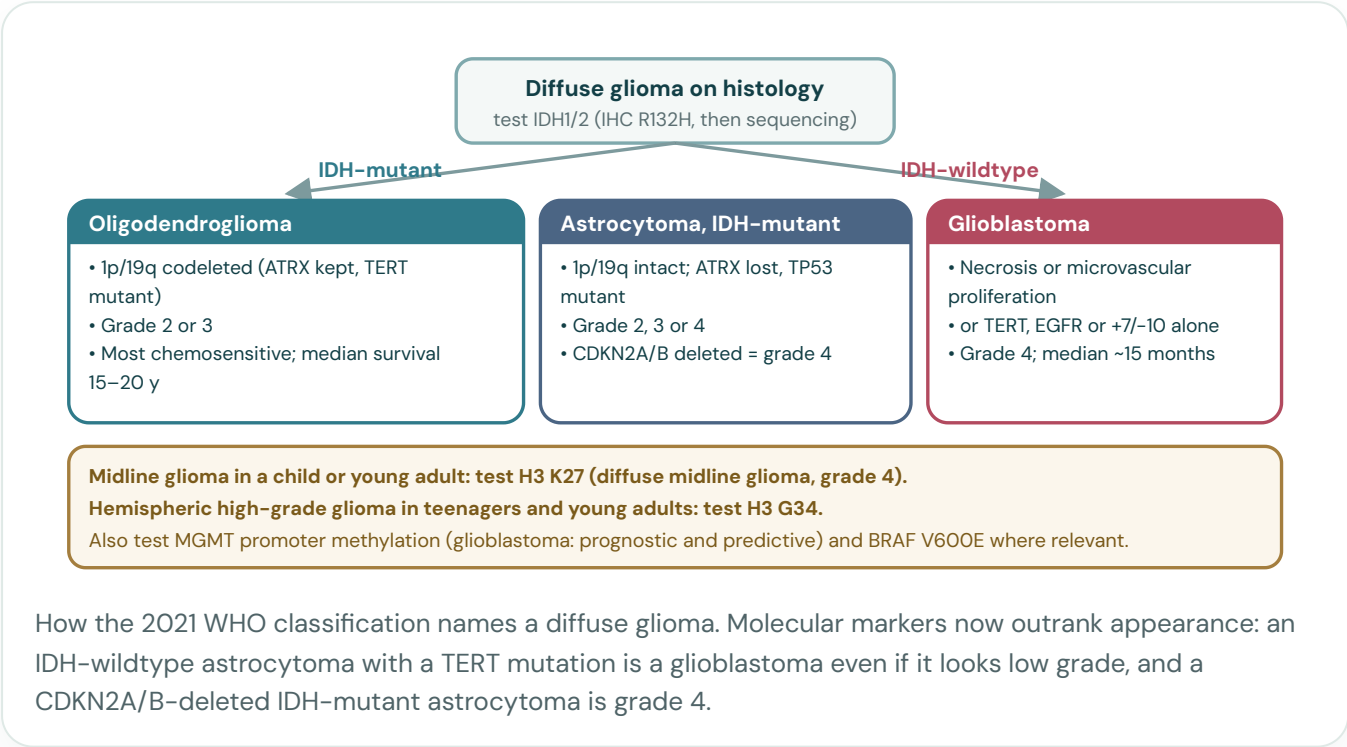


Brain tumours: molecular tests, treatment by setting, supportive care and side effects

Dr. Haritha Chiramana, MD, DM · C.R. Reddy Cancer Center, C.R. Reddy Superspeciality Hospital · drharitha.co.in
Updated 9 October 2026 · No doses · Verify current approvals and product information

A. Molecular tests and what they change





Marker	Diagnostic	Prognostic	Predictive	Practical consequence
IDH1/2 mutation	●	●	●	Vorasidenib (grade 2, residual)
1p/19q codeletion	●	●	●	RT + PCV; most chemosensitive
ATRX loss / TP53	●	○	○	Lineage surrogate (astrocytoma)
MGMT methylation	○	●	●	Temozolomide benefit; elderly choice
CDKN2A/B deletion	●	●	○	Upgrades to grade 4
TERT, EGFR, +7/-10	●	●	○	Defines glioblastoma; no targeted drug yet
H3 K27 / H3 G34	●	●	●	Grade 4; dordaviprone (K27M)
BRAF V600E	●	●	●	Dabrafenib + trametinib
BRAF fusion, FGFR, MYB	●	●	●	Tovorafenib, MEK inhibitors; trials
NTRK fusion	●	○	●	Larotrectinib, entrectinib
MMR loss / hypermutation	○	●	●	Germline CMMRD: anti-PD-1; post-TMZ: little benefit

What each marker is for. Top: why IDH-mutant gliomas are chemosensitive (the oncometabolite 2-hydroxyglutarate blocks DNA demethylation, so MGMT is silenced). Filled circles mark established diagnostic, prognostic and predictive roles; a predictive role means the result changes which treatment works.

Step 1 · Histology + immunohistochemistry panel on every diffuse glioma: IDH1 R132H · ATRX · p53 · Ki-67

Add H3 K27M and H3K27me3 (midline) · H3 G34 (young, hemispheric) · BRAF V600E/VE1 (young or epithelioid)

IDH1 R132H positive

- ATRX lost / p53 strong → astrocytoma (1p/19q not needed)
- ATRX retained → test 1p/19q (NGS or methylation; FISH with care)
- Then CDKN2A/B (grade 4 if deleted)

IDH1 R132H negative

- Under 55 or grade 2–3: sequence IDH1 (132) and IDH2 (172)
- Midline: H3 K27 alteration
- Hemispheric, young: H3 G34
- Child: BRAF, FGFR1, MYB/MYBL1, NTRK (RNA NGS)

IDH-wildtype adult, low grade

- TERT promoter, EGFR amplification, +7/-10 → glioblastoma, grade 4
- None present and H3 wild-type → astrocytoma, IDH-wildtype, NEC
- Methylation profiling to resolve

Step 2 · Treatment-guiding tests: MGMT promoter methylation (every glioblastoma; key over 65)

BRAF V600E · NTRK/FGFR fusions · MMR and tumour mutational burden when hypermutation or a syndrome is suspected

Unresolved, unusual or paediatric tumour → DNA methylation profiling (also gives copy number and MGMT status).

A stepwise testing pathway. Cheap immunohistochemistry answers most questions; sequencing, copy-number testing and methylation profiling are added only where the answer would change the diagnosis or the treatment.

Table A. Molecular tests and what they change

Test	Where it matters	How tested	What it changes	Key evidence
IDH1/IDH2 mutation	Every adult diffuse glioma	IHC for IDH1 R132H; sequence codons 132/172 if negative (especially under 55)	IDH-mutant: astrocytoma or oligodendroglioma, better prognosis; residual grade 2 → vorasidenib option	INDIGO, WHO 2021
1p/19q codeletion	Every IDH-mutant glioma	NGS, methylation array or LOH (FISH alone is imperfect); ATRX retained/p53 negative suggests it	Defines oligodendroglioma; RT + PCV (or temozolomide); chemotherapy alone for very large fields	EORTC 26951/RTOG 9402
MGMT promoter methylation	Glioblastoma (all ages)	Methylation-specific PCR or pyrosequencing; methylated in 40–50%	Predicts temozolomide benefit; temozolomide alone is reasonable in frail methylated patients	Hegi 2005
CDKN2A/B homozygous deletion	IDH-mutant astrocytoma (and oligodendroglioma)	NGS or FISH/copy number	Grade 4 regardless of histology; poor prognosis	CATNON final
TERT promoter, EGFR amplification, +7/-10	IDH-wildtype astrocytoma without necrosis	NGS / copy number	Diagnose glioblastoma; treat as grade 4	WHO 2021

Test	Where it matters	How tested	What it changes	Key evidence
H3 K27 alteration	Midline glioma (thalamus, pons, spinal cord), children and young adults	IHC for H3 K27M and loss of H3K27me3	Diffuse midline glioma grade 4; dordaviprone at recurrence; trials	ONC201 pooled analysis
H3 G34 mutation	Hemispheric high-grade glioma, teens and young adults	IHC / sequencing	Diffuse hemispheric glioma grade 4	WHO 2021
BRAF V600E / BRAF fusion	Paediatric LGG, ganglioglioma, PXA, some adult gliomas	IHC (VE1) or NGS; KIAA1549–BRAF fusion by NGS/FISH	V600E: dabrafenib + trametinib; fusions: tovorafenib, MEK inhibitors	Bouffet 2023, ROAR, FIREFLY-1
MMR deficiency / hypermutation	Glioma in young people with café-au-lait spots or family cancers; recurrence after temozolomide	IHC for MMR proteins, TMB on NGS; germline testing	CMMRD/Lynch counselling; checkpoint inhibitor in selected cases	Bouffet 2016
Medulloblastoma group (WNT, SHH, group 3, group 4)	All medulloblastomas	IHC panel ± methylation; TP53 status in SHH	Risk-adapted craniospinal dose and chemotherapy; germline testing in SHH (TP53, SUFU, PTCH1)	WHO 2021, COG/SIOP protocols
Ependymoma group (ZFTA, YAP1, PFA/PFB)	All intracranial ependymomas	IHC (H3K27me3 loss = PFA), fusion testing; 1q gain	PFA with 1q gain/6q loss: high risk; drives trial eligibility	ACNS0831

B. Treatment by setting

IDH-wildtype glioblastoma after maximal safe resection or biopsy

≤70 years, KPS ≥70

- RT 60 Gy + daily temozolomide, then 6 monthly cycles
- MGMT methylated: lomustine–temozolomide an option for young, fit patients
- Add tumour–treating fields if the patient accepts
- Unmethylated: same standard; consider trials

>70 years, KPS ≥70

- Short-course RT (40/15) + temozolomide
- Methylated and frail: temozolomide alone
- Unmethylated: short-course RT alone
- Decide with the family; function first

KPS <70 (any age)

- Methylated: temozolomide alone or short RT
- Unmethylated: short RT or best supportive care
- Early palliative care
- Steroids at the lowest dose that works

Not recommended first line: bevacizumab (no survival gain: AVAglio, RTOG 0825), nivolumab (CheckMate 498), more than 6 adjuvant cycles (GEINO 14-01).

Glioblastoma: age, function and MGMT decide the plan. MGMT methylation (40–50% of tumours) doubles 2-year survival with temozolomide; in unmethylated tumours the gain is small but no better option exists.

Table B. Systemic and radiation therapy by setting (no doses)

Setting	Standard	Alternatives / notes	Evidence
Glioblastoma, ≤70 y, fit	RT 60 Gy/30 + daily temozolomide → 6 adjuvant cycles	Lomustine–temozolomide (methylated, young, fit); tumour–treating fields with adjuvant phase	EORTC/NCIC, CeTeG/NOA-09, EF-14
Glioblastoma, >70 y or frail	Short-course RT (40/15) + temozolomide	Methylated: temozolomide alone; unmethylated: short RT alone; KPS <50: supportive care	Perry 2017, Nordic, NOA-08
Astrocytoma, IDH-mutant grade 2, residual, no uncontrolled symptoms	Vorasidenib, or watchful waiting	Uncontrolled symptoms/growth: RT + temozolomide (12 cycles) or PCV	INDIGO, RTOG 9802
Astrocytoma, IDH-mutant grade 3	RT 59.4 Gy + 12 cycles adjuvant temozolomide	Concurrent temozolomide adds little; PCV alternative	CATNON final
Astrocytoma, IDH-mutant grade 4	RT + temozolomide (glioblastoma-style or 12 adjuvant cycles)	Trials	Extrapolated from CATNON, EORTC/NCIC
Oligodendroglioma grade 2 (residual) or 3	Grade 3: RT + PCV (or temozolomide); grade 2 residual: vorasidenib option	Very large field: chemotherapy first	EORTC 26951/RTOG 9402, RTOG 9802, INDIGO

Setting	Standard	Alternatives / notes	Evidence
Recurrent glioblastoma	Single agent: lomustine, bevacizumab or temozolomide rechallenge (late, methylated)	Re-resection or re-irradiation for focal relapse; trials; palliative care	EORTC 26101, BELOB, RTOG 1205
BRAF V600E glioma (any age)	Dabrafenib + trametinib	Children with LGG: first line instead of chemotherapy	ROAR, Bouffet 2023
Paediatric LGG, progressive, no V600E	Carboplatin–vincristine or weekly vinblastine	BRAF fusion: tovorafenib; NF1: selumetinib/MEK; RT for older children when needed	COG A9952, FIREFLY-1, PBTC selumetinib
Paediatric HGG (>3 y)	Focal RT + temozolomide → lomustine	BRAF V600E: dabrafenib–trametinib after RT; CMMRD: anti-PD-1	ACNS0423, Hargrave 2023
DIPG	Focal RT (conventional or hypofractionated)	No proven systemic therapy; trials; re-irradiation at progression	Zaghloul 2022
Ependymoma, child, gross total resection	Focal conformal RT	Supratentorial grade 2 GTR: observation possible; post-RT chemotherapy did not help	ACNS0831, Merchant 2009
Brain metastases, driver-positive	CNS-active targeted therapy (osimertinib, alectinib/lorlatinib, tucatinib-based HER2 regimens)	SRS for symptomatic or progressing lesions	See lung and breast modules
Brain metastases, 1–20 small, no CNS-active drug	SRS alone	Cavity SRS after resection; WBRT with hippocampal avoidance + memantine only if SRS not possible	N0574, N107C, NRG CC001

C. Supportive care

Steroids (dexamethasone)

- Only for symptomatic oedema; none if asymptomatic
- Load then 8–16 mg/day for severe, 2–4 mg/day for mild
- Taper to the lowest dose; watch glucose, myopathy
- Avoid before biopsy if lymphoma possible

Seizures

- No prophylaxis if never had a seizure
- After a seizure: levetiracetam (non-enzyme-inducing)
- Avoid phenytoin/carbamazepine with chemo, TKIs
- Rescue benzodiazepine at home near end of life

Venous thrombosis

- No routine prophylaxis except after surgery
- Treat DVT/PE: DOAC preferred, else LMWH
- Higher bleed risk: melanoma, RCC, thyroid, choriocarcinoma
- Non-contrast CT before starting

Infection and stomach

- PJP prophylaxis if steroids or lymphopenia on temozolomide
- H2 blocker rather than PPI with glioblastoma
- Vaccinate; check sugar on steroids
- Early palliative and rehabilitation input

Supportive care that changes everyday outcomes. Steroids are for symptoms, not for the scan; antiseizure drugs are for patients who have had a seizure; DOACs caused less intracranial bleeding than LMWH in glioma cohorts.

Table C. Supportive care essentials

Problem	Do	Avoid	Evidence / note
Vasogenic oedema	Dexamethasone only if symptomatic: about 10 mg load then 8–16 mg/day (severe) or 2–4 mg/day (mild); taper to the lowest dose	Steroids for asymptomatic oedema; steroids before biopsy if lymphoma possible	Vecht 1994 ; bevacizumab for refractory oedema
Raised ICP, impending herniation	Head up, IV dexamethasone, mannitol or hypertonic saline, urgent neurosurgery (shunt/ETV/resection)	Lumbar puncture with mass effect	Emergency
First seizure	Levetiracetam monotherapy; check levels before switching; driving advice	Prophylaxis in seizure-free patients; enzyme inducers (phenytoin, carbamazepine) with chemotherapy or TKIs	SNO/EANO 2021
Stopping antiseizure drugs	Consider only after long seizure freedom and stable tumour; shared decision	Abrupt withdrawal	About 1 in 4 glioma patients relapse after withdrawal
DVT / PE	Non-contrast CT first; DOAC preferred, LMWH if DOAC unsuitable; long-term for glioblastoma	IVC filter routinely; anticoagulation within 48 h of a bleed	Carney 2019, Leader 2020
VTE prevention	Mechanical + pharmacological prophylaxis after surgery; mobilise	Routine outpatient prophylaxis	PRODIGE

Problem	Do	Avoid	Evidence / note
Infection on temozolomide	PJP prophylaxis with steroids or lymphopenia; weekly counts during RT	Live vaccines	NNT ~288 without risk factors (Canadian cohort)
Gastric protection on steroids	H2 blocker when needed	Routine PPIs with glioblastoma (survival association)	Le Rhun 2025 pooled analysis
Cognition, mood, fatigue	Screen each visit; rehabilitation, school/work plans; memantine with WBRT	Ignoring carer burden	RTOG 0614
End of life	Home seizure rescue plan (buccal/nasal benzodiazepine), dysphagia plan, palliative care	Late referral	EANO palliative care guideline

D. Managing common side effects

Table D. Managing common treatment side effects

Side effect	Usual cause	Prevent / monitor	When to stop or refer
Thrombocytopenia, neutropenia	Temozolomide (2–3× more in women), lomustine, PCV	Weekly counts during RT; day 22/29 counts in cycles	Hold TMZ if platelets <100 or ANC <1.5 ×10 ⁹ /L in the concurrent phase; aplastic anaemia is rare but serious
Nausea, constipation	Temozolomide, lomustine, ondansetron	Antiemetic before doses; bowel regimen	Persistent vomiting: check ICP, hyponatraemia
Raised liver enzymes	Temozolomide, vorasidenib (ALT rise ~10% grade ≥3)	LFTs monthly early on	Hold for grade ≥3; restart lower or stop
Pulmonary fibrosis	Lomustine (cumulative)	PFTs with long courses	New breathlessness: stop and investigate
Hypertension, proteinuria, wound problems	Bevacizumab	BP each visit, urine protein	Stop before surgery; stop for bleeding, perforation, arterial clot
Fever, rash	Dabrafenib + trametinib	Pause at fever onset; restart when settled	Persistent fever, ejection fraction fall, eye symptoms
Skin irritation under arrays	Tumour-treating fields	Rotate array position, skin care	Ulceration or infection
Fatigue, hair loss, scalp dermatitis	Cranial RT	Explain early; gentle scalp care	Somnolence weeks after RT is usually self-limited
Steroid myopathy, diabetes, insomnia, infection	Dexamethasone	Lowest dose; morning dosing; glucose checks	Proximal weakness: taper; consider bevacizumab for steroid dependence
Cognitive decline	WBRT, large-field RT, tumour	SRS where possible; hippocampal avoidance; memantine	Neuropsychology and rehabilitation
Endocrine, hearing, growth (children)	Cranial/craniospinal RT, cisplatin	Yearly endocrine review; audiology	Hormone replacement; school support