Dordaviprone (ONC201)
Named patient programme

Indication
H3 K27M-mutant and/or midline diffuse glioma

Regimen details
Dordaviprone 625mg once weekly
(see under "Dose modifications" for dosing in patients with weight <52.5kg)

Cycle frequency
Every 28 days

Number of cycles
Until disease progression or unacceptable toxicity

Administration
Dordaviprone is to be orally administered once weekly (±2 days) with a glass of water. No food should be consumed within 2 hours before or for 2 hours after each dose. If the patient vomits following dosing, no re-dosing is allowed before the next scheduled dose. Missed doses will not be made up if more than 2 days from the intended day of administration.

Pre-medication
N/A

Emetogenicity
Minimal

Additional supportive medication
None

Extravasation
N/A

Investigations – pre first cycle
Standard network pre-SACT tests
ECG (QTc < 480msec)

Investigations –pre subsequent cycles
FBC, U+E (including creatinine), LFT (including AST)

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	≥ 60 mL/min
Bilirubin	≤ 1.5 x ULN
AST	≤ 2 x ULN (or ≤ 5 if liver involvement secondary to

	tumour)
QTc	<480msec

Dose modifications

CTCAE Grade	Relatedness to Dordaviprone	Dosing Management
Grade 1- Grade 2	Related or Not Related	• No change in dose
Grade 3- Grade 4	Related	Hold until ≤ Grade 2. If AE resolves within 2 days, take the dose and resume the original schedule. • If AE resolves to ≤ Grade 2 within 3 weeks, resume dosing at a lower dose level (one less capsule per dose). • If a patient requires an interruption of >3 weeks due to an AE, discontinue dordaviprone permanently. • If neutropenia associated with fever, discontinue dordaviprone permanently. ***Note: following resumption of dosing at a reduced dose, if the same AE recurs and is ≥ Grade 3, discontinue dordaviprone permanently regardless of relatedness.**

Body Weight	Starting Dose on Dosing Days	Dose Reduction 1	Dose Reduction 2
10 to < 12.5 kg	125 mg (1 capsule)	Discontinue or consult with the sponsor	Discontinue
12.5 to < 27.5 kg	250 mg (2 capsules)	125 mg (1 capsule)	Discontinue or consult with the sponsor
27.5 to < 42.5 kg	375 mg (3 capsules)	250 mg (2 capsules)	125 mg (1 capsule)
42.5 to < 52.5 kg	500 mg (4 capsules)	375 mg (3 capsules)	250 mg (2 capsules)
≥ 52.5 kg	625 mg (5 capsules)	500 mg (4 capsules)	375 mg (3 capsules)

Liver Chemistry Stopping Criteria

ALT or AST – absolute	ALT or AST ≥8 × ULN
Bilirubin	ALT or AST ≥3 x ULN and total bilirubin ≥ 2 × ULN (for patients with known Gilbert's syndrome, these criteria apply if total bilirubin ≥2 × ULN, and direct bilirubin >2 × ULN and at least doubled from baseline value) ** Report as an SAE
INR	ALT or AST ≥3 × ULN and international normalized ratio (INR) >1.5 (does not apply to patients receiving anticoagulants) ** Report as an SAE
Symptomatic	ALT or AST ≥3 × ULN and New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia)
ALT or AST – Persistent or Cannot Monitor	ALT or AST ≥5 × ULN but <8 x ULN: persists for ≥2 weeks or cannot be monitored weekly for ≥2 weeks ALT or AST ≥3 x ULN but <5 x ULN: Persists for ≥4 weeks or cannot be monitored weekly for ≥4 weeks

QTc Stopping Criteria

If a clinically significant ECG finding is identified (including, but not limited to changes from baseline in QTc) after starting dordaviprone, the physician will determine if the patient can continue treatment and if any change in patient management is needed. Any new clinically significant finding should be reported as an AE. If a patient has a QTc >

500msec (confirmed with a second tracing), dosing of dordaviprone will be interrupted. If the patient has 2 consecutive weeks with a dosing interruption due to QTc > 500msec, dordaviprone should be discontinued.

Occurrence of any grade of encephalopathy or extrapyramidal syndrome should prompt permanent discontinuation of dordaviprone.

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

Fatigue
Nausea
Reduced lymphocyte count
Headache
Vomiting
Anemia
Decreased apperite
Dizziness
Fall
Hemiparesis
Rash

Significant drug interactions – for full details consult product literature/ reference texts

Strong CYP3A4 inhibitors and inducers (including enzyme-inducing antiepileptic drugs) are prohibited during treatment with dordaviprone because dordaviprone is eliminated by metabolism via CYP3A4 and co-administration will significantly increase dordaviprone exposure. If concomitant medication that is known to induce or inhibit CYP enzymes is medically necessary, it is recommended to avoid administration of such agents on the day of dordaviprone dosing, as well the day before and after dordaviprone dosing. For patients who require Paxlovid (nirmatrelvir and ritonavir) for the treatment of COVID-19 infection, Paxlovid should not be started until 1 day after the most recent dose of dordaviprone and dordaviprone treatment should not be resumed until at least 3 days following the last dose of Paxlovid.

Additional comments

References

Isabel Arrillaga-Romany et al. ONC201 (Dordaviprone) in Recurrent H3 K27M–Mutant Diffuse Midline Glioma. JCO 42, 1542-1552(2024)

THIS PROTOCOL HAS BEEN DIRECTED BY DR LAM, DESIGNATED CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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