A phase 1, open-label, perioperative study of ivosidenib (AG-120) and vorasidenib (AG-881) in recurrent, IDH1-mutant, low-grade glioma: Updated results

Ingo K Mellinghoff[1], Timothy F Cloughesy[2], Patrick Y Wen[3], Jennie W Taylor[4], Elizabeth A Maher[5], Isabel Arrillaga-Romany[6], Katherine B Peters[7], Changho Choi[5], Benjamin M Ellingson[2], Alexander P Lin[3], Sunitha B Thakur[1], Brandon Nicolay[9], Min Lu[9], Kha Le[9], Feng Yin[9], Feng Tai[9], Steven Schoenfeld[9], Shuchi S Pandya[9], Islam Hassan[9], Lori Steelman[9], Jennifer Clarke[4]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]University of California Los Angeles, Los Angeles, CA, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]University of California San Francisco, San Francisco, CA, USA; [5]The University of Texas Southwestern Medical Center, Dallas, TX, USA; [6]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [7]Duke University Medical Center, Durham, NC, USA; [8]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [9]Agios Pharmaceuticals, Inc., Cambridge, MA, USA

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Ivosidenib and Vorasidenib

- **Ivosidenib** (IVO, AG-120, TIBSOVO®)**:** first-in-class, oral, small-molecule inhibitor of **mIDH1**
  - Approved by the US FDA in July 2018 for mIDH1 R/R AML and in May 2019 for newly diagnosed AML
  - Solid tumor proof of concept achieved in an ongoing phase 3 study in mIDH1 cholangiocarcinoma[1]
  - IVO had a brain:plasma ratio of <0.04[2] in preclinical models, as well as preliminary clinical activity in patients with nonenhancing glioma (n=35), with a median PFS of 13 months[3]
- **Vorasidenib** (VOR, AG-881)**:** oral, potent, reversible, brain-penetrant inhibitor of **mIDH1** & **mIDH2**
  - In an orthotopic glioma model, VOR had an IC_{50} of 0.1 ng/ml,[4] inhibited tumor growth, and showed 98% suppression of tumor 2-HG with a brain:plasma ratio of 1.33[5]
  - In an ongoing phase 1 study (n=52 gliomas), as of 26 July 2019, VOR was associated with a favorable safety profile at doses <100 mg once daily (QD)[6]; and resulted in an ORR of 13.6%, including 1 PR, 2 MR, and 77% stable disease, and a median treatment duration of 22 months in nonenhancing glioma (n=22)

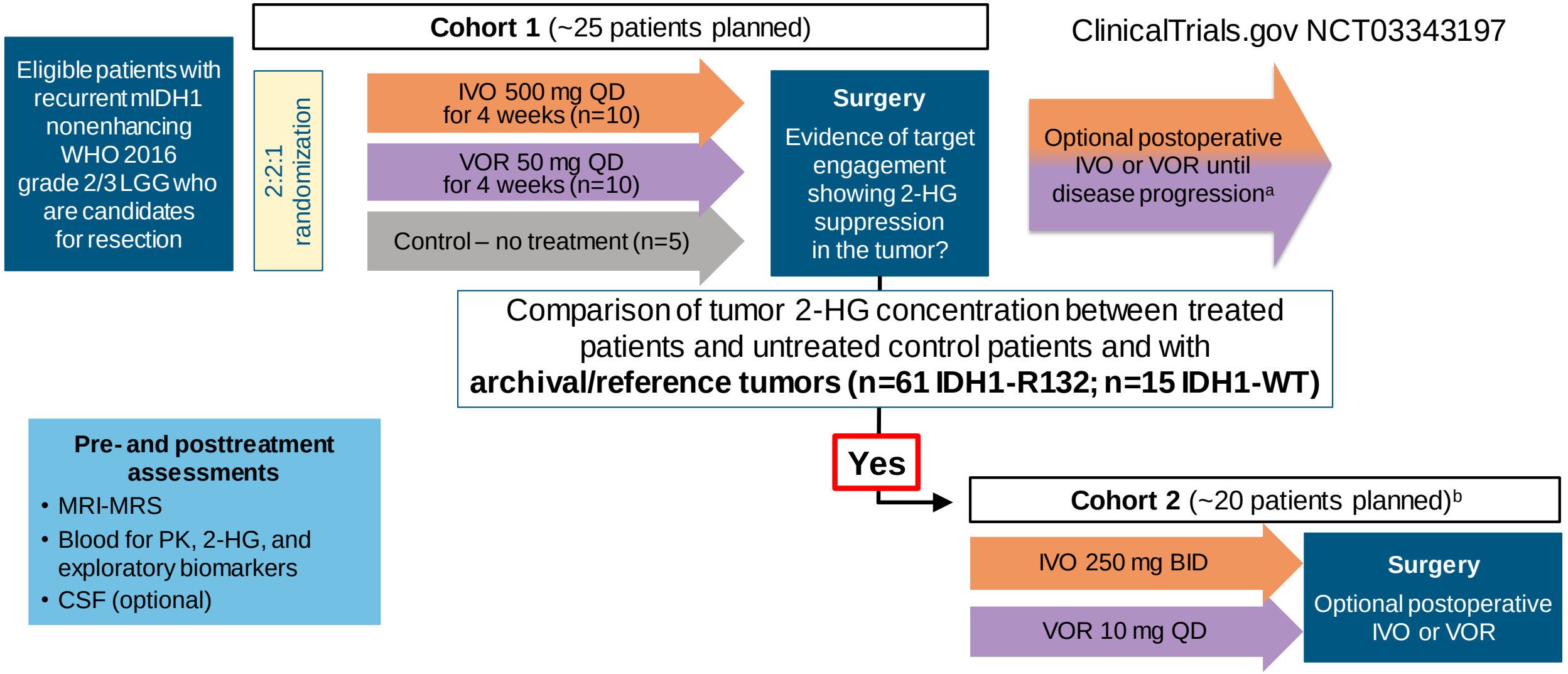
1. ClinicalTrials.gov NCT02989857. Abou-Alfa GK et al. *J Clin Oncol* 2018;36(suppl 4S):TPS545. **2.** Nicolay B et al. *2017 SNO Annual Meeting*: Poster EXTH-59. **3.** ClinicalTrials.gov NCT02073994. Mellinghoff I et al. *2017 SNO Annual Meeting*: Presentation ACTR-46. **4.** Yen K et al. *2017 AACR-NCI-EORTC Annual Meeting:* Poster B126. **5.** Nicolay B et al. *2017 SNO Annual Meeting*: Poster EXTH-34. **6.** ClinicalTrials.gov NCT02481154. Mellinghoff I et al. *2019 EANO 14th Meeting*: Presentation PL3.1. 2-HG = D-2-hydroxyglutarate; AML = acute myeloid leukemia; IC^{50} = 50% inhibitory concentration; mIDH = mutant isocitrate dehydrogenase; MR = minor response; ORR = overall response rate; PFS = progression-free survival; PR = partial response; R/R = relapsed/refractory

Study Objectives

- **Primary**
  - 2-HG concentration in tumors resected following presurgical treatment with IVO or VOR, compared with untreated control tumors
- **Secondary**
  - Safety of IVO and VOR
  - Pharmacodynamics of 2-HG in plasma
  - Pharmacokinetics (PK) in plasma and tumor
  - Preliminary clinical activity by RANO-LGG
- **Exploratory**
  - 2-HG in tumor pre- and posttreatment
  - PK/PD relationship of IVO and VOR in tumor, plasma, and CSF

ClinicalTrials.gov NCT03343197. CSF = cerebrospinal fluid; LGG = low-grade glioma; PK/PD = pharmacokinetic/pharmacodynamic; RANO = Response Assessment for Neuro-oncology, van den Bent MJ et al. *Lancet Oncol* 2011;12(6):583-93.

Study Schema



[a]All patients can opt to receive study drug postoperatively. Patients in the control group will be randomized 1:1 to either IVO or VOR. [b]Second doses of IVO and/or VOR will be tested in Cohort 2. Patients will be randomized 1:1 to either IVO or VOR. BID = twice daily; MRI-MRS = magnetic resonance imaging magnetic resonance spectroscopy; WHO = World Health Organization; WT = wild type

Study Status

- Study was initiated March 2018; enrollment completed April 2019
- 49 patients randomized before surgery
- All patients proceeded to surgery without unplanned delays
- 10 patients discontinued treatment as of 26 July 2019 data cutoff:
  - Disease progression (2 VOR, 3 IVO)
  - Investigator decision (1 VOR, 1 IVO)[b]
  - Did not continue postoperatively (3 IVO)[b]

Disposition, n (%)	Patients who received at least 1 dose pre- and/or postsurgery (N=49)[a]			
	Vorasidenib (n=24)		Ivosidenib (n=25)	
	50 mg QD (n=14)	10 mg QD (n=10)	500 mg QD (n=15)	250 mg BID (n=10)
On treatment	11 (78.6)	10 (100)	12 (80)	6 (60)
Discontinued	3 (21.4)	0	3 (20)	4 (40)

As of the data cutoff, the median (range) postoperative treatment duration (all doses) was 5.42 (0.9–13.5) months for VOR and 6.93 (1.0–13.2) months for IVO; these data continue to mature

[a]Includes all patients who received at least 1 dose of IVO or VOR in the pre- or postsurgery treatment period, untreated control patients are categorized according to postoperative treatment. [b]Reason for discontinuation was updated for 1 IVO-treated patient and 1 VOR-treated patient after the data cut

Baseline Characteristics

	Vorasidenib (N=24)	Ivosidenib (N=25)
Median (range) age, years	49 (31–75)	37.0 (19–66)
Male/female, n	16/8	17/8
KPS score at baseline, n (%) 100% 90% 80%	 8 (33.3) 13 (54.2) 3 (12.5)	 12 (48.0) 12 (48.0) 1 (4.0)
WHO tumor grade, n (%) Grade 2 Grade 3	 22 (91.7) 2 (8.3)	 21 (84.0) 4 (16.0)
Histological subtype, n (%) Oligodendroglioma Astrocytoma Anaplastic oligodendroglioma Anaplastic oligoastrocytoma	 13 (54.2) 11 (45.8) 0 0	 12 (48.0) 11 (44.0) 1 (4.0) 1 (4.0)
1p19q status (if known), n (%) Intact Co-deleted	 11 (45.8) 11 (45.8)	 9 (36.0) 13 (52.0)
Prior surgery, n (%)	24 (100)	25 (100)
Prior radiation therapy, n (%)	7 (29.2)	7 (28.0)
Prior systemic therapy, n (%)	10 (41.7)	14 (56.0)

Untreated controls are categorized according to postoperative randomization. KPS = Karnofsky Performance Status

AEs in ≥10% of Patients Treated (All Causalities)

Ivosidenib	
All patients, n (%)[a]	**All grades (N=25)**
Patients with at least 1 TEAE	25 (100)
Headache	8 (32.0)
Diarrhea	7 (28.0)
Anemia	7 (28.0)
Hypocalcemia	6 (24.0)
Cough	6 (24.0)
Seizure	6 (24.0)
Hypokalemia	5 (20.0)
Nausea	5 (20.0)
Nasal congestion	5 (20.0)
Constipation	4 (16.0)
Hyperglycemia	4 (16.0)
Pruritis	4 (16.0)
Hyponatremia	3 (12.0)
Insomnia	3 (12.0)
Paresthesia	3 (12.0)
Upper respiratory tract infection	3 (12.0)

Vorasidenib	
All patients, n (%)[a]	**All grades (N=24)**
Patients with at least 1 TEAE	23 (95.8)
Diarrhea	7 (29.2)
Fatigue	7 (29.2)
Nausea	7 (29.2)
Headache	6 (25.0)
Constipation	5 (20.8)
Insomnia	4 (16.7)
Anemia	3 (12.5)
Abdominal pain	3 (12.5)

- 8.3% TEAEs of transaminase elevations in VOR group
  - 1 TEAE of grade 3 transaminase elevation at 50 mg QD that resolved with dose interruption
- Grade 3 or higher events occurred in 6 (25.0%) VOR- and 4 (16.0%) IVO-treated patients, with the majority related to postoperative complications
- No patient discontinued treatment owing to an AE

[a]Includes all patients who received at least 1 dose of IVO or VOR in the pre- or postsurgery treatment period, untreated control patients are categorized according to postoperative treatment. Only AEs occurring on or after the first dose of study drug are included. AE = adverse event; TEAE = treatment-emergent adverse event

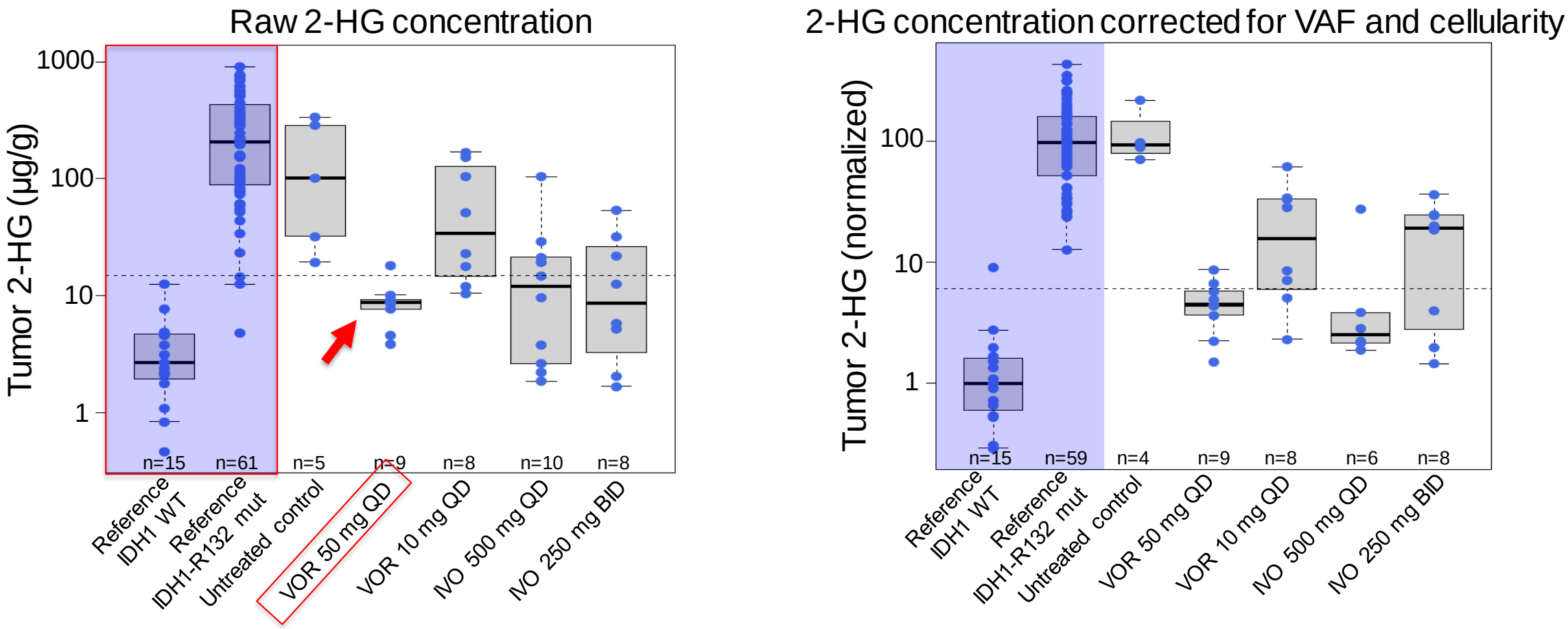
Tumor and Plasma PK

Time of surgery sample	Tumor, ng/g				Plasma C_{avg}, ng/mL			
	VOR 50 mg QD N=9	VOR 10 mg QD N=8	IVO 500 mg QD N=11	IVO 250 mg BID N=9	VOR 50 mg QD N=10	VOR 10 mg QD N=9	IVO 500 mg BID N=11	IVO 250 mg BID N=9
Geometric mean (range) drug concentration	110 (59.8– 190)	66.0 (33.2–113)	233 (105– 604)	278 (109–594)	67.7 (30.5– 139)	20.9 (10.8–33.8)	2618 (1762– 3369)	2430 (1597–3829)

- Tumors obtained from 47 out of 49 randomized patients, with 37 treated and 5 untreated evaluable
- VOR and IVO demonstrated brain penetrance, with mean brain:plasma ratios of 3.16 (VOR 10 mg), 1.74 (VOR 50 mg), 0.13 (IVO 250 mg), and 0.10 (IVO 500 mg)

C_{avg} = average plasma concentration

2-HG Concentrations in Tumors



- Mean percentage reduction in 2-HG (95% CI) of 92.6% (76.1, 97.6) and 91.1% (72.0, 97.0) for VOR 50 mg QD and IVO 500 mg QD, respectively, relative to untreated samples
- Data corrected for VAF and cellularity in IVO-treated samples difficult to interpret owing to limited evaluable samples

Box plots represent median with 25th and 75th percentiles. Dotted line indicates mean +2 deviations for WT reference samples. VAF = variant allelic frequency; mut = mutant

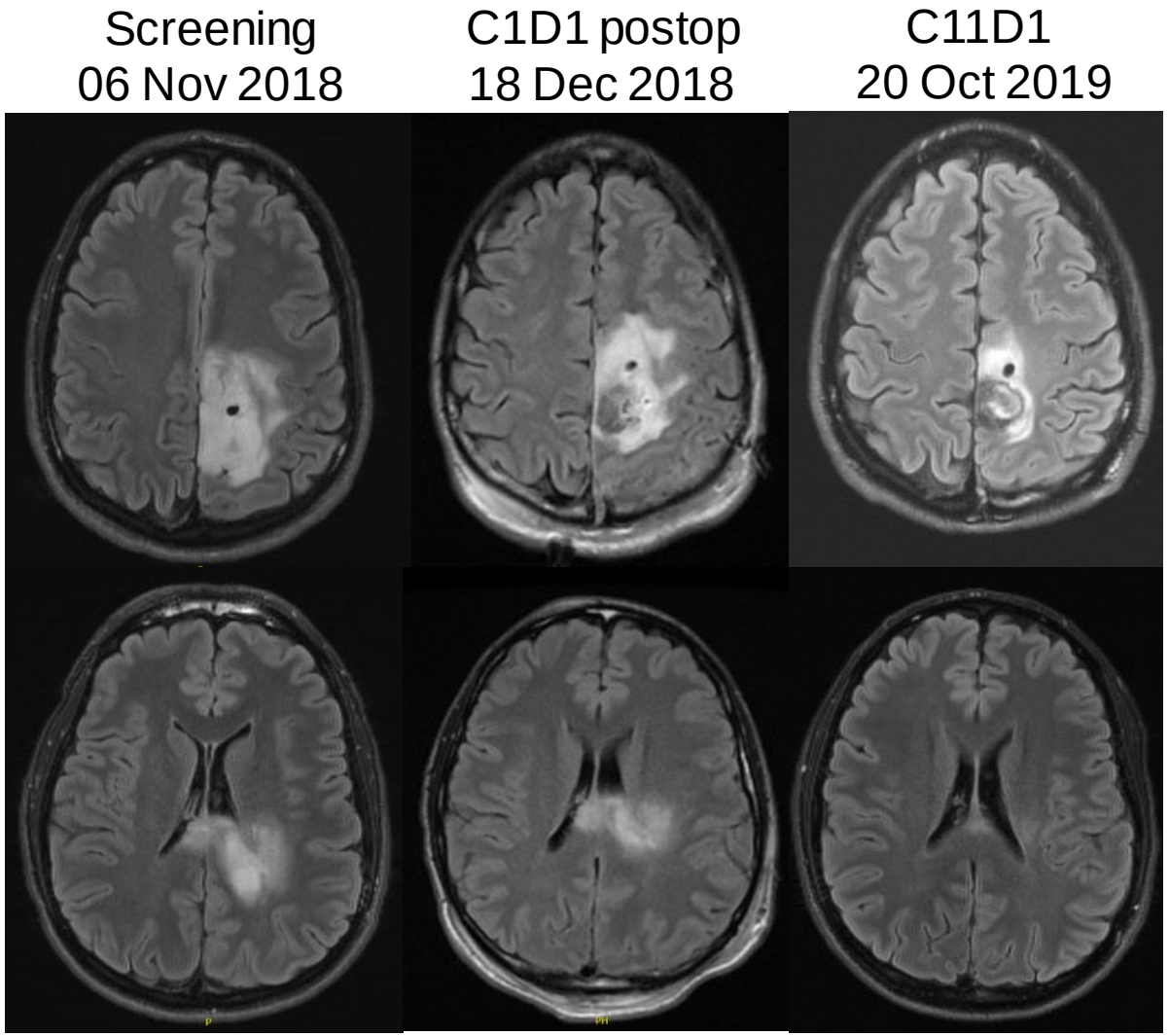
Tumor Response by RANO Criteria According to the Investigator

RANO response, n (%)[a]	Vorasidenib		Ivosidenib	
	50 mg QD (n=13)	10 mg QD (n=8)	500 mg QD (n=13)	250 mg BID (n=8)
Partial response (PR)	2 (15.4)	0	2 (15.4)	0
Minor response (MR)	2 (15.4)	0	2 (15.4)	0
Stable disease (SD)	7 (53.8)	8 (100)	9 (69.2)	7 (87.5)
Progressive disease (PD)	2 (15.4)	0	0	1 (12.5)
Objective response rate (ORR)	4 (30.8)	0	4 (30.8)	0
Disease Control Rate (PR+MR+SD)	11 (84.6)	8 (100)	13 (100)	7 (87.5)

[a]Patients categorized by postsurgery treatment assignment. Patients who were randomized and received at least 1 dose of study treatment are available for efficacy analysis if there was a baseline scan and at least 1 postbaseline scan available at the time of the data cutoff. Evaluable patients without measurable disease following surgery (n=10) are captured as best response of SD. 4 patients had incorrect response recorded, based on measurements entered at time of data cut; response corrected after data cut and is reflected in the table.

Patient With Partial Response on Vorasidenib 50 mg QD

- 31-year-old male
- Diagnosed with grade 2 oligodendroglioma,1p19q co-deleted, in 2016
- Biopsy 2016
- Everolimus 2017–2018
- On-study subtotal resection:
  - Surgery: 59×52 mm
  - Postsurgery baseline: 34×31 mm
- 96.5% 2-HG reduction relative to untreated controls
- Started VOR postoperatively on 14 Jan 2019
- Achieved MR at C7, PR at C11 (56.4% reduction)
- Remains on therapy at C12



C = cycle; D = day

Summary and Conclusions

- Vorasidenib and ivosidenib demonstrate brain penetrance and suppression of 2-HG in resected mIDH1 gliomas at all doses tested
- Ivosidenib 500 mg QD shows a range of 2-HG suppression with a mean reduction of >90% compared with untreated controls; BID dosing of 250 mg produced similar results
- Vorasidenib resulted in consistent and dose-dependent 2-HG suppression with >90% reduction at 50 mg QD compared with untreated controls
- Preliminary efficacy data show objective tumor responses (~30%) and durable disease control with postoperative treatment
- Ivosidenib and vorasidenib continue to have favorable safety profiles at all doses tested
- These data support the selection of vorasidenib 50 mg QD for a global phase 3 study in residual or recurrent mIDH grade 2 glioma

INDIGO Global Phase 3 Study Design

INDIGO | INVESTIGATING VORASIDENIB IN GLIOMA

Key eligibility criteria

- ≥ 12 years of age
- IDH-mutated grade 2 oligodendroglioma or astrocytoma per WHO 2016
- Prior surgery only
- Measurable residual or recurrent disease

1:1 double blind randomization (N=366)

Stratified by 1p19q status and baseline tumor size

Vorasidenib
50 mg QD orally
Continuous 28-day cycles

Matched placebo*

*Centrally-confirmed PD will permit unblinding and crossover

Endpoints

Primary:
PFS (by BIRC)

Secondary/exploratory:
Tumor volume, safety, ORR, OS, QOL, seizures, neuro-cognitive function, time to next intervention

ClinicalTrials.gov
NCT04164901

BIRC = blinded independent review committee; OS = overall survival; QOL = quality of life

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