared with less than 1% of those on RT.

3.3.5. IDH Inhibitor Versus Placebo in Patients Suitable for Deferral (INDIGO)

INDIGO randomized 331 patients to receive vorasidenib 40 mg once daily (n = 168) or placebo (n = 163) [17]. At the second prespecified interim analysis (median follow-up approximately 14 months), median imaging-based PFS by blinded independent central review was 27.7 months (95% CI 17.0 to not estimable) with vorasidenib versus 11.1 months (95% CI 11.0–13.7) with placebo (HR 0.39, 95% CI 0.27–0.56; $p < 0.001$). Time to next intervention also favored vorasidenib (HR 0.26, 95% CI 0.15–0.43). Patients in the placebo arm could cross over to vorasidenib after central confirmation of progression. Grade ≥3 AEs occurred in 22.8% of patients on vorasidenib versus 13.5% on placebo. The most common grade ≥3 AE in the vorasidenib group was increased alanine aminotransferase (9.6%).

An updated double-blind analysis (median follow-up 20.1 months) reported a PFS HR of 0.35 (95% CI 0.25–0.49), with median PFS not reached for vorasidenib versus 11.4 months for placebo. Time to next intervention remained in favor of vorasidenib (HR 0.25, 95% CI 0.16–0.40), with median time to next intervention not reached versus 20.1 months for placebo. During double-blind follow-up (median 20.1 months), health-related quality-of-life scores remained high in both groups. Exploratory testing detected no between-group difference in the measured neurocognitive outcomes [18]. The double-blind INDIGO analyses did not demonstrate that vorasidenib prolongs overall survival compared with placebo [17,18].

3.4. Risk of Bias Analysis

Domain-level RoB 2 judgments are shown in Table 3. All four historical trials were judged to have some concerns overall (mainly related to outcome measurement). PFS was assessed with knowledge of treatment allocation in all cases, and some trials used progression definitions that incorporated both clinical and radiographic criteria. In EORTC 22845, randomization was centrally managed via the EORTC/MRC trial office, but details of allocation concealment were not provided [21]. For NCCTG 86-72-51, the final report was published more than 25 years after the trial had finished, and a prespecified analysis plan was not available [24]. INDIGO was judged to have a low risk of bias in all domains. However, it was unblinded after the interim analysis suggested efficacy, and early stopping for benefit may have led to an overestimate of the treatment effect [26]. The IDH-defined subgroup analyses from RTOG 9802 and EORTC 22033-26033 were exploratory and limited by incomplete tissue availability. The blinded INDIGO comparison provides clear evidence of longer PFS during double-blind follow-up in patients eligible to defer RT and chemotherapy. Longer-term cognitive and survival outcomes remain uncertain. In the historical trials, open-label assessment limited confidence in PFS, and incomplete tissue availability limited molecular subgroup analyses. Supplementary Table S4 summarizes the outcome-specific judgments for each treatment comparison.

3.5. Comparability with INDIGO

The historical trials differed from INDIGO in the indication for treatment, timing of randomization after surgery, molecular classification, and progression assessment. These differences limit comparisons of median PFS across trials. For instance, the median PFS was 40.8 months in the deferred RT arm of EORTC 22845 [21] and 11.1 months in the placebo arm of INDIGO [17], even though neither group was assigned any active anticancer therapy prior to progression. The published data cannot establish how much each factor contributed to this difference, which limits the value of historical PFS estimates as a benchmark for vorasidenib.

4. Discussion

This systematic review identified four randomized phase III trials assessing postoperative RT and chemotherapy in the setting of grade 2 glioma, all of which were considered in conjunction with INDIGO. Each of the trials addressed a different clinical question. Compared with deferral of RT until progression, early RT resulted in a longer PFS without a demonstrated OS benefit [21]. There was no significant difference in PFS between the two RT doses of 50.4 and 64.8 Gy [24]. Addition of PCV to RT resulted in a longer PFS and OS in patients who met the RTOG 9802 historical high-risk criteria [14]. In the initial EORTC 22033-26033 report there was no significant difference in PFS between temozolomide alone and RT, although an exploratory molecular analysis did suggest a benefit for RT in the IDH-mutant, 1p/19q non-codeleted subgroup [7]. Only one of the trials looked at RT in combination with chemotherapy and none of the trials required an IDH mutation as a criterion for entry. In contrast, INDIGO was a trial in a molecularly defined population who were selected for RT and chemotherapy deferral, and in which vorasidenib resulted in a longer PFS and time to next intervention compared to placebo [17,18].

The key finding of this review is methodological: the included trials do not provide a direct or appropriately adjusted comparison of vorasidenib versus RT or chemotherapy. In several historical treatment arms, the median PFS was numerically longer than in the vorasidenib arm of INDIGO, but these estimates come from entirely different trial populations and therefore cannot be used to establish superiority, inferiority, or equivalence. The randomized comparisons within each trial are informative, but each must be interpreted in the context of that trial's population, the treatment decisions made, and the way outcomes were assessed. There are many reasons for this.

Firstly, the trial populations and the clinical questions they were designed to answer are very different. INDIGO enrolled patients who had undergone surgery only, whose most recent surgery was 1–5 years prior to randomization, who had measurable residual or recurrent non-enhancing disease, and who, in the opinion of the investigators, were appropriate for deferral of radiotherapy and chemotherapy [17]. The historical trials examined quite different postoperative treatment decisions. EORTC 22845 compared early radiotherapy with radiotherapy deferred until progression [21]. RTOG 9802 and EORTC 22033-26033 enrolled patients who met trial-specific high-risk criteria [7,14]. So, INDIGO cannot establish the efficacy of vorasidenib in patients who would otherwise be candidates for immediate radiotherapy or chemotherapy, and the historical trials do not demonstrate what the performance of radiotherapy or chemotherapy-based strategies would be in the deferral population that INDIGO selected. EORTC 22845 did have a deferred radiotherapy arm, but that population and the treatment strategy were very different from those in INDIGO, so that arm is not a directly comparable comparator to INDIGO's placebo arm.

Secondly, PFS was measured from different time points and using different methods. In INDIGO, it was measured from randomization (which, in patients with measurable residual or recurrent disease, occurred 1–5 years after the most recent surgery). Progression was assessed by a blinded, independent central review using modified RANO-LGG criteria, with MRI roughly every 12 weeks [17,28]. In the historical trials, PFS was measured from randomization after surgery; imaging was generally less frequent and, in earlier trials, often CT-based, and progression was assessed by the investigator, sometimes incorporating clinical deterioration [21,24]. The frequency of imaging, the imaging modality, and the criteria for progression will all affect when progression is identified and recorded, and hence will have an impact on the PFS that is measured, independent of the actual efficacy of the treatment. The published aggregate data, however, do not allow us

to quantify the relative impact of these differences in assessment, patient selection, and randomization timing on the PFS observed across the trials.

Thirdly, the historical cohorts are not molecularly comparable to INDIGO. The two trials began enrolling in 1986 (before the description of IDH mutations) and were histology-based only (EORTC 22845 also included patients with incompletely resected pilocytic astrocytomas) [21]. The molecular data from the later trials were incomplete and largely retrospective. EORTC 22033-26033 stratified by 1p deletion status, but only 318 of the 477 patients randomized (66.7%) could be subsequently classified by IDH and 1p/19q status, of whom 49 (15.4%) had IDH-wildtype tumors [7]. In RTOG 9802, the initial analysis identified the IDH1 R132H variant by immunohistochemistry [14]. A later genomic analysis classified 106 of the 251 eligible patients (42.2%) by IDH and 1p/19q status and found longer PFS with RT followed by PCV in both IDH-mutant subgroups [8]. Tissue availability and small subgroup sizes limit how confidently these results can be applied to individual molecular subtypes. Under the 2021 WHO classification, some previously defined low-grade gliomas now have a different diagnosis (including IDH-wildtype tumors that meet the molecular criteria for glioblastoma) [2]. IDH-mutant, 1p/19q-codeleted oligodendrogliomas and IDH-mutant, non-codeleted astrocytomas have different prognoses and treatment responses, and their relative proportions in the trials varied [7,8]. These differences in molecular composition and treatment response further undermine any ability to make cross-trial comparisons, and the combined effect of these on the measured PFS cannot be determined from the available aggregate data.

Historical risk criteria also have limitations when applied to molecularly defined gliomas. A pooled analysis published after the April 2026 search cutoff examined patients with grade 2–3 gliomas and found that age ≥40 was not associated with shorter PFS in the IDH-mutant cohort [29]. On the other hand, a retrospective cohort of patients with IDH-mutant grade 2 gliomas showed an association between postoperative residual tumor volume and both PFS and OS [30]. These results highlight the need to re-evaluate traditional prognostic factors in light of modern molecular classification, but they do not provide validated age or residual volume cut-offs to determine when it is safe to defer radiotherapy and/or chemotherapy.

Fourth, the PFS estimates differ markedly in follow-up maturity and treatment era. The 27.7-month median PFS reported for vorasidenib in INDIGO was based on an interim analysis with only approximately 14 months of median follow-up and an upper confidence limit that was not estimable; in the updated double-blind analysis, the median PFS with vorasidenib had not yet been reached [17,18]. Historical trial estimates are based on substantially longer follow-up (up to 20 years) [14,24] and also reflect different imaging, surgical techniques, and subsequent treatment pathways. A mature analysis of EORTC 22033-26033, published after the April 2026 search cutoff, found no significant difference in PFS or OS between RT and temozolomide in the overall population [31]. PFS is an imperfect surrogate for OS in grade 2 glioma. In EORTC 22845, early RT improved PFS without a demonstrated OS benefit compared with deferred RT [21], and the impact of vorasidenib on OS is unknown. Therefore, even a methodologically sound PFS analysis on its own would not necessarily lead to the preferred treatment.

These points emphasize that vorasidenib and RT/chemotherapy have been evaluated in different clinical scenarios rather than as mutually exclusive options. INDIGO demonstrated that vorasidenib prolongs PFS and delays the need for subsequent therapy compared with placebo in settings where RT and chemotherapy could be deferred. However, it did not establish superiority over the strategy of commencing RT or chemo [17,18]. The US regulatory indication is broader than the INDIGO eligibility criteria [32], but the EU indication and the 2025 ASCO-SNO rapid recommendation are specifically for the patient population in whom RT and chemotherapy can be deferred [13,33]. For the patient who

does require postoperative treatment, the guideline recommendations clearly depend on molecular subtype: RT followed by PCV for IDH-mutant, 1p/19q-codeleted grade 2 oligodendroglioma (with temozolomide as an alternative if there is concern about PCV toxicity), and RT with adjuvant temozolomide or PCV for IDH-mutant grade 2 astrocytoma [9,11,12]. Vorasidenib had very limited activity against the enhancing component of the tumor in its first-in-human study [34], whereas INDIGO required measurable non-enhancing disease and allowed only minimal, non-nodular, non-measurable enhancement [17]. So the key unresolved issue is the question of sequencing: does the strategy of commencing vorasidenib in the patient who is eligible for deferral of RT and chemotherapy lead to a delay in the need for RT and chemotherapy and their associated toxicities without compromising the efficacy of the subsequent treatment, overall survival, time to malignant transformation, or long-term neurocognitive outcomes?

Beyond differences in efficacy and the order in which they are given, these therapies have very different toxicity profiles that need to be taken into account, particularly in the context of patients who may have a very long survival. Data on late neurocognitive effects of radiotherapy are heterogeneous; they include patients treated with older RT techniques, and the certainty of the data is low. Chemotherapy has its own distinct toxicities, with grade 3–4 hematologic toxicity occurring in 14% of patients on temozolomide in EORTC 22033-26033, and neutropenia more common with PCV in RTOG 9802 [7,14]. In INDIGO, grade ≥3 AEs were more common with vorasidenib than with placebo, and the most common treatment-related AE was elevation of hepatic transaminases [17]. At a median follow-up of 20.1 months, health-related quality of life was high in both INDIGO arms, and exploratory neurocognitive assessments showed no difference between the groups [18]. Whether deferring RT or chemotherapy preserves long-term neurocognitive function remains unknown. The data therefore do not allow for a reliable direct comparison of the overall toxicity of these treatment strategies.

Despite all the advances, key questions remain about the optimal timing to start IDH inhibition, how long to continue it, and the order in which to administer it in the management of CNS WHO grade 2 IDH-mutant glioma. Emerging evidence suggests that prior IDH inhibition may affect response to subsequent therapy. A study published after the April 2026 search cutoff found that vorasidenib pretreatment improved response to subsequent chemoradiation in a mouse model. An accompanying uncontrolled clinical series reported early results from 29 patients who had received vorasidenib or ivosidenib prior to RT with or without chemotherapy [35]. Whether this translates into improved clinical outcomes remains unknown. To answer this question, prospective randomized trials in appropriate populations for whom the treatment strategies being compared would be clinically appropriate are needed. For patients for whom either strategy is clinically appropriate, a prospective trial could compare initial vorasidenib with RT followed by adjuvant chemotherapy. A separate question is whether adding vorasidenib to postoperative therapy improves outcomes. Such trials would need to assess overall survival, time to malignant transformation, neurocognitive function, health-related quality of life, and late toxicity. In the absence of such comparative data, treatment selection should remain individualized, taking into account molecular subtype, postoperative disease burden, clinical and radiological features, and whether RT and chemotherapy can be appropriately deferred. Where randomization is not possible, comparative observational studies should incorporate individual patient data, contemporary integrated molecular diagnostics, harmonized progression criteria (e.g., RANO 2.0) [36], and explicit target trial emulation. Until such comparative data are available, treatment choice should be individualized.

This review has several limitations. It was not prospectively registered, and the review question, inclusion criteria, and synthesis approach were modified during the peer review process. The search was restricted to English-language reports published from

January 2000 onward. This excluded the 1996 efficacy report from EORTC 22844, which found no significant difference in PFS or OS between 45 and 59.4 Gy [37]. Its findings were consistent with NCCTG 86-72-51 [24], but only one randomized dose comparison contributed to our synthesis. Only four historical randomized trials met the inclusion criteria, and substantial heterogeneity in patient selection, indication for treatment, molecular characterization, timing of treatment after surgery, and PFS assessment precluded quantitative synthesis or valid cross-trial estimates of comparative efficacy. These trials all predated the current era of molecular classification, and the molecularly defined subgroup analyses were retrospective and available for only a subset of patients. INDIGO was identified outside the primary database search and was therefore assessed as the contextual index trial. Data were extracted from published reports rather than from individual patient data; PFS definitions were not harmonized, and confidence in each outcome was assessed qualitatively. The differing follow-up maturity across the treatment eras (particularly the lack of long-term data from INDIGO) also limits the ability to assess OS and late toxicity. The review's strengths include a focus on randomized evidence, a full risk-of-bias assessment at the domain level, clear grouping of treatment strategies, and a structured approach to assessing the relevance of the evidence to the contemporary patient with CNS WHO grade 2 IDH-mutant glioma.

5. Conclusions

Four historical randomized trials met our eligibility criteria. Each addressed a different question about postoperative radiotherapy or chemotherapy in a predominantly histology-defined population. Differences in molecular classification, patient selection, treatment indication, timing after surgery, and the PFS endpoint render these trials of limited value in the contemporary setting of CNS WHO grade 2 IDH-mutant glioma and make any valid indirect comparison with INDIGO impossible. INDIGO evaluated vorasidenib in a molecularly defined population eligible for deferral of both RT and chemotherapy and showed a significant improvement in PFS and a delay in the need for subsequent treatment compared with placebo. However, the available randomized data do not establish the superiority, inferiority, or equivalence of vorasidenib versus RT or chemo-based treatment. Vorasidenib is an evidence-based option when conventional postoperative therapy is appropriately deferred, but it is not established as a replacement for clinically indicated RT or chemotherapy. Longer follow-up and appropriately designed comparative studies are required to determine the optimal timing and sequencing of IDH inhibition with RT and chemotherapy and to establish its impact on OS, malignant transformation, neurocognitive function, HRQoL, and late toxicity.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/brainsci16121322/s1, Table S1: PRISMA 2020 checklist; Table S2: SWiM reporting items. Table S3. Database-specific search strategies for historical trials of postoperative radiotherapy and chemotherapy. Table S4. Certainty of the evidence by clinical question and outcome.

Author Contributions: S.G.A.—Conceptualization, Data curation, Formal analysis, Methodology, Writing—original draft and Writing—review & editing. B.F.L.—Data curation, Formal analysis, Methodology, Writing—original draft and Writing—review & editing. C.R.T.—Formal analysis, Methodology, Writing—original draft and Writing—review & editing. D.T.H.—Formal analysis, Methodology, Writing—original draft and Writing—review & editing. J.M.S.—Writing—original draft and Writing—review & editing. S.D.—Conceptualization, Data Curation, Methodology, Writing—original draft and Writing—review & editing. M.D.—Conceptualization, Methodology,

Writing—original draft and Writing—review & editing, Supervision. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable (review of published data).

Informed Consent Statement: Not applicable.

Data Availability Statement: All data analyzed in this review were extracted from the published reports cited in the article. The data extraction form and extracted data are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Schaff, L.R.; Mellinghoff, I.K. Glioblastoma and other primary brain malignancies in adults: A review. *JAMA* **2023**, *329*, 574–587. https://doi.org/10.1001/jama.2023.0023.
2. Louis, D.N.; Perry, A.; Wesseling, P.; Brat, D.J.; Cree, I.A.; Figarella-Branger, D.; Hawkins, C.; Ng, H.K.; Pfister, S.M.; Reifenberger, G.; et al. The 2021 WHO Classification of Tumors of the Central Nervous System: A summary. *Neuro-Oncol.* **2021**, *23*, 1231–1251. https://doi.org/10.1093/neuonc/noab106.
3. Yan, H.; Parsons, D.W.; Jin, G.; McLendon, R.; Rasheed, B.A.; Yuan, W.; Kos, I.; Batinic-Haberle, I.; Jones, S.; Riggins, G.J.; et al. IDH1 and IDH2 mutations in gliomas. *N. Engl. J. Med.* **2009**, *360*, 765–773. https://doi.org/10.1056/NEJMoa0808710.
4. Liu, Y.; Lang, F.; Chou, F.-J.; Zaghloul, K.A.; Yang, C. Isocitrate dehydrogenase mutations in glioma: Genetics, biochemistry, and clinical indications. *Biomedicines* **2020**, *8*, 294. https://doi.org/10.3390/biomedicines8090294.
5. Venneti, S.; Huse, J.T. The evolving molecular genetics of low-grade glioma. *Adv. Anat. Pathol.* **2015**, *22*, 94–101. https://doi.org/10.1097/PAP.0000000000000049.
6. Sun, H.; Yin, L.; Li, S.; Han, S.; Song, G.; Liu, N.; Yan, C. Prognostic significance of IDH mutation in adult low-grade gliomas: A meta-analysis. *J. Neurooncol.* **2013**, *113*, 277–284. https://doi.org/10.1007/s11060-013-1107-5.
7. Baumert, B.G.; Hegi, M.E.; van den Bent, M.J.; von Deimling, A.; Gorlia, T.; Hoang-Xuan, K.; Brandes, A.A.; Kantor, G.; Taphoorn, M.J.B.; Hassel, M.B.; 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.* **2016**, *17*, 1521–1532. https://doi.org/10.1016/S1470-2045(16)30313-8.
8. Bell, E.H.; Zhang, P.; Shaw, E.G.; Buckner, J.C.; Barger, G.R.; Bullard, D.E.; Mehta, M.P.; Gilbert, M.R.; Brown, P.D.; Stelzer, K.J.; 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.* **2020**, *38*, 3407–3417. https://doi.org/10.1200/JCO.19.02983.
9. Miller, J.J.; Gonzalez Castro, L.N.; McBrayer, S.; Weller, M.; Cloughesy, T.; Portnow, J.; Andronesi, O.; Barnholtz-Sloan, J.S.; Baumert, B.G.; Berger, M.S.; et al. Isocitrate dehydrogenase (IDH) mutant gliomas: A Society for Neuro-Oncology (SNO) consensus review on diagnosis, management, and future directions. *Neuro-Oncol.* **2023**, *25*, 4–25. https://doi.org/10.1093/neuonc/noac207.
10. Morshed, R.A.; Young, J.S.; Hervey-Jumper, S.L.; Berger, M.S. The management of low-grade gliomas in adults. *J. Neurosurg. Sci.* **2019**, *63*, 450–457. https://doi.org/10.23736/S0390-5616.19.04701-5.
11. Mohile, N.A.; Messersmith, H.; Gatson, N.T.; Hottinger, A.F.; Lassman, A.; Morton, J.; Ney, D.; Nghiemphu, P.L.; Olar, A.; Olson, J.; et al. Therapy for diffuse astrocytic and oligodendroglial tumors in adults: ASCO-SNO guideline. *J. Clin. Oncol.* **2022**, *40*, 403–426. https://doi.org/10.1200/JCO.21.02036.
12. Weller, M.; van den Bent, M.; Preusser, M.; Le Rhun, E.; Tonn, J.C.; Minniti, G.; Bendszus, M.; Balana, C.; Chinot, O.; Dirven, L.; et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat. Rev. Clin. Oncol.* **2021**, *18*, 170–186. https://doi.org/10.1038/s41571-020-00447-z.
13. Blakeley, J.; Mohile, N.A.; Messersmith, H.; Lassman, A.B.; Schiff, D. Therapy for Diffuse Astrocytic and 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*, 2129–2133. https://doi.org/10.1200/JCO-25-00250.

14. Buckner, J.C.; Shaw, E.G.; Pugh, S.L.; Chakravarti, A.; Gilbert, M.R.; Barger, G.R.; Coons, S.; Ricci, P.; Bullard, D.; Brown, P.D.; et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N. Engl. J. Med.* **2016**, *374*, 1344–1355. https://doi.org/10.1056/NEJMoa1500925.
15. Taal, W.; Bromberg, J.E.C.; van den Bent, M.J. Chemotherapy in glioma. *CNS Oncol.* **2015**, *4*, 179–192. https://doi.org/10.2217/cns.15.2.
16. Lawrie, T.A.; Gillespie, D.; Dowswell, T.; Evans, J.; Erridge, S.; Vale, L.; Kernohan, A.; Grant, R. Long-term neurocognitive and other side effects of radiotherapy, with or without chemotherapy, for glioma. *Cochrane Database Syst. Rev.* **2019**, *8*, CD013047. https://doi.org/10.1002/14651858.CD013047.pub2.
17. Mellinghoff, I.K.; van den Bent, M.J.; Blumenthal, D.T.; Touat, M.; Peters, K.B.; Clarke, J.; Mendez, J.; Yust-Katz, S.; Welsh, L.; Mason, W.P.; et al. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. *N. Engl. J. Med.* **2023**, *389*, 589–601. https://doi.org/10.1056/NEJMoa2304194.
18. Cloughesy, T.F.; van den Bent, M.J.; Touat, M.; Blumenthal, D.T.; Peters, K.B.; Ellingson, B.M.; Clarke, J.L.; Mendez, J.; Yust-Katz, S.; Welsh, L.; et al. Vorasidenib in IDH1-mutant or IDH2-mutant low-grade glioma (INDIGO): Secondary and exploratory endpoints from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* **2025**, *26*, 1665–1675. https://doi.org/10.1016/S1470-2045(25)00472-3.
19. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. https://doi.org/10.1136/bmj.n71.
20. Campbell, M.; McKenzie, J.E.; Sowden, A.; Katikireddi, S.V.; Brennan, S.E.; Ellis, S.; Hartmann-Boyce, J.; Ryan, R.; Shepperd, S.; Thomas, J.; et al. Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline. *BMJ* **2020**, *368*, l6890. https://doi.org/10.1136/bmj.l6890.
21. van den Bent, M.J.; Afra, D.; de Witte, O.; Ben Hassel, M.; Schraub, S.; Hoang-Xuan, K.; Malmström, P.-O.; Collette, L.; Piérart, M.; Mirimanoff, R.; et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: The EORTC 22845 randomised trial. *Lancet* **2005**, *366*, 985–990. https://doi.org/10.1016/S0140-6736(05)67070-5.
22. Wahl, M.; Phillips, J.J.; Molinaro, A.M.; Lin, Y.; Perry, A.; Haas-Kogan, D.A.; Costello, J.F.; Dayal, M.; Butowski, N.; Clarke, J.L.; et al. Chemotherapy for adult low-grade gliomas: Clinical outcomes by molecular subtype in a phase II study of adjuvant temozolomide. *Neuro-Oncol.* **2017**, *19*, 242–251. https://doi.org/10.1093/neuonc/now176.
23. Rudà, R.; Pellerino, A.; Pace, A.; Carapella, C.M.; Dealis, C.; Caroli, M.; Faedi, M.; Bello, L.; Migliore, E.; Marchese, G.; et al. Efficacy of initial temozolomide for high-risk low grade gliomas in a phase II AINO (Italian Association for Neuro-Oncology) study: A post-hoc analysis within molecular subgroups of WHO 2016. *J. Neurooncol.* **2019**, *145*, 115–123. https://doi.org/10.1007/s11060-019-03277-x.
24. Breen, W.G.; Anderson, S.K.; Carrero, X.W.; Brown, P.D.; Ballman, K.V.; O'Neill, B.P.; Curran, W.J.; Abrams, R.A.; Laack, N.N.; Levitt, R.; 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.* **2020**, *22*, 830–837. https://doi.org/10.1093/neuonc/noaa021.
25. Sterne, J.A.C.; Savović, J.; Page, M.J.; Elbers, R.G.; Blencowe, N.S.; Boutron, I.; Cates, C.J.; Cheng, H.-Y.; Corbett, M.S.; Eldridge, S.M.; et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* **2019**, *366*, l4898. https://doi.org/10.1136/bmj.l4898.
26. Bassler, D.; Briel, M.; Montori, V.M.; Lane, M.; Glasziou, P.; Zhou, Q.; Heels-Ansdell, D.; Walter, S.D.; Guyatt, G.H. STOPIT-2 Study Group. Stopping randomized trials early for benefit and estimation of treatment effects: Systematic review and meta-regression analysis. *JAMA* **2010**, *303*, 1180–1187. https://doi.org/10.1001/jama.2010.310.
27. Karim, A.B.M.F.; Afra, D.; Cornu, P.; Bleehan, N.; Schraub, S.; De Witte, O.; Darcel, F.; Stenning, S.; Pierart, M.; Van Glabbeke, M. Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BRO4: An interim analysis. *Int. J. Radiat. Oncol. Biol. Phys.* **2002**, *52*, 316–324. https://doi.org/10.1016/S0360-3016(01)02692-X.
28. van den Bent, M.J.; Wefel, J.S.; Schiff, D.; Taphoorn, M.J.B.; Jaeckle, K.; Junck, L.; Armstrong, T.; Choucair, A.; Waldman, A.D.; Gorlia, T.; et al. Response assessment in neuro-oncology (a report of the RANO group): Assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol.* **2011**, *12*, 583–593. https://doi.org/10.1016/S1470-2045(11)70057-2.
29. Kinslow, C.J.; Minniti, G.; Brown, P.D.; Vogelbaum, M.A.; Ballman, K.V.; Mercurio, A.; Siegelin, M.D.; Kocakavuk, E.; Tuohy, K.; Mansouri, A.; et al. Prognostic and predictive effect of age in molecularly defined lower-grade gliomas. *J. Clin. Oncol.* **2026**, *44*, 2811–2823. https://doi.org/10.1200/JCO-25-01846.

30. Karschnia, P.; Young, J.S.; Wijnenga, M.M.J.; Sciortino, T.; Teske, N.; Corell, A.; Wagner, A.; Youssef, G.; Park, Y.W.; Häni, L.; et al. A prognostic classification system for extent of resection in IDH-mutant grade 2 glioma: An international, multicentre, retrospective cohort study with external validation by the RANO resect group. *Lancet Oncol.* **2025**, *26*, 1638–1650. https://doi.org/10.1016/S1470-2045(25)00534-0.
31. Baumert, B.G.; Hegi, M.E.; van den Bent, M.J.; von Deimling, A.; Gorlia, T.; Hoang-Xuan, K.; Brandes, A.A.; Sargos, P.; Taphoorn, M.J.B.; Vauleon, E.; et al. Temozolomide versus radiotherapy as first-line therapy for low-grade glioma: Mature results of a randomized phase III trial (EORTC 22033-26033/NCIC-CTG/TROG/MRC-CTU). *J. Clin. Oncol.* **2026**, *44*, 2800–2810. https://doi.org/10.1200/JCO-25-02735.
32. U.S. Food and Drug Administration. FDA Approves Vorasidenib for Grade 2 Astrocytoma or Oligodendroglioma with a Susceptible IDH1 or IDH2 mutation. 2024. Available online: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-vorasidenib-grade-2-astrocytoma-or-oligodendroglioma-susceptible-idh1-or-idh2-mutation (accessed on 5 November 2026).
33. European Medicines Agency. Voranigo: EPAR—Product Information. Available online: https://www.ema.europa.eu/en/documents/product-information/voranigo-epar-product-information_en.pdf (accessed on 2 November 2026).
34. Mellinghoff, I.K.; Penas-Prado, M.; Peters, K.B.; Burris, H.A., 3rd; Maher, E.A.; Janku, F.; Cote, G.M.; de la Fuente, M.I.; Clarke, J.L.; Ellingson, B.M.; et al. Vorasidenib, a dual inhibitor of mutant IDH1/2, in recurrent or progressive glioma; results of a first-in-human phase I trial. *Clin. Cancer Res.* **2021**, *27*, 4491–4499. https://doi.org/10.1158/1078-0432.CCR-21-0611.
35. Shi, D.D.; Calvo Fernández, E.; Puliyappadamba, V.T.; Lanman, T.A.; Xiao, Y.; Wen, Z.; Minor, M.; Prost, D.; Lasica, A.B.; Cai, F.; et al. Vorasidenib improves response to subsequent chemoradiation in a genetically engineered mouse model of IDH-mutant glioma. *Sci. Transl. Med.* **2026**, *18*, eaee5876. https://doi.org/10.1126/scitranslmed.aee5876.
36. Wen, P.Y.; van den Bent, M.; Youssef, G.; Cloughesy, T.F.; Ellingson, B.M.; Weller, M.; Galanis, E.; Barboriak, D.P.; de Groot, J.; Gilbert, M.R.; et al. RANO 2.0: Update to the Response Assessment in Neuro-Oncology criteria for high- and low-grade gliomas in adults. *J. Clin. Oncol.* **2023**, *41*, 5187–5199. https://doi.org/10.1200/JCO.23.01059.
37. Karim, A.B.; Maat, B.; Hatlevoll, R.; Menten, J.; Rutten, E.H.; Thomas, D.G.; Mascarenhas, F.; Horiot, J.C.; Parvinen, L.M.; van Reijn, M.; et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. *Int. J. Radiat. Oncol. Biol. Phys.* **1996**, *36*, 549–556. https://doi.org/10.1016/s0360-3016(96)00352-5.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.