Vorasidenib (VOR; AG-881), an inhibitor of mutant IDH1 and IDH2, in patients with recurrent/progressive glioma: Updated results from the phase I non-enhancing glioma population

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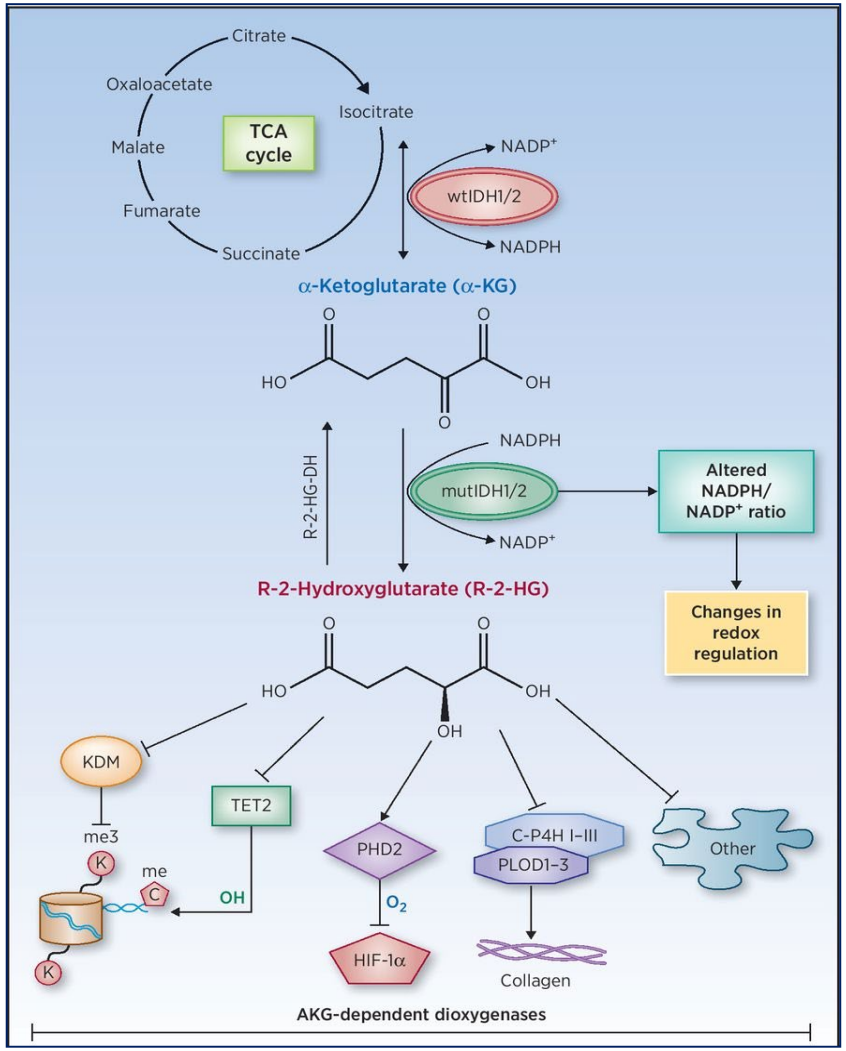
Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting Virtual Format, May 29–31, 2020

Disclosures

- Consulting or Advisory Role: Agios, Black Diamond Therapeutics, Debiopharm Group, Puma Biotechnology, Voyager Therapeutics
- Travel, Accommodations, Expenses: Agios, AstraZeneca, Puma Biotechnology, Roche, Voyager Therapeutics
- Honoraria: Roche
- Research Funding: Amgen, General Electric, Lilly

Isocitrate Dehydrogenase (IDH) in Cancer

- Isocitrate dehydrogenase 1 and 2 mutations (m*IDH1/2*) occur in approximately 80% and 4% of low-grade gliomas, respectively
- Accumulation of D-2-hydroxyglutarate leads to epigenetic dysregulation and impaired differentiation, promoting tumorigenesis
- IDHIFA® (enasidenib), an IDH2 inhibitor, approved in 2017 in mIDH2 relapsed/refractory acute myeloid leukemia (AML)
- TIBSOVO® (ivosidenib), an IDH1 inhibitor, approved in 2018 in m*IDH1* relapsed/refractory AML, and in 2019 in patients with m*IDH1* newly diagnosed AML who are ≥ 75 years old or who have comorbidities precluding the use of intensive induction chemotherapy



Clark O, Yen K, Mellinghoff IK. *Clin Cancer Res* 2016;22:1837

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m*IDH1* = mutant *IDH1*; m*IDH2* = mutant *IDH2*

Vorasidenib (VOR; AG-881)

- Potent, oral, reversible, brain-penetrant, first-in-class pan-inhibitor of mIDH1/2:
  - In an orthotopic glioma model, VOR had IC_{50} of 0.1 ng/mL, inhibited tumor growth, and showed 98% suppression of 2-HG with brain:plasma ratio of 1.33[1]
  - In a phase 1 perioperative study, once-daily VOR 50 mg showed brain penetrance and > 90% reduction in 2-HG, with an ORR of 31% in non-enhancing glioma patients compared with untreated controls[2]
- Preliminary safety and efficacy data from an ongoing phase 1 study of patients with m*IDH1/2* advanced solid tumors (N = 93), including glioma (n = 52), has been previously reported[2,3]
- Here we report updated safety and efficacy data in the non-enhancing glioma patient population (n = 22) as of 3Mar2020

2-HG = D-2-hydroxyglutarate; IDH1/2 = isocitrate dehydrogenase 1/2; mIDH1/2 = mutant IDH1/2; ORR = objective response rate

1. Nicolay B et al. *2017 SNO Annual Meeting*: Poster EXTH-34. **2.** Mellinghoff IK et al. *2019 SNO Annual Meeting*: Oral presentation ACTR-66. **3.** Mellinghoff IK et al. *2018 SNO Annual Meeting*: Oral presentation ACTR-31.

Study Design

Phase 1, single-arm, multicenter, open-label, dose escalation study of oral VOR in patients with m*IDH1/2* advanced solid tumors (N = 93)

Glioma (n = 52)

Enhancing glioma (n = 30)

Non-enhancing glioma (n = 22)

Non-glioma tumors[a] (n = 41)

Key eligibility criteria:

- ≥ 18 years
- Histologically or cytologically confirmed glioma with documented m*IDH1/2*, that has recurred or progressed following standard therapy
- ECOG performance status score of 0–2
- Evaluable disease by RANO-LGG criteria

Primary objectives:

- Safety and tolerability
- MTD and/or RP2D

Secondary objectives:

- Pharmacokinetics and pharmacodynamics
- Preliminary clinical activity (ORR, PFS)
  - Tumor response assessed locally by MRI every eight weeks using RANO-LGG criteria

Exploratory objectives:

- Change in tumor volumetric growth rate in non-enhancing glioma
- Pharmacodynamic evaluation of tissue and plasma

[a]Cholangiocarcinoma, chondrosarcoma, adenocarcinoma, colon cancer, colorectal cancer, liver cancer, pancreatic cancer, non-small cell lung cancer, rectal carcinoma, and signet cell adenocarcinoma
ECOG = Eastern Cooperative Oncology Group; mIDH1/2 = mutant isocitrate dehydrogenase 1/2; MRI = magnetic resonance imaging; MTD = maximum tolerated dose; ORR = objective response rate; PFS = progression-free survival; RANO-LGG = response assessment in neuro-oncology for low-grade glioma; RP2D = recommended phase 2 dose

Treatment Status: Non-Enhancing Glioma

Disposition, n (%)	Dose level/QD					Total (N = 22)
	10 mg (n = 3)	25 mg (n = 1)	50 mg (n = 5)	100 mg (n = 7)	200 mg (n = 6)	
On treatment	3	0	2	1	2	8 (36.4)
Discontinued treatment	0	1	3	6	4	14 (63.6)
Disease progression	0	0	2	5	3	10 (45.5)
Adverse event	0	0	0	1	1	2 (9.1)
Withdrawal by patient	0	1	1	0	0	2 (9.1)

- Enrollment completed in June 2017
- Study remains ongoing as of 3Mar2020 data cutoff; median treatment duration for the non-enhancing glioma population is 25.8 months

No non-enhancing glioma patients received 300 mg QD
QD = once daily

Baseline Characteristics: Non-Enhancing Glioma

	Total treated (N = 22)
Median (range) age, years	47.0 (16–73)
Male/female, n	8/14
ECOG status at baseline, n (%) 0 1	 11 (50.0) 11 (50.0)
IDH1 mutation, n (%)[a] IDH2 mutation, n (%)	20 (90.9) 1 (4.5)
WHO tumor grade, n (%) Grade II Grade III	 17 (77.3) 5 (22.7)
1p19q intact, n (% of those tested)[b]	9 (52.9)
Prior radiation therapy, n (%)	8 (36.4)
Prior systemic therapy, n (%)	14 (63.6)
Median (range) number of prior systemic therapies	2 (1–4)
Type of prior systemic therapy, n (%) Temozolomide Procarbazine/CCNU/Vincristine	 13 (59.1) 2 (9.1)

[a]One patient did not have biopsy, presumed IDH mutation by the investigator as evidenced by consistent 2-HG elevation by MRS
[b]Missing for five patients
ECOG = Eastern Cooperative Oncology Group; IDH = isocitrate dehydrogenase; MRS = magnetic resonance spectroscopy

AEs ≥10% (Non-Enhancing Glioma Patients, All Causalities)

All patients, n (%)	All grades (N = 22)	Grade 3 or higher (N = 22)
Patients with at least one AE	22 (100)	6 (27.3)
Alanine aminotransferase increased	14 (63.6)	2 (9.1)
Aspartate aminotransferase increased	13 (59.1)	2 (9.1)
Nausea	10 (45.5)	0
Headache	9 (40.9)	0
Neutrophil count decreased	7 (31.8)	1 (4.5)
Fatigue	6 (27.3)	0
Hyperglycemia	6 (27.3)	0
Seizure	5 (22.7)	1 (4.5)
White blood cell count decreased	5 (22.7)	0
Constipation	4 (18.2)	0
Diarrhea	4 (18.2)	0
Hypoglycemia	4 (18.2)	0
Cough	3 (13.6)	0
Vomiting	3 (13.6)	0

AE = adverse event

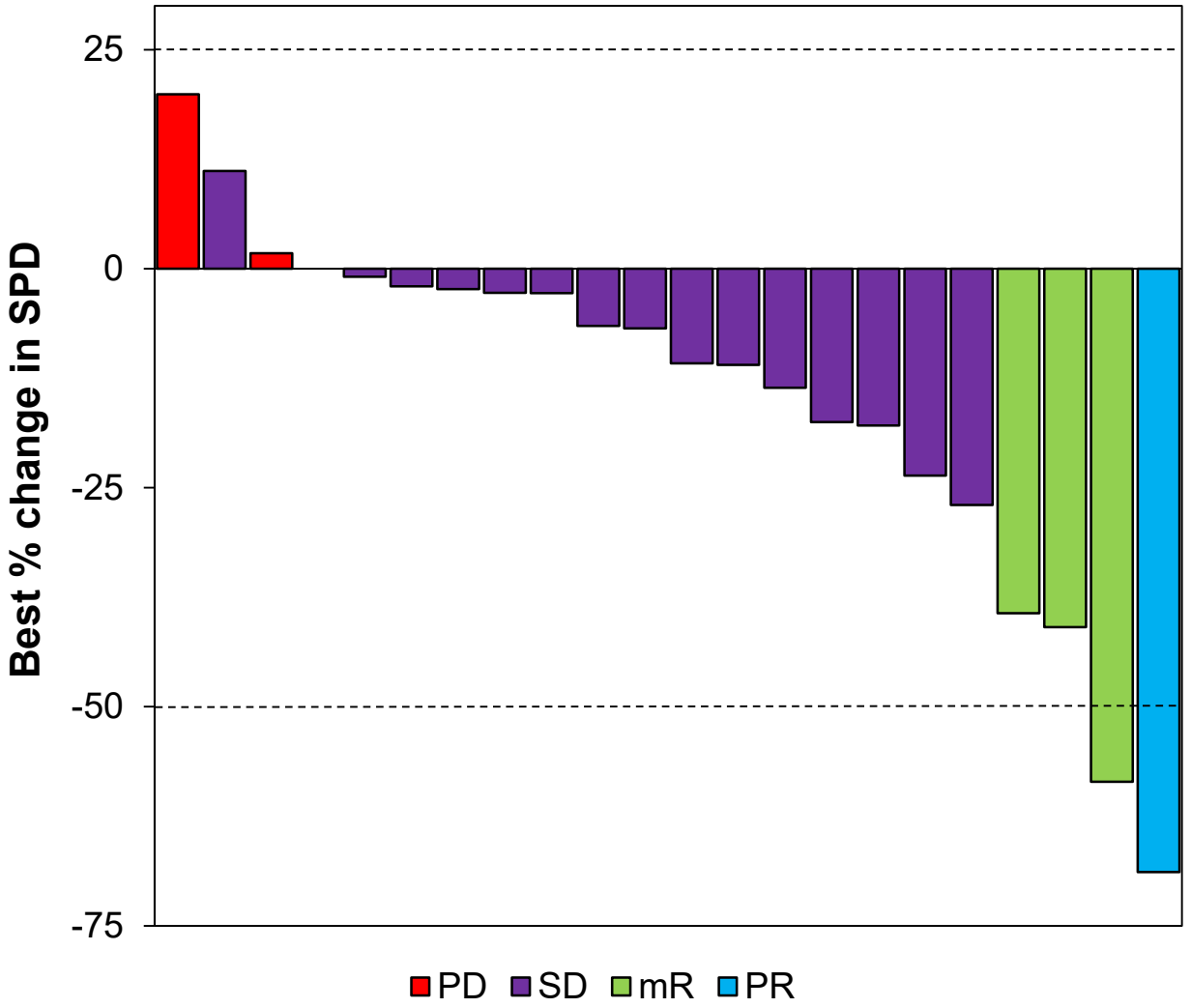
Transaminase Elevation Is Dose Dependent in Non-Enhancing Glioma Patients

New or worsening AE at actual dose, n (%)[a]	10 mg QD (n = 3)[b]	25 mg QD (n = 1)[b]	50 mg QD (n = 11)[b]	100 mg QD (n = 13)[b]	200 mg QD (n = 12)[b]	Total (N = 22)
No AE	3 (100.0)	1 (100.0)	6 (54.5)	3 (23.1)	3 (25.0)	8 (36.4)
Grade 1	0	0	5 (45.5)	4 (30.8)	4 (33.3)	7 (31.8)
Grade 2	0	0	0	5 (38.5)	3 (25.0)	4 (18.2)
Grade 3	0	0	0	0	2 (16.7)	2 (9.1)
Grade 4	0	0	0	1 (7.7)	0	1 (4.5)

- Transaminase AEs were not associated with elevated bilirubin
- AEs occurred in five (38.5%) patients at doses of below 100 mg QD and were grade 1
- AEs were reversible with dose modification and interruption
- Two patients discontinued due to transaminase elevations

[a]For each dose received, patients are counted either as having no ALT and/or AST AE or at the highest grade of a new onset or worsening ALT and/or AST AE. New is defined as onset > 1 day after a previous ALT or AST AE resolved. Due to intra-patient dose escalation, patients may be counted at more than one dose level. No non-enhancing glioma patients received 300 mg QD
[b]N value for each dose level indicates the number of patients who received that dose at any time during the study
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DLT = dose-limiting toxicity; QD = once daily

Best Percent Change from Baseline by the Investigator: Non-Enhancing Glioma

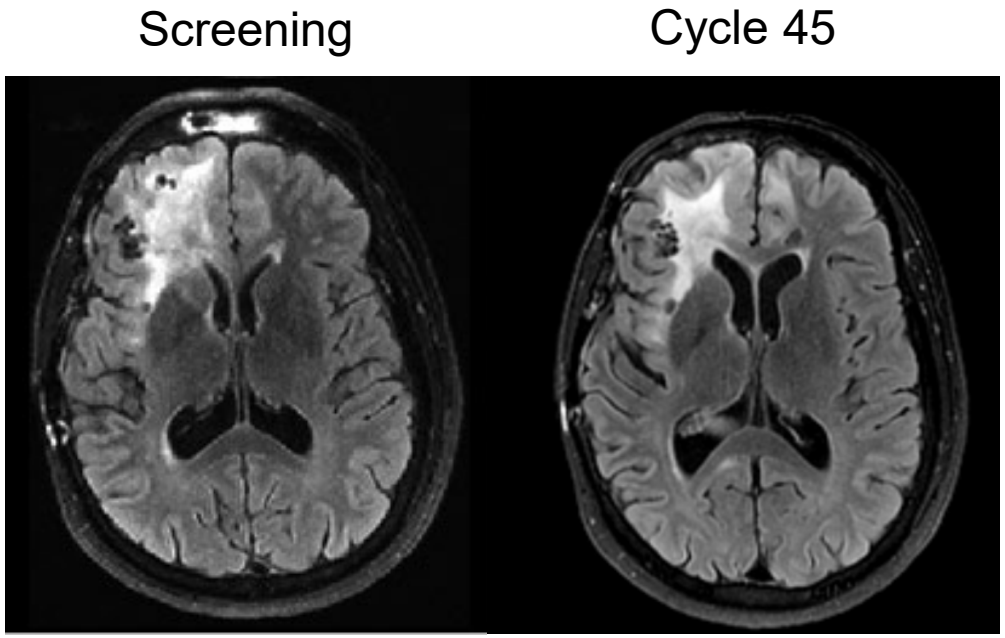


- VOR showed an ORR[a] of 18.2% in patients with non-enhancing disease (N = 22)
  - 1 patient achieved partial response
  - 3 patients achieved minor response[b]
- 16 (72.7%) patients had stable disease as their best response

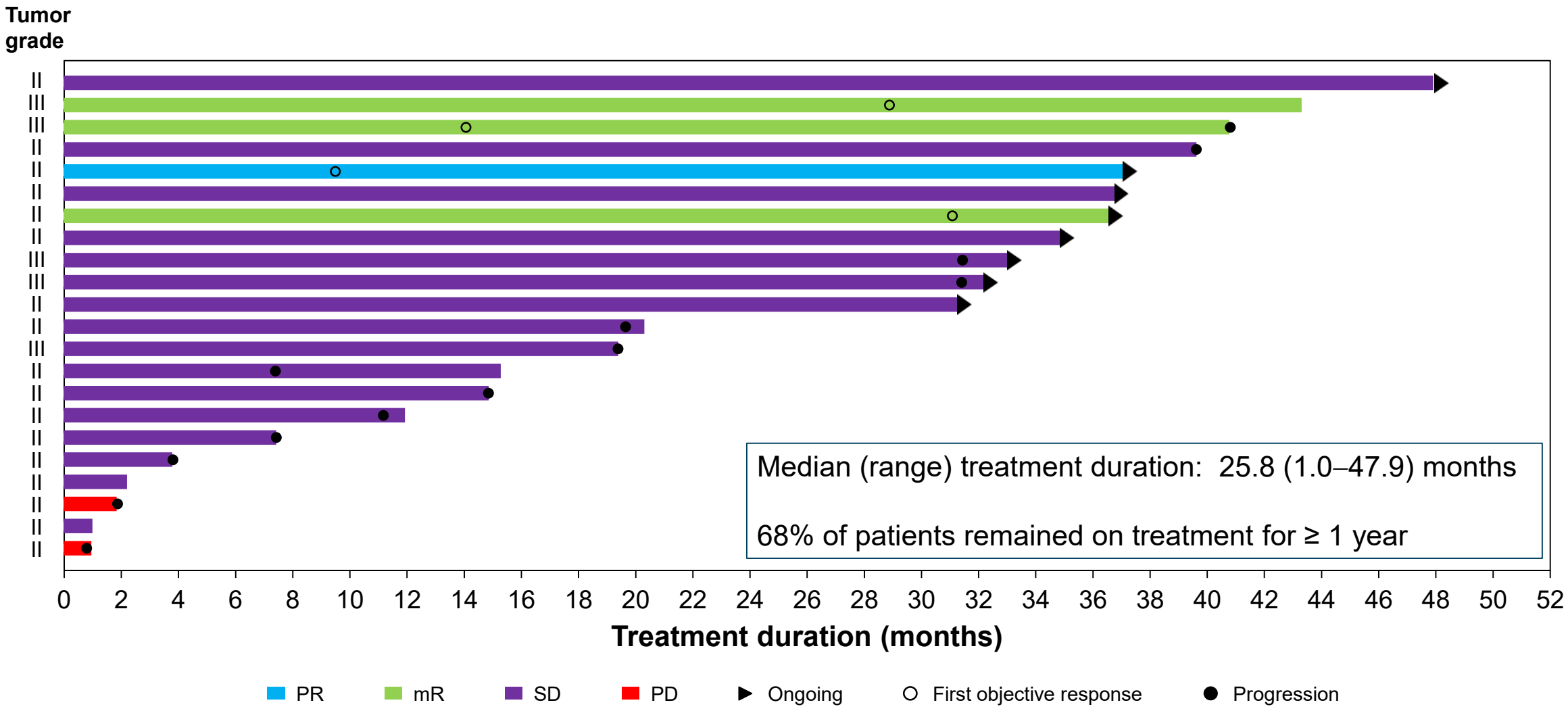
[a]Response assessed by RANO-LGG (van den Bent M et al. *Lancet Oncol* 2011;12:583–93); objective response rate includes complete response, partial response, and minor response
[b]mR is defined as ≥ 25% but < 50% decrease in tumor measurements relative to baseline; one patient had > 50% reduction from baseline that had not been confirmed with subsequent scan and is therefore categorized as mR
mR = minor response; ORR = objective response rate; PD = progressive disease; PR = partial response; RANO-LGG = response assessment in neuro-oncology for low-grade glioma; SD = stable disease; SPD = sum of product of diameters

Case Study: Patient with Minor Response

- WHO grade III, Diffuse Glioma IDH1-R132H, 1p19q co-del
- Resection: 2007
- RT: 2007
- TMZ 2007–2008
- Started VOR Nov 2015
- **MR Apr 2018 (Cycle 32) sustained for 14 months (at 200 mg QD)**

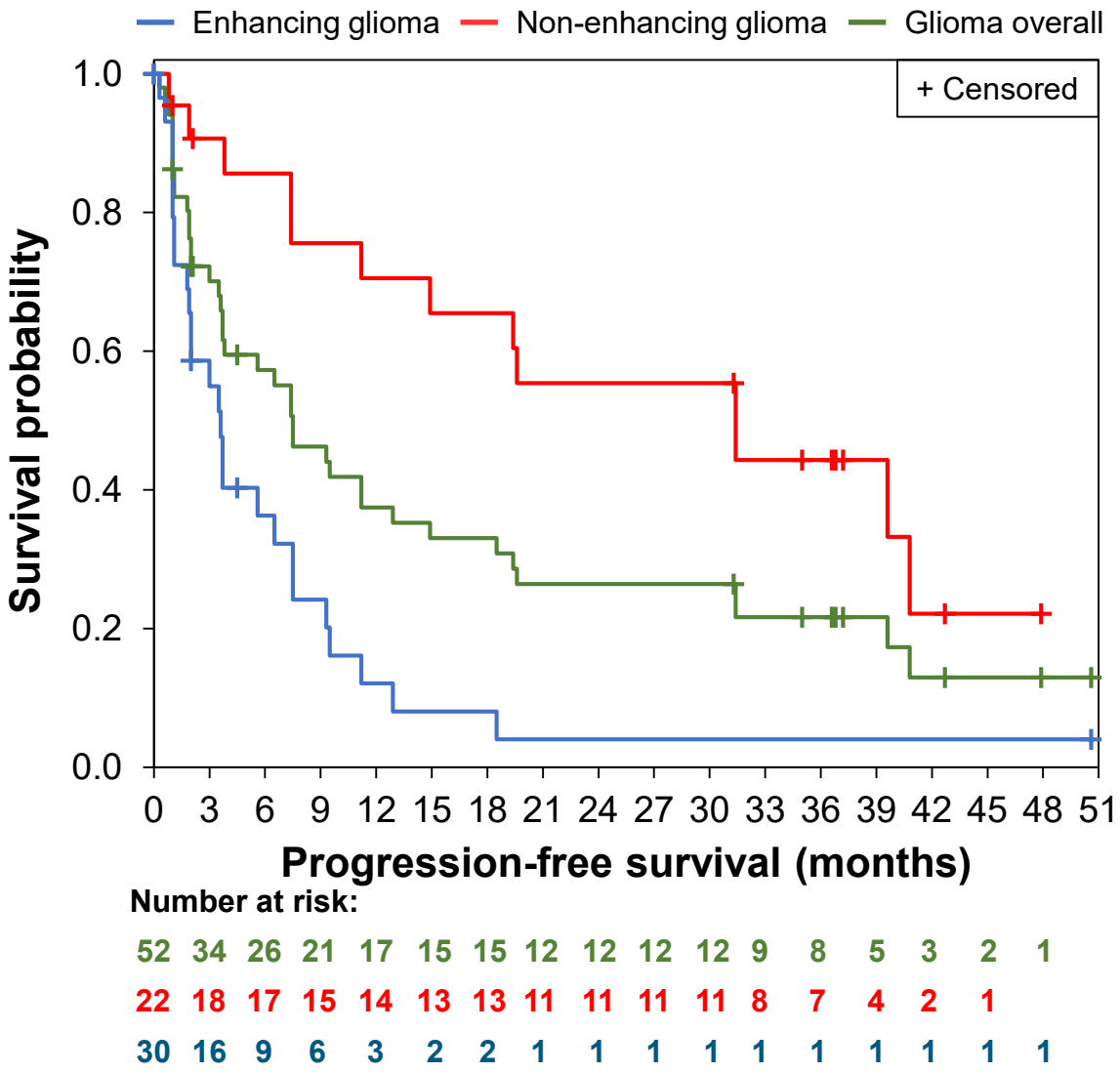


Treatment Duration and Best Response: Non-Enhancing Glioma



mR defined as ≥ 25% but < 50% decrease in tumor measurements compared with baseline
mR = minor response; PD = progressive disease; PR = partial response; RANO-LGG = response assessment in neuro-oncology for low-grade glioma; SD = stable disease

Progression-Free Survival: Overall Glioma Population



- With 75.0% of events reported, median PFS in the overall glioma population (N=52) was 7.5 months (95% CI 3.7, 12.9)
- In non-enhancing glioma patients (N=22), median PFS was 31.4 months (95% CI 11.2, 40.8) with 59.1% events reported
  - 24-month PFS was 55.4%

Progression-free survival refers to the time from first dose date to first occurrence of documented confirmed relapse, disease progression, or death due to any cause

Summary and Conclusions

- VOR (below 100 mg QD) continues to be associated with a favorable safety profile in this previously treated population with non-enhancing glioma
- VOR showed encouraging preliminary activity with median PFS of 31.4 months among the non-enhancing glioma population, and PFS duration extending to 24 months or longer in 55% of patients
- VOR (50 mg QD) is under evaluation in the INDIGO study (see poster #TPS2574), an ongoing, global, randomized phase 3 study in grade 2 non-enhancing m*IDH1/2* glioma patients who have had surgery only (ClinicalTrials.gov NCT04164901)

DLT = dose-limiting toxicity; PFS = progression-free survival; QD = once daily

Acknowledgments

- We would like to thank the principal investigators, their institutions, and most importantly, the patients who took part in this study
- This clinical study was funded by Agios Pharmaceuticals, Inc.

Editorial support was provided by Vanessa Ducas, PhD, Excel Medical Affairs, Fairfield, CT, USA, and supported by Agios