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.
- *Vorasidenib is provided via named patient program by Servier Laboratory Limited / Bionical Emas, starting from April 2024.*

Eligibility

Inclusion criteria

1) Be at least 12 years of age.
2) Be able to understand and willing to sign informed consent.
3) Have predominantly non-enhancing Grade 2 oligodendroglioma or astrocytoma per WHO 2021 criteria.
4) Have had at least 1 prior surgery for glioma (biopsy, sub-total resection, gross-total resection), with the most recent surgery having occurred at least 1 year and not more than 5 years before the date of treatment initiation, and no other prior anticancer therapy, including chemotherapy and radiotherapy.
5) Have confirmed IDH1 (IDH1 R132H/C/G/S/L mutation variants tested) or IDH2 (IDH2 R172K/M/W/S/G mutation variants tested) gene mutation status disease by local or other accredited laboratory testing with immunohistochemistry or NGS panel.
6) Available 1p19q status by local laboratory or accredited laboratory testing (eg, fluorescence in situ hybridization, comparative genomic hybridization array, sequencing).
7) Have MRI-evaluable, measurable, non-enhancing disease, assessed on 2D T2-weighted or 2D T2-weighted fluid-attenuated inversion recovery MRI with ≤4 mm slice thickness and no interslice gap. Measurable non-enhancing disease is defined as a least 1 target lesion measuring ≥1 cm × ≥1 cm (bidimensional). Centrally confirmed, minimal, non-nodular, non-measurable enhancement that has not changed between the 2 most recent scans will be permitted.
8) Have Karnofsky performance status (KPS) ≥80%
9) Have expected survival of ≥12 months.
10) Have adequate bone marrow function as evidenced by:
    a. Absolute neutrophil count ≥1,500 mm^3 or ≥1.5 × 10^9/L
    b. Hemoglobin ≥9 g/dL
    c. Platelets ≥100,000 mm^3 or ≥100 × 10^9/L
11) Have adequate hepatic function as evidenced by:
    a. Serum total bilirubin ≤1.5 × upper limit of normal (ULN) unless considered due to Gilbert's disease, and
    b. Aspartate aminotransferase at or below ULN and alanine aminotransferase at or below ULN, and
    c. Alkaline phosphatase ≤2.5 × ULN
12) Have adequate renal function as evidenced by:
    a. Serum creatinine ≤2.0 × ULN, OR
    b. Creatinine clearance >40 mL/min based on the Cockcroft-Gault glomerular filtration rate estimation: (140 − Age) × (Weight in kg) × (0.85 if female) / 72 × Serum Creatinine
13) Have recovered from any clinically relevant toxicities associated with any prior surgery for the treatment of glioma unless stabilized under medical management.
14) Female subjects of childbearing potential must have a negative serum pregnancy test before the start of therapy.

Exclusion criteria

1) Have had any prior anticancer therapy other than surgery (biopsy, sub-total resection, gross total resection) for treatment of glioma including systemic chemotherapy, radiotherapy, vaccines, small-molecules, IDH inhibitors, investigational agents, etc.

2) Have high-risk features as assessed by the neuro-oncologist or neuro-oncology MDT, including significant brainstem involvement either as primary location or by tumor extension, clinically relevant functional or neurocognitive deficits due to the tumor in the opinion of the Investigator (deficits resulting from surgery are allowed), or uncontrolled seizures (defined as persistent seizures interfering with activities of daily life AND failed 3 lines of antiepileptic drug regimens including at least 1 combination regimen)
3) Are pregnant or breastfeeding.
4) Have a known hypersensitivity to any of the components of vorasidenib.
5) Are taking any medications that are cytochrome P450 (CYP) 3A or CYP2C9 substrates with a narrow therapeutic index (alfentanil, dihydroergotamine, pimozide, terfenadine, astemizole, everolimus, quinidine, cisapride, ergotamine, sirolimus, cyclosporine, fentanyl, tacrolimus, phenytoin, warfarin)
6) Have known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, known positive human immunodeficiency virus antibody results, or AIDS-related illness. Subjects with a sustained viral response to HCV treatment or immunity to prior HBV infection will be permitted. Subjects with chronic HBV that is adequately suppressed by institutional practice will be permitted.
7) Have known active inflammatory gastrointestinal disease, chronic diarrhoea, previous gastric resection or lap band dysphagia, short-gut syndrome, gastroparesis, or other condition that limits the ingestion or gastrointestinal absorption of drugs administered orally. Gastroesophageal reflux disease under medical treatment is allowed (assuming no drug interaction potential).

Regimen details

Vorasidenib 40 mg OD (≥40kg) or 20mg OD (<40kg) will be taken orally on Days 1 to 28 in 28-day cycles. Dosing is continuous; there are no planned inter-cycle rest periods.

Cycle frequency

Every 28 days

Number of cycles

Continue the treatment until,

1) confirmed radiographic disease progression by the neuro-oncologist or neuro-oncology MDT;
2) development of unacceptable toxicity;
3) the need for initiation of surgery, chemotherapy, radiotherapy, or other anticancer therapy in the opinion of the neuro-oncology MDT in the absence of radiographic disease progression;
4) confirmed pregnancy;
5) death;
6) withdrawal of consent from treatment;
7) lost to follow-up;
8) or Sponsor ending supply of the drug, whichever occurs first.

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 thereafter.

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 on study for management of adverse events. Re-escalation may be allowed at the discretion of neuro-oncologist.
- Dose interruptions up to 28 days will be permitted at the discretion of the neuro-oncologist for reasons including management of adverse events.
- If the patient cannot resume vorasidenib within 28 days, the patient should be discontinued from the treatment.

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 event (AE) / side effects (elevated liver transaminases – ALT/AST)	Action	Liver function monitoring
Grade 1 (> ULN – 3.0 x ULN)	Continue vorasidenib	Monitor liver function weekly until stabilized or improved
Grade 2 (>3.0 – 5.0 x ULN)	First occurrence – hold dose of vorasidenib and investigate other causes. Once resolved to grade 1 or baseline, resume treatment at the same dose. Second occurrence – hold dose of vorasidenib. Once resolved to grade 1 or baseline, resume treatment at 1 dose level lower. Third occurrence – hold dose of vorasidenib. Once resolved to grade 1 or baseline, resume treatment at 1 dose level lower. Fourth occurrence – permanently discontinue vorasidenib.	Monitor liver function twice weekly of initial elevation, then decrease to once weekly if stabilized.
Grade 3 (>5.0 – 20 x ULN) without bilirubin elevation	First occurrence – hold dose of vorasidenib and investigate other causes. Once resolved to grade 1 or baseline, resume treatment at 1 dose level lower. Second occurrence – permanently discontinue vorasidenib.	Monitor liver function twice weekly of initial elevation, then decrease to once weekly if stabilized.
Grade 2 or 3 (>3.0 – 20 x ULN) with total bilirubin elevation (>2x ULN)	First occurrence – hold dose of vorasidenib and investigate other causes. If an alternative cause is identified, consider rechallenge at 1 dose level reduction. Discontinue vorasidenib if no alternative cause is identified or a second occurrence after rechallenge.	Urgently investigate other causes of LFT derangement – biliary tract obstruction or infection. Monitor liver function twice weekly of initial elevation, then decrease to once weekly if stabilized.
Grade 4 (>20x ULN)	First occurrence: permanently discontinue vorasidenib	Consider hospitalisation to evaluate.

- 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.

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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