INDIGO: A global, randomized, double-blind, phase III study of vorasidenib (VOR; AG-881) vs placebo in patients with residual or recurrent grade II glioma with an isocitrate dehydrogenase 1/2 (*IDH1/2*) mutation

TPS2574

Ingo K Mellinghoff[1], Martin J van den Bent[2], Jennifer L Clarke[3], Elizabeth A Maher[4], Katherine B Peters[5], Mehdi Touat[6], John F de Groot[7], Macarena I De La Fuente[8], Isabel Arrillaga-Romany[9], Wolfgang Wick[10], Benjamin M Ellingson[11], Steven Schoenfeld[12], Hua Liu[12], Kha Le[12], Min Lu[12], Lori Steelman[12], Islam Hassan[12], Shuchi S Pandya[12], Patrick Y Wen[13], Timothy F Cloughesy[11]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [3]University of California San Francisco, San Francisco, CA, USA; [4]University of Texas Southwestern Medical Center, Dallas, TX, USA; [5]Duke University Medical Center, Durham, NC, USA; [6]AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, Service de Neurologie 2-Mazarin, Paris, France; [7]MD Anderson Cancer Center, Houston, TX, USA; [8]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [9]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [10]University of Heidelberg and DKFZ, Heidelberg, Germany; [11]University of California Los Angeles, Los Angeles, CA, USA; [12]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [13]Dana-Farber/Harvard Cancer Center, Boston, MA, USA

Email: medinfo@agios.com

BACKGROUND

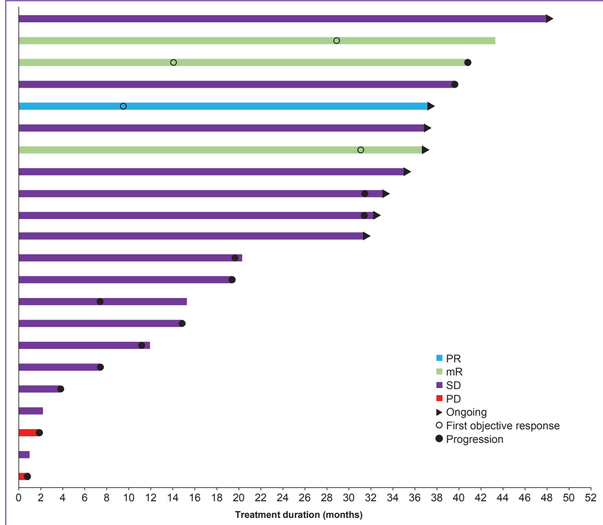
Low-grade gliomas (LGGs) and *IDH* mutations

- LGGs (World Health Organization [WHO] grade 2) are often diagnosed in younger patients, are incurable, and ultimately progress to high-grade gliomas[1,2]
  - There are no approved targeted therapies for LGG[3]
- The current treatment options consist of surgery followed by observation ('watch and wait') for patients with lower risk of disease progression, or postoperative chemoradiotherapy in the high-risk population[1,3]
- Mutations in the metabolic enzymes isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) occur in approximately 80% and 4% of LGGs, respectively,[4,5] occurring early in tumorigenesis, leading to neomorphic production of D-2-hydroxyglutarate (2-HG)[6,7]
  - Targeting IDH mutations early in the treatment course may delay progression and the need for more aggressive therapies
- Vorasidenib (VOR; AG-881) is an oral, potent, reversible, brain-penetrant pan inhibitor of mutant IDH1/2 (mIDH1/2) enzymes

Efficacy and safety of VOR in glioma trials

- VOR was evaluated in a phase 1 dose escalation study (ClinicalTrials.gov NCT02481154) in 93 patients with m*IDH1/2* solid tumors, including gliomas (N = 52)[8]
  - 17/22 (77.3%) patients with nonenhancing glioma were grade 2; 9 (52.9%, out of 17 tested) were 1p19q not co-deleted
  - In the nonenhancing glioma population, VOR showed prolonged disease control (**Figure 1**), with median progression-free survival (PFS) of 31.4 months (95% CI 11.2, 40.8) with 59.1% of events reported, and PFS rate at 24 months was 55.4%
  - VOR (doses < 100 mg once daily [QD]) was associated with a favorable safety profile, with no grade ≥ 2 transaminase elevation adverse events, in patients with nonenhancing glioma
  - See Presentation 2504 (Mellinghoff I et al) for further details on these data[8]
- Example magnetic resonance imaging (MRI) findings for a patient with glioma who achieved a partial response following treatment on VOR are shown in **Figure 2**

Figure 1. VOR treatment duration and best response for patients with nonenhancing glioma in a phase 1 study (n = 22)[8]



mR = minor response; SD = stable disease; PD = progressive disease; PR = partial response

- In a phase 1 perioperative study of nonenhancing m*IDH1* glioma (ClinicalTrials.gov NCT03343197), in patients who received VOR 50 mg QD and were evaluable for response postoperatively (n = 13), the objective response rate (ORR) was 30.8%[9]
- At the same dose, VOR demonstrated a geometric mean brain:plasma ratio of 1.74, and a median (95% CI) 2-HG reduction of 92.6% (76.1, 97.6) in resected tumors, relative to untreated samples, confirming brain penetrance and activity of VOR 50 mg QD
- Based on the observed safety profile and clinical activity, 50 mg QD (uncoated tablets) was selected as the starting dose for the phase 3 INDIGO study

Figure 2. MRI of a patient with grade 2 nonenhancing glioma with a partial response following VOR treatment in a phase 1 study[10]

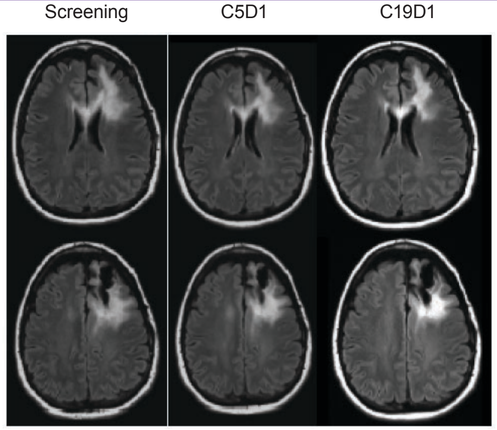


Image courtesy of Dr T Cloughesy

Patient was a 49-year-old female diagnosed with grade 2 oligodendroglioma 1p19q co-deleted. Tumor was resected in 2013 and no other treatment was administered prior to starting VOR. As of 03Mar2020, the patient had remained on treatment for 37 months, with a sustained partial response of 22 months.
C = cycle; D = day

OBJECTIVES OF THE PHASE 3 INDIGO STUDY

Primary objective

- To demonstrate the efficacy of VOR compared with placebo, based on radiographic PFS in patients with residual or recurrent grade 2 oligodendroglioma and astrocytoma with an *IDH1/2* mutation, and who have undergone surgery as their only treatment

Secondary objectives

- To compare the efficacy of VOR with placebo, based on ORR and tumor growth rate as assessed by volume
- To evaluate time to next intervention and health-related quality of life (HRQoL) by Functional Assessment of Cancer Therapy – Brain (FACT-Br) questionnaire

INDIGO STUDY DESIGN

- INDIGO is a global, multicenter, double-blind, randomized, placebo-controlled, phase 3 study in patients with residual or recurrent grade 2 glioma with an *IDH1/2* mutation (ClinicalTrials.gov NCT04164901)
- Study design and schedules of study assessments are shown in **Figure 3**
- Safety data will be reviewed regularly throughout the study, and efficacy data at planned interim analysis, by an independent data monitoring committee

INDIGO STUDY DESIGN (CONTINUED)

Figure 3. INDIGO study design and schema for assessments

Double-blind, randomized, placebo-controlled, phase 3 study (ClinicalTrials.gov NCT04164901)

Key inclusion criteria

- ≥ 12 years of age
- Grade 2 oligodendroglioma or astrocytoma per WHO 2016 criteria, not in need of immediate treatment and without high-risk features
- Centrally confirmed m*IDH1/2* status
- ≥ 1 surgery for glioma ≥ 1 year but ≤ 5 years before randomization
- Karnofsky performance status ≥ 80%
- Centrally confirmed measurable nonenhancing disease evaluable by MRI

Key exclusion criteria

- Any prior anticancer therapy, other than surgery, for the treatment of glioma (eg, systemic chemotherapy, radiotherapy, vaccines, small molecules, IDH inhibitors, investigational agents)
- High-risk features as assessed by the investigator, including brainstem involvement (primary location or tumor extension), clinically relevant functional or neurocognitive deficits due to the tumor (deficits resulting from surgery are allowed), or uncontrolled seizures (persistent seizures interfering with activities of daily life AND 3 failed lines of antiepileptic drug regimens including ≥ 1 combination regimen)

Eligible patients with m*IDH1/2* oligodendroglioma or astrocytoma

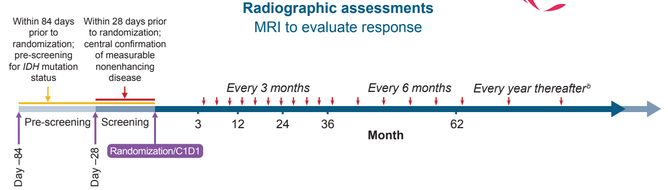
1:1 double-blind randomization (n = 366)
Stratified by 1p19q status (intact vs co-deleted) and baseline tumor size (≥ 2 cm vs < 2 cm)

VOR:
40 mg QD coated tablet[a] orally in continuous 28-day cycles

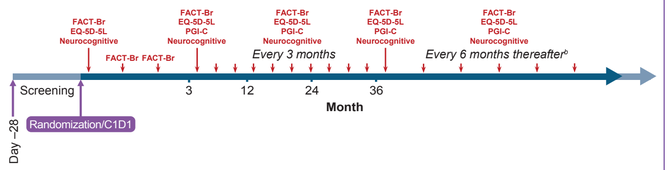
Crossover to VOR:
Permitted upon centrally confirmed radiographic PD

Placebo:
Matched dose QD orally in continuous 28-day cycles

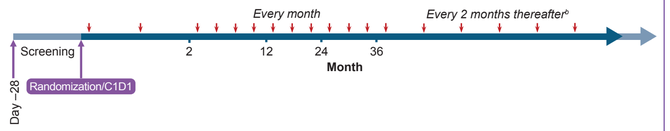
Radiographic assessments
MRI to evaluate response



HRQoL and neurocognitive assessments



Seizure assessments



Study endpoints

Primary
- Radiographic PFS[c] per blinded independent review committee

Secondary
- Safety and tolerability
- Tumor growth rate assessed by volume
- Time to next intervention
- ORR
- OS
- HRQoL by FACT-Br
- Plasma pharmacokinetics

Exploratory
- Seizure activity
- HRQoL by EQ-5D-5L
- Neurocognitive function
- PGI-C

Statistics

Assuming a median PFS of 18 months in the control arm, the study has 80% power to detect a hazard ratio of 0.667 with a 1-sided alpha of 0.025

Patients who cross over from placebo arm to receive VOR follow the same schedule of assessments
[a]40 mg starting dose of coated tablet formulation introduced in Amendment 1. Patients enrolled under the original protocol started with 50 mg QD uncoated tablet and were switched to 40 mg QD coated tablet
[b]Until withdrawal of consent, centrally confirmed radiographic PD, death, the patient is lost to follow-up, or until the end of study/study termination
[c]Time from date of randomization to date of first occurrence of radiographic PD or death due to any cause
EQ-5D-5L = EuroQol 5-Dimensions 5 Levels; OS = overall survival; PGI-C = Patient Global Impression of Change

SUMMARY AND CURRENT STATUS

- **The favorable safety profiles and encouraging preliminary efficacy data of VOR from phase 1 studies in patients with nonenhancing glioma support the development of VOR in the phase 3 INDIGO study**
  - **In a phase 1 dose escalation study, median PFS in patients receiving VOR was 31.4 months, and 24-month PFS rate was 55.4%[8]**
- **The global phase 3 INDIGO study in patients with grade 2 m*IDH1/2* glioma who have had surgery as their only treatment is currently enrolling in the US**
  - **The study will also be activated at centers outside the US, including throughout Canada, Europe, and Israel**
  - **Further information is available at www.indigostudy.com**

Acknowledgments
We thank the participating patients and their families.

Disclosures
This study is funded by Agios Pharmaceuticals, Inc.
Full author disclosures are available through the ASCO meeting library.
Editorial assistance was provided by David Pertab, PhD, Excel Medical Affairs, Glasgow, UK, supported by Agios Pharmaceuticals, Inc.

References

1. Weller M et al. *Lancet Oncol* 2017;18:e315–29.
2. McAleer MF, Brown PD. *Semin Radiat Oncol* 2015;25:210–8.
3. Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Central Nervous System Cancers (Version 1.2020). https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed Apr 16, 2020.
4. Yan H et al. *N Engl J Med* 2009;360:765–73.
5. Hartmann C et al. *Acta Neuropathol* 2009;118:469–74.
6. Cohen A et al. *Curr Neurol Neurosci Rep* 2013;13:345.
7. Dang L et al. *Nature* 2009;462:739–44.
8. Mellinghoff I et al. *2020 ASCO Annual Meeting*; Presentation 2504.
9. Mellinghoff I et al. *24th SNO Annual Scientific Meeting* 2019: ACTR-66.
10. Mellinghoff I et al. *23rd SNO Annual Scientific Meeting* 2018: ACTR-31.

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting Virtual Format, May 29–31, 2020