Vorasidenib for recurrent or residual low-grade glioma with IDH1 or IDH2 mutation

Indication

Patients 12 years of age or older who had residual or recurrent histologically confirmed grade 2 oligodendroglioma or astrocytoma (according to the WHO 2016/2021 criteria) with confirmed IDH1 and IDH2 mutation status.

Regimen details

Vorasidenib 40 mg OD will be taken orally. Dosing is continuous; there are no planned inter-cycle rest periods.

Cycle frequency

Every 28 days for 2 years then every 3 months

Number of cycles

Continue until disease progression or unacceptable toxicity

Administration

Oral

Pre-medication

Nil

Emetogenicity

Low

Additional supportive medication

Nil

Extravasation

Not applicable

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST) **every 2 weeks for the first 2 months** of treatment and monthly until 2 years and then as clinically indicated.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 40 mL/min
Bilirubin	≤ 1.5 x ULN
ALT or AST	< 1.5 x ULN

Renal impairment

No starting dose adjustment is recommended for patients with renal impairment (creatinine clearance [CLcr] > 40 mL/min estimated by Cockcroft-Gault). The pharmacokinetics and safety of vorasidenib have not been studied in patients with CLcr ≤ 40 mL/min or renal impairment requiring dialysis. Vorasidenib should be used with caution in patients with CLcr ≤ 40 mL/min or who require dialysis.

Hepatic impairment

No starting dose adjustment is recommended for patients with mild or moderate (Child-Pugh class A or B) hepatic impairment. The pharmacokinetics and safety of vorasidenib have not been studied in patients with severe hepatic impairment (Child-Pugh class C). Patients with pre-existing severe hepatic impairment may be treated with vorasidenib only after careful risk/benefit assessment and should be closely monitored.

Dose modifications

The first dose reduction level will be from 40 mg QD to 20 mg OD, and if necessary, a second dose reduction from 20 mg OD to 10 mg OD will be permitted for management of adverse events. Re-escalation may be allowed at the discretion of neuro-oncologist.

Adverse event (AE) / side effects (other than elevated liver transaminases)	**Action**
Grade 2 nausea or vomiting	Consider holding dose of vorasidenib until resolution of AE to grade 1 within 28 days of supportive therapy, then resume treatment at the current dose level.
Grade 3 AEs	**First occurrence** – hold dose of vorasidenib and manage with supportive therapy according to stand of care. Upon resolution to grade 1 or baseline, resume treatment at 1 dose level reduction. **Second occurrence** – if the same grade 3 AE occurs, discontinue vorasidenib.
Grade 3 hypophosphataemia (asymptomatic)	**First occurrence** - hold dose of vorasidenib and manage with supportive therapy according to stand of care. Upon resolution to grade 1 or baseline, resume treatment at current dose level. **Second occurrence** - hold dose of vorasidenib and manage with supportive therapy according to stand of care. Upon resolution to grade 1 or baseline, resume treatment at 1 dose level reduction. **Third occurrence** – discontinue vorasidenib.
Grade 4 AEs – except neutropenia without fever, thrombocytopenia without bleeding	**First occurrence** – discontinue vorsadenib
Grade 4 AE - neutropenia without fever, thrombocytopenia without bleeding	**First occurrence** – hold dose of vorasidenib and manage with supportive therapy according to stand of care. Upon resolution to grade 1 or baseline, resume treatment at 1 dose level reduction. Second occurrence, if the same grade 4 AE occurs despite dose reduction, discontinue vorasidenib.

Adverse Reaction	Severity	Management and Dosage Modifications
Hepatotoxicity (Elevation of ALT or AST)	Grade 1 ALT or AST increase >ULN to 3 x ULN *without* concurrent total bilirubin >2 x ULN	Continue vorasidenib at current dose. Monitor liver enzymes weekly until recovery to <Grade 1.
	Grade 2 ALT or AST >3 to 5 x ULN *without* concurrent total bilirubin >2 x ULN	First Occurrence: Withhold vorasidenib and monitor liver enzymes twice per week until recovery to ≤Grade 1 or baseline. • Recovery in ≤28 days, resume vorasidenib at the same dose. • Recovery in >28 days, resume vorasidenib at reduced dose Recurrence: Withhold vorasidenib and monitor liver enzymes twice per week until recovery to ≤Grade 1 or baseline, and resume vorasidenib at reduced dose
	Grade 3 ALT or AST >5 to 20 x ULN *without* concurrent total bilirubin >2 x ULN	First Occurrence: Withhold vorasidenib and monitor liver enzymes twice per week until recovery to ≤Grade 1 or baseline. • Recovery in ≤28 days, resume vorasidenib at reduced dose • If not recovered in ≤28 days, permanently discontinue vorasidenib. Recurrence: Permanently discontinue vorasidenib and monitor liver enzymes twice per week until recovery to ≤Grade 1 or baseline.
	Grade 2 or 3 Any ALT or AST >3 to 20 x ULN *with* concurrent total bilirubin >2 x ULN in absence of clear alternative explanation	Permanently discontinue vorasidenib and monitor liver enzymes twice per week until recovery to ≤Grade 1 or baseline.
	Grade 4 Any ALT or AST >20 x ULN	Permanently discontinue vorasidenib and monitor liver enzymes twice per week until recovery to ≤Grade 1 or baseline.

- Following dose reduction, dose re-escalation may be considered after 3 months if no LFT elevations are observed.

Adverse effects - for full details consult product literature/ reference texts

Overall, vorasidenib was associated with mainly low-grade toxic effects. Adverse events of grade 3 or higher were observed in 38 patients (22.8%) who received vorasidenib and in 22 (13.5%) who received placebo. The most common adverse event of grade 3 or higher was an increased alanine aminotransferase level (in 9.6% of the patients who received vorasidenib and in none of those who received placebo). Other adverse events of grade 3 or higher that were more common with vorasidenib than with placebo were an increased aspartate aminotransferase level (in 4.2% of the patients who received vorasidenib and in no patients who received placebo).

Event	Vorasidenib (N=167)		Placebo (N=163)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Any adverse event	158 (94.6)	38 (22.8)	152 (93.3)	22 (13.5)
Increased alanine aminotransferase	65 (38.9)	16 (9.6)	24 (14.7)	0
Increased aspartate aminotransferase	48 (28.7)	7 (4.2)	13 (8.0)	0
Increased γ-glutamyltransferase	26 (15.6)	5 (3.0)	8 (4.9)	2 (1.2)
Coronavirus disease 2019	55 (32.9)	0	47 (28.8)	0
Fatigue	54 (32.3)	1 (0.6)	52 (31.9)	2 (1.2)
Headache	45 (26.9)	0	44 (27.0)	1 (0.6)
Diarrhea	41 (24.6)	1 (0.6)	27 (16.6)	1 (0.6)
Nausea	36 (21.6)	0	37 (22.7)	0
Dizziness	25 (15.0)	0	26 (16.0)	0
Seizure	23 (13.8)	7 (4.2)	19 (11.7)	4 (2.5)
Constipation	21 (12.6)	0	20 (12.3)	0

Significant drug interactions

Strong CYP1A2 inhibitors

Co-administration of vorasidenib with strong CYP1A2 inhibitors (fluvoxamine and ciprofloxacin) may increase vorasidenib plasma concentration. Concomitant use of strong CYP1A2 inhibitors should be avoided and consider alternative therapies that are not strong inhibitors of CYP1A2 during treatment with Vorasidenib.

Moderate CYP1A2 inducers

Co-administration of vorasidenib with moderate CYP1A2 inducers (phenytoin and rifampicin) may decrease vorasidenib plasma concentration. Consider alternative therapies that are not moderate CYP1A2 inducers during treatment with Vorasidenib.

Effect of vorasidenib on other medicinal products: Cytochrome P450 (CYP) substrates with narrow therapeutic index

Co-administration of vorasidenib with CYP2C19 or CYP3A4 substrates with narrow therapeutic index (including, but not limited to, alfentanil, carbamazepine, cyclosporine, everolimus, fentanyl, ifosfamide, pimozide, quinidine, sirolimus, tacrolimus, tamoxifen) may decrease the plasma concentrations of these medicinal products. Concomitant use of CYP2C19 and CYP3A4 substrates with narrow therapeutic index should be avoided in patients taking Vorasidenib.

Sensitive substrates of CYP enzymes without narrow therapeutic index

Co-administration of vorasidenib with sensitive substrates of CYP3A4 without narrow therapeutic index (including, but not limited to, apixaban, buspirone, darunavir, ibrutinib, midazolam, saquinavir, tipranavir, triazolam) may decrease the plasma concentrations of these medicinal products. Consider alternative therapies that are not sensitive substrates of CYP3A4 during treatment with Vorasidenib.

Hormonal contraceptives

Vorasidenib may decrease concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended during the treatment and for at least 3 months after the last dose.

Additional comments

Nil

References

Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al. INDIGO Trial Investigators. Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma. N Engl J Med. 2023 Aug 17;389(7):589-601. doi: 10.1056/NEJMoa2304194. Epub 2023 Jun 4. PMID: 37272516

Vorasidenib for treating astrocytoma or oligodendroglioma with IDH1 or IDH2 mutations after surgery in people 12 years and over [ID6407] https://www.nice.org.uk/guidance/indevelopment/gid-ta11498

THIS PROTOCOL HAS BEEN DIRECTED BY DR SANDERSON, DESIGNATED LEAD CLINICIAN FOR CNS CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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