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Phase 2, multicenter, randomized clinical study to evaluate the efficacy and safety of safusidenib in patients with high-grade isocitrate dehydrogenase 1 (*IDH1*)-mutant glioma

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Background

- *IDH1*-mutant astrocytomas (including grades 2-4) are recognized as a distinct entity by the WHO CNS 2021 classification based on their unique molecular and clinical features[1]
- Standard of care for grade 3/4 *IDH1*-mutant astrocytoma includes maximal safe resection followed by RT or chemoradiation and adjuvant TMZ[2,3]
  - While this treatment is effective at prolonging PFS, all patients will eventually progress, at which point salvage therapies provide nominal benefit[4,5]
- There is a clear unmet need for the treatment of patients with grade 3/4 *IDH1*-mutant astrocytoma to delay progression after current standard therapy[2,3,6,7]
- No targeted treatment is currently approved for grade 3/4 *IDH1*-mutant glioma
- Safusidenib, a novel, potent, oral mutant IDH1 inhibitor with high blood-brain barrier permeability, demonstrated promising phase 1 activity in patients with recurrent or progressive high-grade and contrast-enhancing *IDH1*-mutant glioma (NCT03030066)[8]
  - The ORRs were 17.1% for enhancing tumors and 33.3% for nonenhancing tumors
    - This response rate is higher than response rates seen with other IDH inhibitors in enhancing glioma (ORR of 8% [2 PRs] with olutasidenib,[9] ORRs of 0% with ivosidenib[10] and vorasidenib[11])
  - In the 35 enhancing tumors assessed by RANO, there were 2 CRs and 4 PRs
  - Responses were durable, with 1 patient with grade 4 *IDH1*-mutant astrocytoma having a CR lasting approximately 174 weeks
  - Further development of safusidenib in high-grade *IDH1*-mutant glioma is warranted

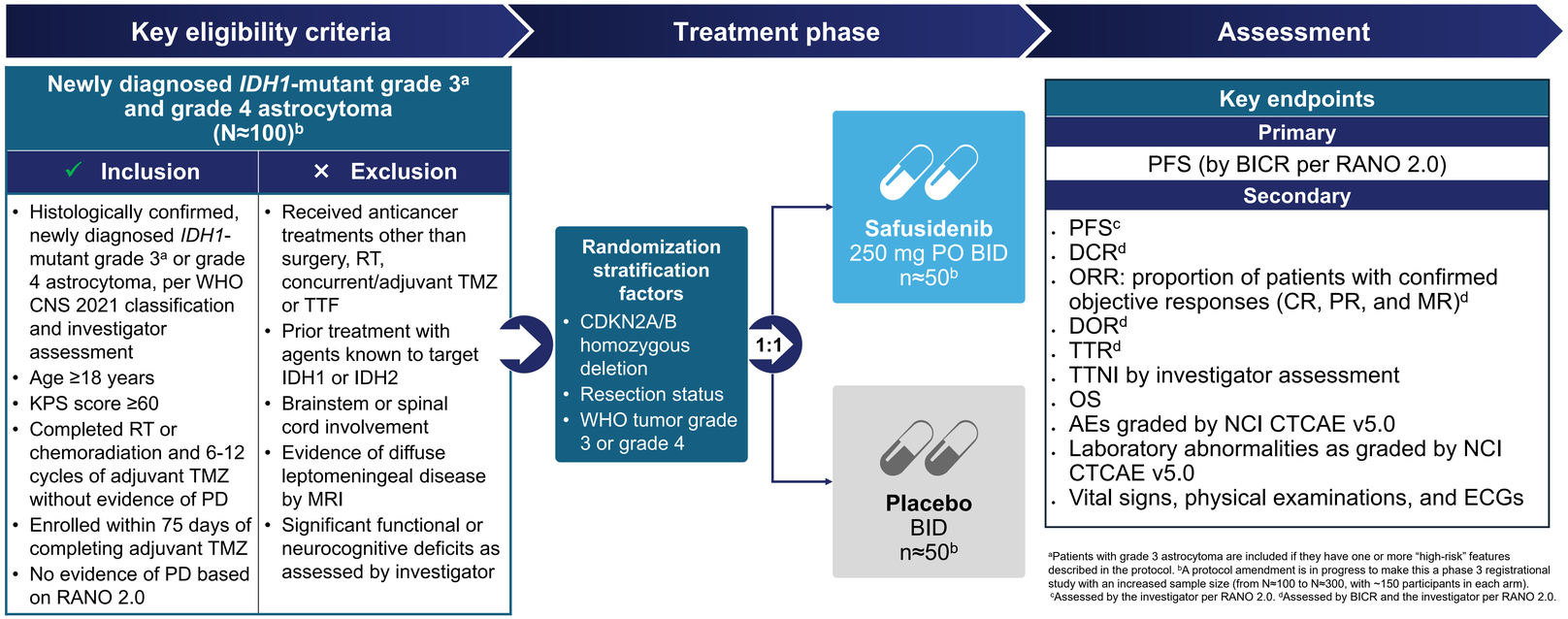
Methods

- This is a currently enrolling phase 2, global, randomized clinical study (NCT05303519), evaluating the efficacy and safety of safusidenib in patients with *IDH1*-mutant glioma
  - A protocol amendment is in progress to make this a phase 3 registrational study with an increased sample size (from N≈100 to N≈300)
- The study includes the following 2 parts:
  - Part 1 assessed safusidenib in patients in the US with grade 2/3 *IDH1*-mutant glioma and completed enrollment in December 2023
  - Here, we present the study design of part 2 that will assess safusidenib in patients with *IDH1*-mutant grade 3 and grade 4 astrocytoma (**Figure 1**)
- Approximately 300 adult patients from up to 50 sites in China, Australia, and the US will be randomized
- Randomization will be stratified by:
  - CDKN2A/B homozygous deletion
  - Resection status after the most recent surgery per investigator assessment
  - Tumor grade per investigator assessment
- Patients will receive safusidenib (250 mg PO BID) or placebo after SOC RT or chemoradiation and ≥6 cycles (maximum of 12 cycles) of adjuvant TMZ
- Key eligibility criteria and endpoints are listed in **Figure 1**
- Recruitment for the study is ongoing

Purpose

- NCT05303519 is a currently recruiting, phase 2, global, randomized clinical study in patients with *IDH1*-mutant grade 3 and grade 4 astrocytoma that will evaluate the efficacy and safety of safusidenib as maintenance treatment (250 mg PO BID) after SOC radiation or chemoradiation and adjuvant TMZ treatment

Figure 1. Study Design



[a]Patients with grade 3 astrocytoma are included if they have one or more "high-risk" features described in the protocol. [b]A protocol amendment is in progress to make this a phase 3 registrational study with an increased sample size (from N≈100 to N≈300, with ~150 participants in each arm). [c]Assessed by the investigator per RANO 2.0. [d]Assessed by BICR and the investigator per RANO 2.0.

Abbreviations

AE, adverse event; BICR, Blinded Independent Central Review; BID, twice daily; CNS, central nervous system; CR, complete response; DCR, disease control rate; DOR, duration of response; ECG, electrocardiogram; IDH1, isocitrate dehydrogenase 1; KPS, Karnofsky Performance Status; MR, minor response; MRI, magnetic resonance imaging; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, oral administration; PR, partial response; RANO, Response Assessment in Neuro-Oncology; RT, radiation therapy; SOC, standard of care; TMZ, temozolomide; TTF, tumor treating fields; TTNI, time to next intervention; TTR, time to response; US, United States; WHO, World Health Organization.

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Poster

The study @ clinicaltrials.gov

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