TIP-06

# SIGMA: A Phase 3 Study Evaluating Maintenance Safusidenib vs Placebo Following Radiotherapy or Chemoradiotherapy and Adjuvant Temozolomide in Patients With Isocitrate Dehydrogenase 1 (*IDH1*)-Mutant Astrocytoma With High-Risk Features

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## Background

- *IDH*-mutant astrocytomas are a distinct category of adult-type diffuse glioma per WHO CNS 2021 criteria, based on their unique molecular and clinical features[1]
- IDH inhibitors represent a paradigm shift in neuro-oncology, giving select patients with Grade 2 *IDH*-mutant glioma their first targeted treatment option[2]
- However, standard-of-care treatment for most *IDH1*-mutant astrocytomas remains maximal safe resection followed by RT/CRT and adjuvant TMZ[2,3]
  - Although RT/CRT and adjuvant TMZ prolongs PFS,[4] patients almost inevitably experience PD, at which point, salvage therapies are limited[2]
  - For patients with *IDH1*-mutant glioma, high tumor grade and risk factors including contrast enhancement, residual tumor after surgery, and certain molecular features are associated with earlier PD and poor prognosis[5–8]
  - There is, therefore, a clear unmet need for effective targeted treatments in *IDH1*-mutant astrocytoma that can delay PD after RT/CRT and adjuvant TMZ

## Rationale

- Safusidenib is an investigational oral mutant-IDH1 inhibitor with high potency, selectivity, and blood-brain barrier permeability[9] that has recently been granted fast track designation by the US FDA for treatment of *IDH1*-mutant glioma[10]
  - Safusidenib demonstrated encouraging clinical activity and a favorable risk-benefit profile in patients with *IDH1*-mutant glioma in Phase 1 (NCT03030066) and Phase 2 (NCT04458272) studies[11,12]
  - Additionally, safusidenib achieved encouraging responses in patients with *IDH1*-mutant glioma across histological grades and risk groups, including those with high-grade disease or tumor contrast enhancement[11]
  - These findings support further evaluation of safusidenib in patients with *IDH1*-mutant astrocytoma with high grade or high-risk features following RT/CRT and adjuvant TMZ

**See poster CTNI-11 at this meeting for updated data from this Phase 2 study**

## Study Aim

- SIGMA (NCT05303519) is an ongoing, Phase 3, randomized, double-blind study evaluating the efficacy and safety of **maintenance safusidenib** vs placebo following RT/CRT and adjuvant TMZ in patients with ***IDH1*-mutant astrocytoma** with high grade or high-risk features[13]
- A preceding dose-finding part of this study established the RP2D of safusidenib as 250 mg BID
- An open-label, single-arm, exploratory cohort from this study is also ongoing to evaluate safusidenib in RT/CT-naïve patients with Grade 3 *IDH1*-mutant oligodendroglioma

**See poster TIP-08 at this meeting for more information on this exploratory cohort**

## Study Design: SIGMA (NCT05303519)

### Key Eligibility Criteria

#### Inclusion Criteria

- Histologically confirmed, *IDH1*-mutant Grade 2,[a] 3,[a] or 4 astrocytoma, per WHO CNS 2021 classification[1] and INV assessment
- Age ≥18 years
- KPS ≥60
- No tumor recurrence or PD between first day of RT and randomization by local assessment per RANO 2.0
- Completed RT/CRT, and 6–12 cycles of adjuvant TMZ

#### Exclusion Criteria

- Prior anticancer therapy other than surgery, RT, concurrent or adjuvant TMZ, or TTF[b]
- Prior treatment with anti-angiogenic agents, agents known to target IDH1 or IDH2, or other investigational agents for glioma

### Treatment

Patients with Grade 2,[a] 3,[a] or 4 ***IDH1*-mutant astrocytoma** following RT/CRT and adjuvant TMZ

**(N≈300)**

1:1[c]

**Safusidenib**
250 mg PO BID

*28-day continuous cycles until PD or discontinuation*

**Placebo**
PO BID

Randomization stratified by:
- *CDKN2A/B* homozygous deletion status, per local testing (yes vs no)
- Resection status, per INV assessment (GTR vs non-GTR)
- WHO tumor Grade 2, 3, or 4, per INV assessment

### Study Endpoints

#### Primary Endpoint

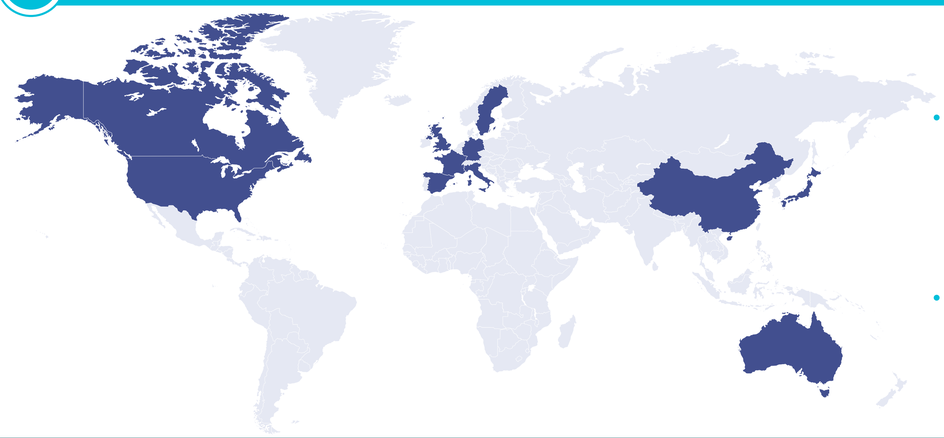
- PFS per RANO 2.0 by BICR

#### Secondary Endpoints

- PFS per RANO 2.0 by INV
- ORR (CR, PR, MR)[d]
- Disease control rate[d]
- Duration of response[d]
- Time to response[d]
- Time to next intervention
- Overall survival
- Safety
- Seizure activity
- HRQoL by FACT-Br and QOLIE-10-P scores
- Pharmacokinetics

[a]Patients with Grade 2 or 3 astrocytoma must have ≥1 risk factor as defined in the study protocol. [b]Must be discontinued prior to randomization. [c]Randomization within 28–75 days after the final dose of adjuvant TMZ. [d]BICR and INV assessed, per RANO 2.0.

## Trial Progress



- The international Phase 3 SIGMA study (NCT05303519) is ongoing, with approximately 80 sites across Australia, Canada, China, France, Germany, Italy, Japan, Spain, Sweden, UK, and USA selected as of October 2026
- The first patient was enrolled in SIGMA in October 2025

## Summary

- There is an unmet need for effective targeted therapies that delay PD and maintain quality of life in patients with *IDH1*-mutant astrocytoma following treatment with RT/CRT and adjuvant TMZ
- Safusidenib is an investigational mutant-IDH1 inhibitor with high potency, selectivity, and blood-brain barrier permeability that has shown encouraging efficacy in patients with *IDH1*-mutant glioma[9,11,12]
- The ongoing Phase 3, randomized, double-blind SIGMA study (NCT05303519) will evaluate maintenance safusidenib vs placebo in adults with *IDH1*-mutant astrocytoma with high grade or high-risk features[13]

## Abbreviations

BICR, blinded independent central review; BID, twice daily; CDKN2, cyclin-dependent kinase inhibitor 2; CNS, central nervous system; CR, complete response; CRT, chemoradiotherapy; CT, chemotherapy; FACT-Br, Functional Assessment of Cancer Therapy-Brain; FDA, Food and Drug Administration; GTR, gross total resection; HRQoL, health-related quality of life; IDH1/2, isocitrate dehydrogenase 1/2; INV, investigator; KPS, Karnofsky Performance Status; MR, minor response; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PO, orally; PR, partial response; QOLIE-10-P, Patient Weighted Quality of Life in Epilepsy Questionnaire; RANO, Response Assessment in Neuro-Oncology; RP2D, recommended Phase 2 dose; RT, radiation therapy; TMZ, temozolomide; TTF, Tumor Treating Fields; UK, United Kingdom; USA, United States of America; WHO, World Health Organization.

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