Supplementary Materials

Numbers in square brackets refer to the reference list of the main article.

Table S1. Search terms and results for each database.

Database	Search Results	Search Terms
PubMed	113	("vorasidenib"[Title/Abstract] OR "AG-881"[Title/Abstract]) AND (glioma OR astrocytoma OR oligodendroglioma OR "diffuse glioma" OR "low-grade")
Scopus	152	TITLE-ABS-KEY ((vorasidenib OR "AG-881") AND (glioma OR astrocytoma OR oligodendroglioma OR "diffuse glioma" OR "low-grade"))
Web of Science	137	TS= ((vorasidenib OR "AG-881") AND (glioma OR astrocytoma OR oligodendroglioma OR "diffuse glioma" OR "low-grade"))

Table S2. Detailed characteristics of included studies (12 reports of 10 studies).

Study	Country	Study design	Study period	Sample size	Eligible patients receiving vorasidenib	WHO grade	IDH subtype	Intervention	Comparator	Follow-up
Mellinghoff et al. (2021) [48]	United States	Multicenter, open-label, first-in-human phase 1 dose-escalation trial	Jun 2015 – Jun 2017	52 glioma patients (93 total solid tumors)	Recurrent/progressive IDH1/2-mutant glioma after standard therapy (enhancing and non-enhancing)	Grade 2 (48.1%), grade 3 (42.3%), grade 4 (7.7%)	IDH1 (92.3%), IDH2 (5.8%)	Vorasidenib once daily in continuous 28-day cycles (10–300 mg)	None (single-arm)	Median treatment duration: 26.8 months (non-enhancing glioma); 3.3 months (enhancing glioma)
Mellinghoff et al. (2023a) [49]	United States	Randomized, multicenter, open-label, perioperative phase 1 trial	Mar 2018 – Apr 2019	49 patients	Recurrent non-enhancing IDH1-R132H-mutant glioma scheduled for surgery; 24 vorasidenib-treated (including 2 untreated preoperative controls), 25 ivosidenib-treated	Grade 2 (91.7% of vorasidenib-treated; 87.8% overall)	IDH1-R132H	Vorasidenib (10 or 50 mg daily) or Ivosidenib (500 mg daily or 250 mg twice daily) before surgery, followed by postoperative treatment	Untreated perioperative control arm (5 patients)	Median postoperative treatment: vorasidenib 14.3 months; Ivosidenib 15.1 months; follow-up ongoing
Mellinghoff et al. (2023b) [50]	77 centers in 10 countries	Double-blind, RCT, placebo-	Jan 2020 – Sep 2022	331 randomized (168	Residual/recurrent WHO grade 2	Grade 2	IDH1 or IDH2	Vorasidenib 40 mg once daily	Placebo	Median follow-up 14.2 months

		controlled phase 3 trial (INDIGO)		vorasidenib, 163 placebo); 167 vorasidenib-treated	IDH1/2-mutant glioma after surgery only, non-enhancing disease, no prior RT/CT					from randomization (data cut-off 6 September 2022); 52 placebo patients crossed over to vorasidenib
Cloughesy et al. (2025) [25] — linked report of INDIGO	77 centers in 10 countries	Secondary and exploratory endpoints of the double-blind phase 3 RCT	Jan 2020 – Feb 2022 (enrolment); blinded follow-up to unblinding on 7 March 2023	331 (168 vorasidenib, 163 placebo)	As INDIGO	Grade 2	IDH1 or IDH2	Vorasidenib 40 mg once daily	Placebo	Median follow-up 20.1 months (IQR 15.9–23.8)
Himstead et al. (2025) [77]	United States	Single-patient case report	Not reported	1 patient	Recurrent non-enhancing WHO grade 3 oligodendroglioma treated via expanded access	Grade 3	IDH1 R132H-mutant, 1p/19q-codeleted	Vorasidenib 40 mg once daily	None	8 months
Rudà et al. (2025) [78]	Italy	Single-patient case report	Oct 2024- Jun 2025	1 patient	Residual WHO grade 2 IDH-mutant oligodendroglioma with persistent postoperative seizures	Grade 2	IDH1 R132H	Vorasidenib 40 mg daily	None	8 months
Dipasquale et al. (2026) [79]	Italy and Netherlands	Multicenter retrospective pilot cohort study	Apr 2024 – Jan 2025	10 patients	WHO grade 3 IDH-mutant glioma after surgery alone (8 residual, 2 recurrent); good performance status; predominantly non-enhancing residual disease	Grade 3	IDH-mutant (predominantly IDH1 R132H)	Vorasidenib 40 mg once daily	None	Median 11.5 months (range 7.5–17.4 months)
Kim et al. (2026) [80]	United States	Single-patient case report	Not reported	1 patient	WHO grade 2 IDH-mutant brainstem astrocytoma after biopsy	Grade 2	IDH1 R132C	Vorasidenib 40 mg once daily	None	11 months
Mandonnet (2026) [76]	France	Retrospective single-center case series	Surgeries 2016–2021; INDIGO enrolment Mar 2021- Jan 2022	8 patients	Patients previously enrolled in the INDIGO trial (no additional eligibility criteria)	Grade 2	IDH-mutant (subtype not individually specified)	Vorasidenib (7 immediate; 1 after placebo crossover)	Pre-treatment tumor growth within the same patients	Median follow-up under vorasidenib 45.5 months (range 3–56), measured from treatment initiation (March 2023 for the crossover patient); drug

										exposure not reported
Touat et al. (2026) [75] — linked report of the Mandonnet series	France	Two-patient molecular case report (INDIGO participants; cases 2 and 4 of the Mandonnet series)	2018–2025	2 patients	Vorasidenib non-responders who discontinued within the first year for progression	Grade 2 astrocytoma	IDH-mutant (subtype not specified)	Vorasidenib within INDIGO	None	Approximately 5 and 9 months on vorasidenib; follow-up to 2025 after rescue therapy
Schultz et al. (2026) [81]	United States	Retrospective single-center cohort study	Jan 2020- Dec 2025	29 patients	IDH-mutant gliomas previously treated with ivosidenib, including WHO grade 2–4 tumors	Grade 2 astrocytoma (31.0%); grade 3 astrocytoma (10.3%); grade 4 astrocytoma (10.3%); grade 2 oligodendroglioma (34.5%); grade 3 oligodendroglioma (13.8%)	IDH1 R132H (97.0%), IDH1 R132C (3.0%)	Vorasidenib after prior ivosidenib	None (single-arm sequential therapy cohort)	Follow-up from diagnosis: median 5.6 years (range 1.4–19.6), not comparable with on-treatment follow-up; on-treatment follow-up not reported (data cut-off 15 December 2025)
Simicic et al. (2026) [82]	United States	Prospective longitudinal imaging biomarker study	Not reported	18 enrolled (13 ivosidenib, 5 vorasidenib); 14 in final MRS analysis (9 ivosidenib, 5 vorasidenib)	IDH-mutant glioma receiving ivosidenib or vorasidenib	Grade 2-3 astrocytoma and oligodendroglioma	IDH1 and IDH2 mutant	Ivosidenib (500 mg daily) or vorasidenib (40 mg daily)	Baseline versus on-treatment imaging (within-patient comparison)	Median on-treatment follow-up 3.9 months (median scan interval 4.3 months)

Linked reports are listed with their parent study.

Table S3. Patient demographics and baseline characteristics.

Study	Age	Sex	Histology	Astrocytoma/Oligodendroglioma	1p/19q status	Tumor location	Surgical procedure, extent and residual disease	Prior RT	Prior chemotherapy	ECOG/KPS
Mellinghoff et al. (2021) [48]	Median 42.5 years (range 16–73)	50.0% male, 50.0% female	Diffuse glioma (enhancing and non-enhancing)	Not separately reported	Intact 38.5%; Deleted 30.8%; Unknown 30.8%	Not reported	All had previous standard treatment; 21.2% had surgery only. Extent of resection and residual volume not reported.	57.7%	75.0% received prior systemic therapy (median 2 prior therapies)	ECOG 0: 34.6%; ECOG 1: 59.6%; ECOG 2: 1.9%
Mellinghof	Median 49	Vorasidenib	Diffuse low-grade	Astrocytoma 45.8%,	Codeleted: 50.0%	Not reported	All had previous	29.2%	41.7%	KPS ≥80 in

f et al. (2023a) [49]	years (vorasidenib); 37 years (ivosidenib)	: 66.7% male; Ivosidenib: 68.0% male	glioma	Oligodendroglioma 54.2%	(Vorasidenib), 52.0% (Ivosidenib)		surgery and underwent on-study resection; 11 had no postoperative residual disease. Formal pre-treatment EOR categories not reported.	(vorasidenib); 28.0% (ivosidenib)	(vorasidenib); 56.0% (ivosidenib)	all patients; majority KPS 90–100
Mellinghoff et al. (2023b) [50]	Median 40.5 years (Vorasidenib vs 39 years (Placebo)	Male: 60.1% vs 52.8%	Diffuse glioma	Oligodendroglioma 52.4% vs 51.5%; Astrocytoma 47.6% vs 48.5%	Codeleted: 52.4% vs 51.5%; Non-codeleted: 47.6% vs 48.5%	Frontal lobe: 63.7% vs 70.6%	All had ≥1 previous surgery; 25.0% had ≥2 surgeries in the vorasidenib arm. Measurable residual/recurrent disease required; formal EOR categories not reported.	None	None	KPS ≥80; >53% had KPS 100
Himstead et al. (2025) [77]	71 years	Male	Oligodendroglioma	Oligodendroglioma	Codeleted	Left parietal region	Subtotal re-resection; postoperative residual tumor volume 45 cm3.	None	None	Not reported
Rudà et al. (2025) [78]	52 years	Male	Oligodendroglioma	Oligodendroglioma	Codeleted	Right frontotemporoinsular (insula)	Subtotal resection; postoperative residual tumor volume 32.2 cm3.	None	None	Not reported
Dipasquale et al. (2026) [79]	Median 52 years (range 31–74)	60.0% male, 40.0% female	6 astrocytoma; 4 oligodendroglioma	Oligodendroglioma (40.0%)	Present in oligodendrogliomas; CDKN2A/B homozygous deletion in 1 patient; absent in most tested patients	Frontal lobe	5 complete (maximal T2/FLAIR) resections, 3 submaximal and 2 minimal resections; 8 residual and 2 recurrent tumors; 2 tumors contrast-enhancing before surgery, none after	None	None	90–100 in all patients
Kim et al. (2026) [80]	20 years	Female	Astrocytoma	Astrocytoma	Non-codeleted (astrocytoma)	Brainstem (left greater than right; dorsal pons extending to	Stereotactic biopsy only; no cytoreductive resection.	None	None	Not reported

						cervicomedullary junction)				
Mandonnet (2026) [76]	Median 42.5 years (range 32–54)	Not reported	Diffuse WHO grade 2 glioma	Not reported	1 patient codeleted; 7 non-codeleted	Frontal (3), Insular (4), Temporal (1)	Awake resection in all patients; median EOR 98% (range 92%–100%); postoperative volume range 0–6.5 cm3.	None	None	Not reported
Touat et al. (2026) [75]	32 and 41 years	Male (2/2)	Astrocytoma	Astrocytoma (2/2)	Not reported	Right fronto-insular; left temporal	Awake resection: subtotal (95%, residual 6.5 cm^3) and gross-total resection with slowly growing recurrence (12 cm^3 at inclusion)	None	None	Not reported
Schultz et al. (2026) [81]	Median 42 years (IQR 36–52; range 25–72)	66.0% male, 34.0% female	IDH-mutant astrocytoma and oligodendroglioma	Astrocytoma: 15 (51.7%); Oligodendroglioma: 14 (48.3%)	Not reported	Not reported	Resection in 23/29 patients (79.3%); EOR and residual volume not reported.	16 patients (55.2%)	Temozolomide 52%; PCV 7%; lomustine 7%; bevacizumab 10%; pembrolizumab 3%	ECOG collected but baseline values Not reported
Simicic et al. (2026) [82]	Median 46 years (range 25–73)	64.0% male, 36.0% female	Astrocytoma (grade 2–3) and oligodendroglioma (grade 2–3)	Astrocytoma 7 (50.0%); Oligodendroglioma 7 (50.0%)	Codeleted in oligodendrogliomas	Not reported	Surgery only in 11/14 patients (79%); EOR and residual volume not reported.	21% previously received RT	PCV in 21%; remainder surgery only	Not reported

Surgical terminology retained as reported; maximal T2/FLAIR, complete, gross-total, and supramaximal resection are not interchangeable.

Table S4. Detailed treatment exposure, stopping criteria, and discontinuation.

Study	Dose	Schedule and planned stopping rule	Observed treatment duration or follow-up	Treatment setting	Dose interruption or reduction	Status at data cut-off/reason for discontinuation
Mellinghoff et al. (2021) [48]	Dose escalation 10–300 mg once daily (starting dose 25 mg)	Continuous 28-day cycles until disease progression or unacceptable toxicity	Non-enhancing: median 26.8 months, range 1.0–50.9; enhancing: median 3.3 months, range 0.2–53.6	Recurrent/progressive disease after standard therapy	13.5%	Non-enhancing: 8/22 remained on treatment; progression 10/22, adverse events 2/22, withdrawal 2/22. Enhancing: 1/30 remained on treatment; progression 24/30, withdrawal 5/30
Mellinghoff et al. (2023a) [49]	50 mg daily or 10 mg daily	28 (+7) days before surgery, followed by optional	Median postoperative duration 14.3 months, range	Perioperative (pre- + post-surgery)	Intra-patient dose escalation permitted; dose reductions	17/24 remained on vorasidenib; 5/24

		continuous postoperative treatment until progression or unacceptable toxicity	0.9–22.6		not reported	discontinued because of progression and 2/24 by investigator decision
Mellinghoff et al. (2023b) [50]	40 mg orally once daily	Continuous 28-day cycles until independently confirmed progression, unacceptable toxicity, need for other anticancer therapy, pregnancy, withdrawal, or investigator decision	Median follow-up 14.2 months (primary) and 20.1 months (linked report) from randomization; median completed treatment duration not reported	Postoperative (surgery-only watch-and-wait population)	Interruption for AEs 29.9% vs. 22.7%; reduction for AEs 10.8% vs. 3.1%	131/167 (78.4%) remained on vorasidenib at database lock; 24 discontinued after progression, 6 because of adverse events, 5 withdrew, and 1 was withdrawn by the investigator
Himstead et al. (2025) [77]	40 mg orally once daily	Continuous oral therapy	8 months; treatment ongoing	Adjuvant therapy following recurrent grade 3 disease after subtotal resection	None	Temporary 2-week interruption for transaminitis; resumed at 40 mg
Rudà et al. (2025) [78]	40 mg orally once daily	Continuous daily oral treatment	Seizure-free and on treatment at 8 months; eighth cycle ongoing	Postoperative treatment for residual disease	None	None
Dipasquale et al. (2026) [79]	40 mg orally once daily	Continuous oral treatment; stopping rule not prospectively standardised because treatment was provided through an early-access program	Median follow-up 11.5 months; range 7.5–17.4; median treatment duration not separately reported	First postoperative treatment after surgery	Temporary interruption in 3/10 (hepatotoxicity; median 23 days to resolution); reduction to 20 mg in 1/10 after grade 3 transaminase elevation	8/10 (80.0%) remained without progression; 2 discontinued after progression and received radiotherapy/chemotherapy.
Kim et al. (2026) [80]	40 mg orally once daily	Continuous oral treatment	11 months; treatment ongoing	First-line systemic therapy after biopsy	None	None
Mandonnet (2026) [76]	40 mg once daily (INDIGO protocol; 7 vorasidenib arm, 1 placebo crossover)	Continuous INDIGO-protocol treatment; discontinued for progression/reoperation or continued while clinical benefit was maintained	Median follow-up under vorasidenib 45.5 months (range 3–56) from treatment initiation; exposure not separately reported	Postoperative treatment	Not reported	5/8 (62.5%) remained on vorasidenib; 3 (37.5%) underwent reoperation after 3, 10, and 36 months
Schultz et al. (2026) [81]	Not reported	Continuous oral treatment	Follow-up from diagnosis median 5.6 years; on-treatment exposure reported only for discontinuers (median 3.5 months, range 1.4–5.4); median previous ivosidenib duration 10.6 months	Sequential treatment after ivosidenib	Not reported	22/29 (75.9%) on treatment at data cut-off; the publication also reports 9 discontinuers (inconsistent with 22/29 continuing); 1 discontinued for subjective cognitive decline
Simicic et al. (2026) [82]	Vorasidenib 40 mg daily; Ivosidenib 500 mg daily	Continuous routine clinical treatment; no predefined stopping strategy reported	Vorasidenib subgroup: median 3.7 months, IQR 3.0–4.6; no patient discontinued during imaging follow-up	Routine clinical treatment following surgery ± chemoradiotherapy	None	None

"Continuous" indicates repeated administration without a predefined number of cycles; it does not demonstrate that lifelong therapy is required. Follow-up is not equivalent to treatment exposure unless stated.

Table S5. Detailed efficacy, seizure, and clinical outcomes.

Study	Objective response rate	Progression-free survival	Overall survival	Tumor volume	Seizure control	Clinical outcome	Other outcomes
Mellinghoff et al. (2021) [48]	RANO-LGG (non-enhancing; includes minor response): 18.2% (1 PR + 3 MR); RANO (enhancing): 0%	Overall glioma: 7.5 months; non-enhancing: 36.8 months (95% CI 11.2–40.8); Enhancing: 3.6 months (95% CI 1.8–6.5)	Not reported	Sustained tumor shrinkage observed in multiple patients; volumetric reduction demonstrated in exploratory analysis	Not assessed as an efficacy outcome. Seizure occurred as an AE in 15/52 patients (28.8%); grade ≥3 in 4/52 (7.7%). Baseline-adjusted seizure frequency and attribution were not reported.	Not reported	Not reported
Mellinghoff et al. (2023a) [49]	RANO-LGG (includes minor response): 42.9% at 50 mg (2 PR, 4 MR); 10.0% at 10 mg	Immature; ongoing	Not reported	Tumor 2-HG reduced by 92.6% with vorasidenib 50 mg	Not assessed as an efficacy outcome. Aura was reported in 3/24 vorasidenib-treated patients as an AE.	Not reported	Increased DNA hydroxymethylation, reduced proliferation, reversal of proneural/stemness signatures, increased immune activation
Mellinghoff et al. (2023b) [50]	Modified RANO-LGG (blinded independent review); best overall response reported in trial supplement	Vorasidenib vs. placebo: 27.7 vs. 11.1 months; HR 0.39 (0.27–0.56), P < 0.001. Linked report (20.1 months): not reached vs. 11.4 months; HR 0.35 (0.25–0.49). TTNI HR 0.26 (0.15–0.43); updated 0.25 (0.16–0.40)	Not reported (immature; follow-up ongoing)	Tumor growth rate −1.3% (−3.2 to 0.7) vs. +14.4% (12.0 to 16.8) per 6 months (linked report)	Primary report: seizure outcomes not presented. Linked report (exploratory, patients with ≥1 seizure): 18.2 (8.4–39.5) vs. 51.2 (22.9–114.8) seizures per person-year	FACT-Br total score stable and similar between arms; no difference in five neurocognitive domains (linked report)	
Himstead et al. (2025) [77]	Stable disease (best response)	Not reported	Alive at 8 months	Residual tumor volume decreased from 45 cm3 to 40 cm3 (11% reduction) after 8 months of treatment	Not reported	Clinically stable	First reported use in CNS WHO grade 3 oligodendroglioma; transaminitis resolved after 2-week interruption
Rudà et al. (2025) [78]	PET partial response	Not reported	Alive at 8 months	progressive volume reduction (baseline, 3 and 6 cycles)	Approximately 2 seizures/week at baseline; seizure-free from month 1 through month 8 without ASM modification.	Not reported	F-DOPA PET demonstrated metabolic response preceding MRI changes
Dipasquale et al. (2026) [79]	Stable disease in all patients as best response	6-month PFS 90.0%; 12-month PFS 77.1%	Not reported	Median residual T2/FLAIR diameter 2.8 cm after surgery	3/5 (60.0%) improved. Two became seizure-free after cycle 1 without ASM changes; one improved from approximately 2 focal motor seizures/day to 1 every 15 days, with concurrent cenobamate	Not reported	No deterioration in KPS despite progression

					introduction.		
Kim et al. (2026) [80]	Radiological response	Not reached	Alive at 11 months	Significant reduction in T2/FLAIR lesion size with reduced mass effect	Not reported	Marked clinical improvement with near-complete resolution of diplopia and facial myokymia	First reported clinical and radiologic response in IDH-mutant brainstem astrocytoma
Mandonnet (2026) [76]	2/8 patients (25.0%) demonstrated tumor shrinkage with slope inversion	Not reported as PFS; 3/8 with unchanged growth slope underwent reoperation after 3, 10, and 36 months	Not reported	Median tumor diameter slope decreased from 4.25 mm/year before treatment to 0.15 mm/year during vorasidenib	All 8 presented with seizures (5 focal/partial and 3 generalized); longitudinal seizure outcomes during treatment were not reported.	Not reported	Three distinct radiological response patterns identified: progression, stabilization, response
Touat et al. (2026) [75]	Progressive disease by RANO-LGG in both	Progression after approximately 9 and 5 months	Alive; one recurred with CSF dissemination after rescue therapy, one stable	Growth 5.4 → 6.1 and 4.8 → 7.0 mm/year (before vs. during vorasidenib)	Seizure-free on levetiracetam before treatment; not reported during treatment	Rescue surgery, PCV, and radiotherapy effective	IDH mutation, MGMT status, and methylation class preserved at progression
Schultz et al. (2026) [81]	Not reported as ORR; RANO 2.0 (retrospective); stable disease predominant	Grade 2: 6-month PFS 94.4%; grade 3-4: 43.8%	Grade 3-4: 6-month OS 80%; 12-month OS 66.7%; no deaths among grade 2 patients during study period	Not reported	No seizure-specific longitudinal outcome reported.	Two patients switching because of toxicity experienced symptom resolution	Disease stabilization was the predominant radiographic response
Simicic et al. (2026) [82]	Not assessed using conventional radiographic response criteria	Not reported	Not reported	Growth arrest with small non-significant decrease (P = 0.08; pooled ivosidenib and vorasidenib)	No clinical seizure outcome reported; study discussed 2-HG as a potential epileptogenic mediator.	Not reported	Significant reductions in 2-HG, total choline and glutamine during treatment

Response rates obtained with RANO-LGG (which includes minor responses), RANO 2.0, volumetric, or diameter-slope methods are not comparable.

Table S6. Detailed safety outcomes.

Study	Any Adverse Effect	Common Adverse Effect	ALT elevation	AST elevation	Adverse events	Dose interruption	Dose reduction	Treatment discontinuation	Death
Mellinghoff et al. (2021) [48]	100%	Fatigue, seizure, headache, nausea, ALT increased, AST increased, neutrophil count decreased, cough, diarrhea, WBC decreased, aphasia, hypoglycemia, upper respiratory tract infection (any-grade, >10% in glioma cohort)	44.2% (grade ≥3: 5.8%)	40.4% (grade ≥3: 3.8%)	Grade ≥3: 19.2%; serious AEs: 17.3%	Not reported	13.5%	3.8% discontinued due to AE	None

Mellinghoff et al. (2023a) [49]	100% (24/24)	Headache, nausea, diarrhea, fatigue (vorasidenib); headache, anemia, diarrhea, seizures (ivosidenib)	20.8% (grade ≥3: 4.2%)	16.7% (grade ≥3: 0%)	Grade ≥3: 29.2%	Not reported	Not reported (intra-patient dose escalation permitted)	None	None
Mellinghoff et al. (2023b) [50]	94.6% vs. 93.3%	ALT increase (38.9%), COVID-19 (32.9%), fatigue (32.3%), headache (26.9%), diarrhea (24.6%), nausea (21.6%), dizziness (15.0%), seizure (13.8%), constipation (12.6%)	38.9% vs. 14.7% (grade ≥3: 9.6% vs. 0%)	28.7% vs. 8.0% (grade ≥3: 4.2% vs. 0%)	Grade ≥3: 22.8% vs. 13.5%	29.9% vs. 22.7%	10.8% vs. 3.1%	3.6% vs 1.2%	None
Cloughesy et al. (2025) [25]	Not extracted	Grade ≥3: increased ALT, AST, seizures, GGT	Grade ≥3: 10% vs. 1%	Grade ≥3: 5% vs. 0%	Serious AEs 12% vs. 6%	Not extracted	Not extracted	<5% for AEs	No treatment-related deaths
Himstead et al. (2025) [77]	Mild asymptomatic transaminitis	Grade 1 transaminitis	Grade 1 transaminitis (ALT/AST not separated)	See ALT	No grade ≥3	Temporary 2-week interruption	None	None	None
Rudà et al. (2025) [78]	None reported	None (normal liver enzymes)	None	None	None	None	None	None	None
Dipasquale et al. (2026) [79]	Hepatotoxicity in 3/10	ALT/AST elevation	3/10 (grade 2 in 2, grade 3 in 1)	3/10 (reported together with ALT)	Grade 3 in 1/10	3/10 (median 23 days to resolution)	1/10 (20 mg)	None because of toxicity	None
Kim et al. (2026) [80]	None	None reported	No	No	None	None	None	None	None
Mandonnet (2026) [76]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Three patients stopped because of tumor progression requiring reoperation (not toxicity-related)	None
Schultz et al. (2026) [81]	Joint pain, fatigue, headache, hepatotoxicity, mood changes, myalgia	Hepatotoxicity, fatigue, headache, joint pain, myalgia	Grade 1 hepatotoxicity in 6 patients (21%)	Not separately reported	No grade ≥3 reported; grade ≥2 fatigue (3), headache (1), myalgia (1)	Not reported	None	One patient discontinued because of subjective cognitive decline; no discontinuations for hepatotoxicity	None
Simicic et al. (2026) [82]	Pooled across agents: 50% (grade 1: 29%; grade 2: 21%)	Not reported by agent	Not reported	Not reported	Grade ≥3: 0% (pooled)	Not reported	Not reported	None	None

Values are vorasidenib vs. placebo for INDIGO.

Table S7. Detailed imaging and molecular biomarker outcomes.

Study	Imaging	F-DOPA PET	MRS	2-HG reduction	Tumor kinetics	Molecular findings
Mellinghoff et al. (2021) [48]	MRI used for RANO/RANO-LGG response assessment	Not reported	Not reported	Not reported	Sequential tumor volume measurements demonstrated reduction after treatment in representative patients	Next-generation sequencing of archival tissue (29 patients); no association between individual co-mutations and tumor response identified
Mellinghoff et al. (2023a) [49]	MRI assessed by RANO-LGG	Not reported	Not reported	Vorasidenib 50 mg reduced tumor 2-HG by 92.6%; Ivosidenib 500 mg reduced 2-HG by 91.1%	Not reported	Not reported
Mellinghoff et al. (2023b) [50]	MRI using modified RANO-LGG criteria with blinded independent review	Not reported	Not reported	Not reported	Not reported	Not reported
Himstead et al. (2025) [77]	Serial MRI demonstrated persistent non-enhancing disease with reduction in T2/FLAIR abnormality	Not reported	Functional MRI performed preoperatively for language mapping (not treatment response)	Not reported	Estimated pre-treatment tumor growth rate 0.27 cm3/month; volume of diametric expansion 0.87 mm/year	IDH1 R132H mutation; retained ATRX; 1p/19q codeletion; mutations in TERT, CIC and FUBP1; no CDKN2A/B deletion; no NOTCH1 mutation
Rudà et al. (2025) [78]	Stable disease on RANO with slight progressive tumor shrinkage		Not reported	Not reported	Serial MRI and PET demonstrated progressive	IDH1 R132H mutation; 1p/19q codeletion; pTERT mutation; CDKN2A/B intact; Ki-67 <5%; no necrosis or microvascular proliferation
Dipasquale et al. (2026) [79]	MRI and 18F-FET PET	FET PET before treatment in 80%; significant uptake in 5 (median TBRmax/mean 3.19); one progressor had high uptake	Not reported	Not reported	Two patients developed T2/FLAIR progression during follow-up	All IDH R132H-mutant; Ki-67 median 7%; CDKN2A/B tested in 9 patients; MYCN amplification in one patient; one astrocytoma-high-grade methylation class; MGMT available in 5 patients (4 methylated
Kim et al. (2026) [80]	Serial MRI every 3 months	Not performed	Not performed	Not reported	Progressive reduction in tumor burden over 9–11 months	IDH1 R132C mutation; TP53 mutation; PMS1 mutation; ATRX negative
Mandonnet (2026) [76]	Serial 3T MRI every 3 months with manual FLAIR volumetry	Not performed	Not performed	Not performed	Median slope reduced from 4.25 to 0.15 mm/year; 3 progression, 3 stabilization, 2 response	Only IDH-mutant status reported; no detailed molecular subgroup analysis
Schultz et al. (2026) [81]	MRI assessed using RANO 2.0 criteria	Not reported	Not reported	Not reported	Radiographic response assessed by RANO 2.0;	IDH1 R132H (97.0%); IDH1 R132C (3.0%)

					disease stabilization predominated	
Simicic et al. (2026) [82]	Serial MRI with volumetric FLAIR assessment	Not reported	Longitudinal 2-HG-optimized single-voxel PRESS spectroscopy	Significant 2-HG reduction overall ($P < 0.001$) and in vorasidenib subgroup ($n = 5$; $P < 0.01$; Cohen's d 2.14)	Growth arrest with slight volume reduction; metabolic response preceded major volumetric changes	IDH1/IDH2-mutant gliomas; significant reductions in 2-HG, total choline and glutamine identified as imaging biomarkers of treatment response
Touat et al. (2026) [75]	MRI (RANO-LGG)	Not reported	Not reported	Not reported	Growth 5.4 → 6.1 and 4.8 → 7.0 mm/year	Targeted NGS, array CGH, and EPIC methylation: IDH mutation and methylation class (astrocytoma, IDH-mutant, lower grade) preserved; MGMT unchanged; shift toward higher-grade features in one patient

Table S8. Eligibility assessment of cited vorasidenib publications that were not included as separate studies.

Publication	Content	Decision	Reason
Cloughesy et al., Lancet Oncol 2025 [25]	INDIGO secondary and exploratory endpoints	Included (linked report)	Second report of an included study (PRISMA 2020)
Touat et al., Neurooncol Pract 2026 [75]	Two vorasidenib non-responders with molecular profiling	Included (linked report)	Same patients as cases 2 and 4 of Mandonnet 2026
Garcia et al., J Neurooncol 2025 [26]	IDH inhibitors in recurrent high-grade gliomas	Excluded	Outcomes not reported separately for vorasidenib
Drummond et al., Nat Med 2025 [83]	Perioperative IDH inhibition in treatment-naive glioma	Excluded	Intervention was safusidenib, not vorasidenib
Johnson et al., Nature 2026 [84]	Genetic and cell-state evolution of IDH-mutant glioma	Excluded	No vorasidenib-specific clinical outcomes
de la Fuente et al., Neuro Oncol 2025 [52]	Role of vorasidenib	Excluded	Narrative review
Seyve and Ducray, Curr Opin Oncol 2025 [54]	Open questions on vorasidenib	Excluded	Narrative review
Darlix et al., Neurooncol Pract 2025 [55]	Who will benefit from vorasidenib?	Excluded	Narrative review
Kim et al., J Korean Neurosurg Soc 2026 [61]	Targeting IDH-mutant glioma with vorasidenib	Excluded	Narrative review
Schiff, Neuro Oncol 2026 [62]	INDIGO incremental insights	Excluded	Editorial
Lanman and Gonzalez Castro, Cancers 2025 [57]	Systematic review of mutant IDH inhibitor trials	Excluded	Systematic review (used for citation searching)
Kessel et al., Cancer 2026 [53]	Cost-effectiveness of vorasidenib	Excluded	Economic model without patient-level outcomes

Table S9. PRISMA 2020 checklist [63].

Section and topic	Item	Checklist item	Location in manuscript
Title	1	Identify the report as a systematic review	Title
Abstract	2	See PRISMA 2020 for Abstracts checklist	Abstract; Table S10
Rationale	3	Rationale in context of existing knowledge	Section 1, paragraphs 1–4
Objectives	4	Explicit statement of objectives	Section 1, final paragraph; Section 2.1; Table 1
Eligibility criteria	5	Inclusion/exclusion criteria and grouping for syntheses	Section 2.3; Table 1
Information sources	6	Databases, registers, other sources, and dates searched	Section 2.2

Search strategy	7	Full search strategies	Table S1
Selection process	8	Methods to decide eligibility, number of reviewers, independence	Section 2.4
Data collection process	9	Methods to collect data, number of reviewers	Section 2.4
Data items	10a	Outcomes sought	Section 2.4; Table 1
Data items	10b	Other variables sought	Section 2.4
Study risk of bias assessment	11	Tools used and number of reviewers	Section 2.6
Effect measures	12	Effect measures for each outcome	Section 2.5
Synthesis methods	13a	Process to decide which studies were eligible for each synthesis	Section 2.5
Synthesis methods	13b	Data preparation for synthesis	Section 2.5
Synthesis methods	13c	Methods to tabulate or display results	Section 2.5; Tables 2–8; Figures 2–3
Synthesis methods	13d	Methods to synthesize results and rationale	Section 2.5 (SWiM; no meta-analysis)
Synthesis methods	13e	Methods to explore heterogeneity	Section 2.5
Synthesis methods	13f	Sensitivity analyses	Not applicable (no meta-analysis)
Reporting bias assessment	14	Methods to assess risk of bias due to missing results	Section 2.7
Certainty assessment	15	Methods to assess certainty	Section 2.7
Study selection	16a	Results of search and selection (flow diagram)	Section 3.1; Figure 1
Study selection	16b	Studies that appear eligible but were excluded, with reasons	Section 3.1; Table S8
Study characteristics	17	Cite and present characteristics of each study	Section 3.2; Table 2; Tables S2–S3
Risk of bias in studies	18	Risk of bias for each study	Section 3.11; Tables 9–12
Results of individual studies	19	Summary statistics and effect estimates for each study	Sections 3.4–3.10; Tables 3–8; Tables S4–S7
Results of syntheses	20a	Characteristics and risk of bias among contributing studies	Sections 3.2, 3.6; Figure 2
Results of syntheses	20b	Results of statistical syntheses	Not applicable (narrative synthesis); Section 3.6
Results of syntheses	20c	Investigations of heterogeneity	Section 3.6 (by population group)
Results of syntheses	20d	Sensitivity analyses	Not applicable
Reporting biases	21	Risk of bias due to missing results	Section 4.12
Certainty of evidence	22	Certainty for each outcome	Section 3.12; Table 13
Discussion	23a	General interpretation	Sections 4.1–4.3
Discussion	23b	Limitations of the evidence	Sections 4.2, 4.12
Discussion	23c	Limitations of the review processes	Section 4.12
Discussion	23d	Implications for practice, policy, and research	Sections 4.4–4.11; Section 5
Registration and protocol	24a	Registration information	Section 2.1 (not registered)
Registration and protocol	24b	Where the protocol can be accessed	Section 2.1 (no protocol prepared)
Registration and protocol	24c	Amendments to registration or protocol	Section 2.1 (changes during peer review)
Support	25	Sources of financial or non-financial support	Funding statement
Competing interests	26	Declaration of competing interests	Conflicts of Interest statement
Availability of data, code, and other materials	27	Availability of data and materials	Data Availability Statement; Tables S1–S8

Locations refer to section, table, and figure numbers to avoid mismatch with page/line numbers after typesetting.

Table S10. PRISMA 2020 for Abstracts checklist [63].

Section and topic	Item	Checklist item	Reported?
Title	1	Identify the report as a systematic review	Yes
Objectives	2	Explicit statement of main objectives	Yes (Background)

Eligibility criteria	3	Inclusion and exclusion criteria	Yes (Methods)
Information sources	4	Sources and date last searched	Yes (Methods)
Risk of bias	5	Methods used to assess risk of bias	Yes (Methods)
Synthesis of results	6	Methods used to present and synthesize results	Yes (Methods: SWiM, GRADE, population strata)
Included studies	7	Number of studies and participants and relevant characteristics	Yes (Results)
Synthesis of results	8	Results for main outcomes	Yes (Results)
Limitations of evidence	9	Brief summary of limitations of evidence	Yes (certainty ratings; very low certainty outside INDIGO)
Interpretation	10	General interpretation and implications	Yes (Conclusions)
Funding	11	Primary source of funding	No external funding (declared in manuscript)
Registration	12	Register name and number	Not registered (stated in Methods)

Table S11. SWiM (Synthesis Without Meta-analysis) reporting checklist [64].

SWiM item	Description	Location
1. Grouping studies for synthesis	Clinical population groups (a)–(e), with rationale	Section 2.5; Table 1; Figure 2
2. Describe the standardized metric and transformation methods	Effect estimates reported as published (HR, proportions, medians); no transformation	Section 2.5
3. Describe the synthesis methods	Structured narrative synthesis; no pooling; no vote counting	Section 2.5
4. Criteria used to prioritize results	RCT prioritized for efficacy; design hierarchy within groups	Section 2.5
5. Investigation of heterogeneity	Descriptive, by population, enhancement, grade, prior therapy, and design	Sections 2.5, 3.6
6. Certainty of evidence	GRADE, including rating without a single pooled estimate	Sections 2.7, 3.12; Table 13
7. Data presentation methods	Tables by domain and population; evidence map; forest plot of INDIGO subgroups	Tables 2–8; Figures 2–3
8. Reporting results	Results reported per group, with response criteria stated explicitly	Section 3.6; Table 5
9. Limitations of the synthesis	Single RCT, heterogeneity, overlap, inconsistent reporting	Section 4.12