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4430
A perioperative study of safusidenib in patients with IDH1 mutated glioma

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Background

IDH mutations cause aberrant accumulation of (R)-2-hydroxyglutarate (2-HG), an “oncometabolite” that has pleotropic effects on tumorigenesis. Mutant-IDH inhibition significantly improves progression free survival in patients with *IDH* mutated WHO grade 2 glioma, however most patients will progress, with a lack of understanding on mechanistic reasons for failure.

Methods

This is an open-label single arm perioperative trial of Safusidenib an oral, blood brain barrier penetrant *IDH1* R132X inhibitor. Patients with *IDH1* mutated glioma (no prior radiation or chemotherapy), received Safusidenib for four weeks following surgical biopsy and prior to definitive resection (Part A) and then continued Safusidenib until toxicity or progression (Part B). Translational endpoints include paired whole genome transcriptome sequencing (WGTS), single nuclei RNA sequencing (snRNAseq), spatial transcriptomics, spatial metabolomics and sampling of blood and CSF for circulating tumor DNA (ctDNA). Here we report outcomes for Part A of the study.

Results

As of May/02/2024 10 patients with IDH mut glioma have been enrolled. The mean age was 37, with 40% male; six had prior surgical resection. Treatment has been well tolerated with ongoing follow-up. The mean Safusidenib tumor concentration was 2654 ng/g (range 957.0 – 4810) with tumor:plasma ratio 0.33. On-target activity was confirmed with reduction in 2-HG 86% from biopsy (mean 75.0mM, range 7.8-203) to surgery (10.3mM, range 2.3 – 30.8), validated with spatial metabolomics. As expected, we observed increased abundance of metabolites feeding glycolysis and reduction in the TCA cycle. Paired snRNAseq demonstrates transcriptional shift post treatment with increased AC-like cell state as well as reduction in heterogeneity pointing towards a more differentiated state. Notably, we identify reduction in synaptic programs on treatment, and decreased strength of neuron-tumor interactions suggesting a systemic effect of mutant-IDH inhibition.

Conclusions

Taken together, these results provide detailed understanding on mechanism of IDH inhibition for glioma, and a proof of concept of the perioperative approach to advance drug development in glioma.

Clinical trial identification

NCT05577416.

Legal entity responsible for the study

Royal Melbourne Hospital.

Funding

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Disclosure

J.R. Whittle: Financial Interests, Personal and Institutional, Research Funding, Advisory Board: AnHeart Therapeutics; Financial Interests, Personal, Advisory Board: Servier, MSD; Non-Financial Interests, Personal, Advisory Role: Roche. K. Drummond: Financial Interests, Institutional, Research Funding: AnHeart Therapeutics. All other authors have declared no conflicts of interest.