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

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[8], 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], 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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IDH Mutations in Cancer

- Somatic mutations in the metabolic enzymes isocitrate dehydrogenase (IDH) occur in many cancers. IDH mutations are particularly common in lower-grade gliomas (LGG; WHO grade 2/3)[1,2] and include mutations in IDH1 (~80%) and IDH2 (~4%)
- The mIDH proteins have a gain-of-function enzyme activity catalyzing the reduction of alpha-ketoglutarate (α-KG) to the "oncometabolite" D-2-hydroxyglutarate (2-HG)[3,4]
- 2-HG inhibits α-KG–dependent enzymes, resulting in epigenetic dysregulation, impaired cellular differentiation, and oncogenesis[5-7]
- In preclinical models of leukemia, glioma, and sarcoma, inhibitors of mIDH enzymes blocked 2-HG production and showed antitumor activity[8-9]

1. Yan H et al. *N Engl J Med* 2009;360:765-73. **2.** The Cancer Genome Atlas Research Network. *N Engl J Med* 2015;372:2481-98. **3.** Dang L et al. *Nature* 2009;462:739-44. **4.** Ward PS et al. *Cancer Cell* 2010;17:225-34. **5.** Lu C et al. *Nature* 2012;483:474-8. **6.** Saha SK et al. *Nature* 2014;513:110-4. **7.** Xu W et al. *Cancer Cell* 2011;19:17-30. **8.** Wang F et al. *Science* 2013 340:622-6. **9.** Rohle D et al. *Science* 2013 340:626-30.

Inhibitors of Mutant IDH

- **Enasidenib** (IDHIFA®)**:** first-in-class, oral, small-molecule inhibitor of **mIDH2:**
  - Approved by the US FDA for mIDH2 relapsed/refractory acute myeloid leukemia (R/R AML)
- **Ivosidenib** (AG-120, TIBSOVO®)**:** first-in-class, oral, small-molecule inhibitor of **mIDH1**:
  - Approved by the US FDA for mIDH1 R/R AML and newly diagnosed AML
  - In an orthotopic glioma model, ivosidenib showed up to 85% suppression of tumor 2-HG, despite low brain penetrance with a brain:plasma ratio of <0.04[1]
  - In an ongoing phase 1 study (n=66 gliomas), ivosidenib was associated with a favorable safety profile at 500 mg QD; and resulted in an ORR of 5.7%, including 1 MR and 83% stable disease, with a median PFS of 13 months in nonenhancing glioma (n=35)[2]
- **Vorasidenib** (AG-881)**:** oral, potent, reversible brain-penetrant inhibitor of **mIDH1 and mIDH2:**
  - In an orthotopic glioma model, vorasidenib inhibited growth and showed 98% suppression of tumor 2-HG with a brain:plasma ratio of 1.33[3]
  - In an ongoing phase 1 study (n=52 gliomas), vorasidenib was associated with a favorable safety profile at doses <100 mg QD; and resulted in an ORR of 9.1%, including 1 PR, 1 MR, and 82% stable disease, with a median treatment duration of 15 months (PFS NE) in nonenhancing glioma (n=22)[4]

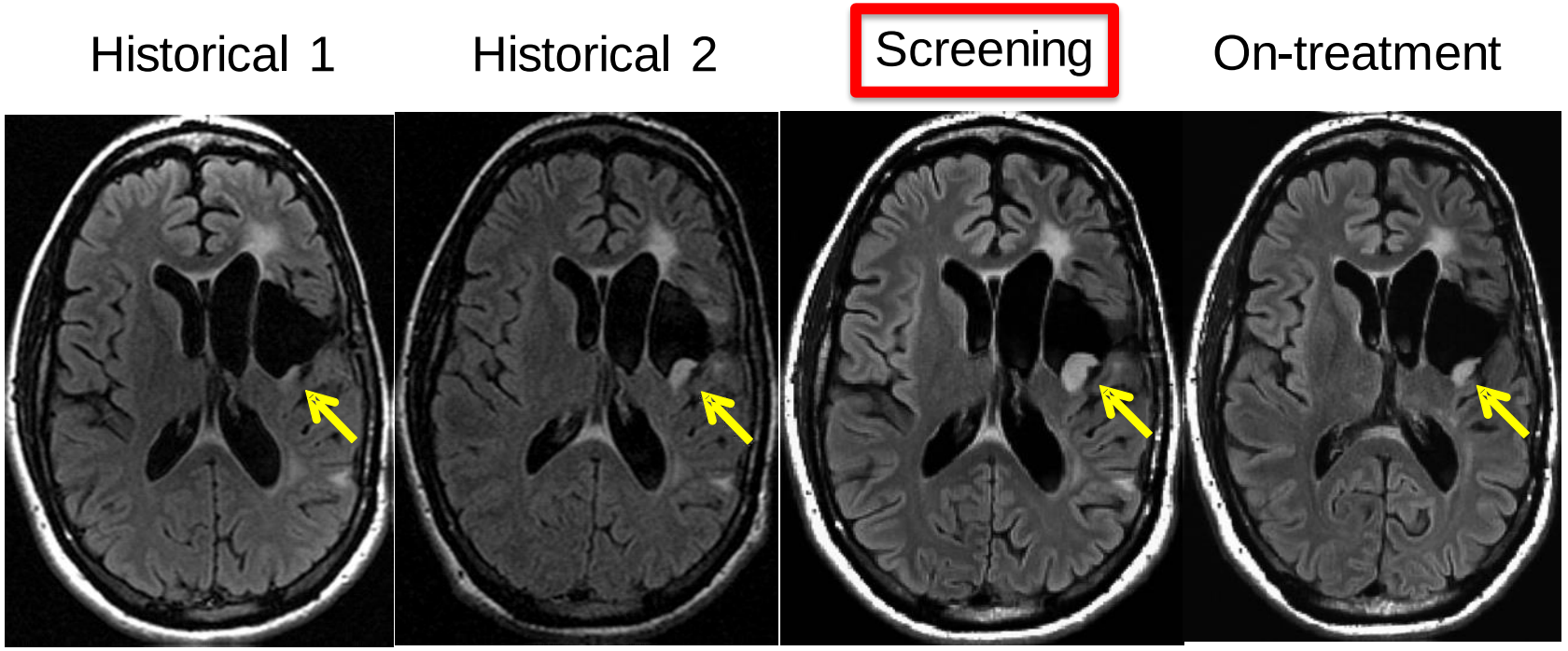
1. Nicolay B et al. 2017 SNO Annual Meeting: Poster EXTH-59. **2.** ClinicalTrials.gov NCT02073994. Mellinghoff I et al. 2017 SNO Annual Meeting: Presentation ACTR-46.
3. Nicolay B et al. 2017 SNO Annual Meeting: Poster EXTH-34. **4.** ClinicalTrials.gov NCT02481154. Mellinghoff I et al. 2018 SNO Annual Meeting: Presentation ACTR-31.
QD = once daily; ORR = overall response rate; MR = minor response; PFS = progression-free survival; PR = partial response; NE = not evaluable

Clinical Activity With Ivosidenib (500 mg QD)

- Anaplastic oligo 1p19q co-del
- Tumor resection 2009
- Radiation 2010
- TMZ 2010–2012
- **Ivosidenib start 12/2015**

  H1 MRI: 7/2014

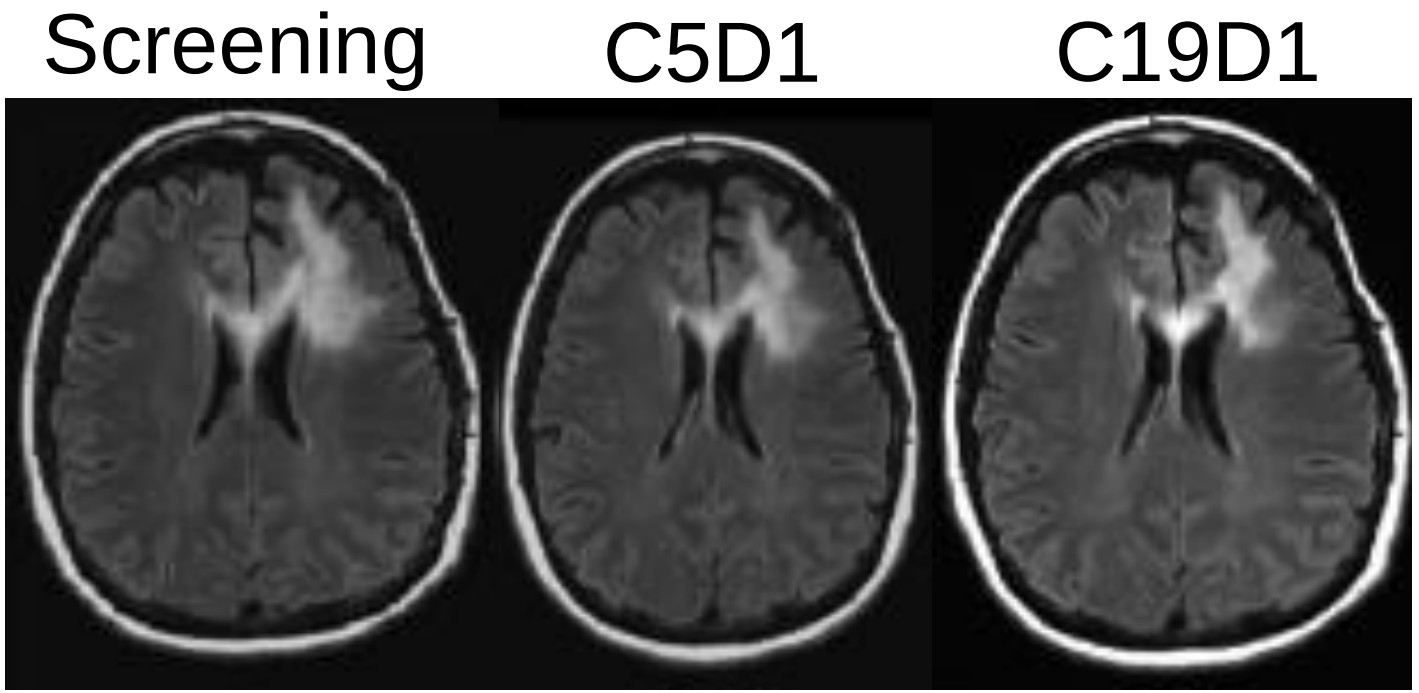
  H2 MRI: 5/2015
- **Remains on ivosidenib (17.0 mos @ May 2017 cutoff)**
- Best RANO response SD



Previously presented at 2017 SNO Annual Meeting, Mellinghoff et al. Presentation ACTR-46.
Co-del = co-deleted; TMZ = temozolomide; MRI = magnetic resonance imaging

Clinical Activity With Vorasidenib (50 mg QD)

- Oligo 1p19q co-del
- Tumor resection 2013
- No other treatment
- **Vorasidenib 100 mg QD start 1/2017**
- **Decreased to 50 mg QD May 2017**
- **Remains on vorasidenib (19.0 mos @ Jul 2018 cutoff)**
- Best RANO response PR April 2018



Previously presented at 2018 SNO Annual Meeting, Mellinghoff I et al. Presentation ACTR-31.

Study Objectives

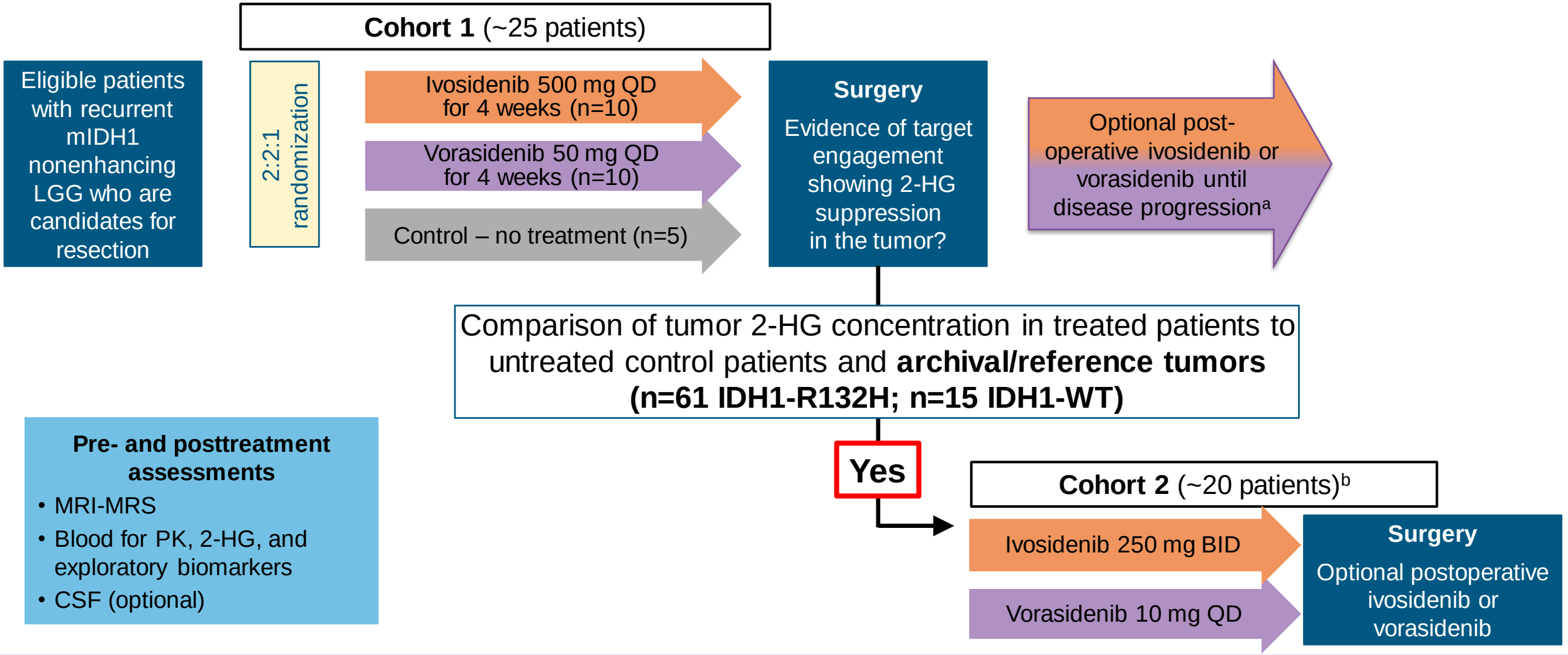
- **Primary**:
  - Determine 2-HG concentration in tumors resected following presurgical treatment with ivosidenib or vorasidenib compared with untreated control tumors in patients with recurrent, nonenhancing, grade 2/3 glioma with an IDH1-R132H mutation
- **Secondary**:
  - Safety of ivosidenib and vorasidenib
  - Pharmacodyamics (PD) of 2-HG in plasma
  - Pharmacokinetics (PK) of ivosidenib and vorasidenib in plasma and tumor
  - Preliminary clinical activity of ivosidenib and vorasidenib by RANO-LGG
- **Exploratory**:
  - 2-HG concentration by MRS in tumor pre- and posttreatment
  - PD and PK in CSF
  - PK/PD relationship of ivosidenib and vorasidenib in tumor, plasma, and CSF

ClinicalTrials.gov NCT03343197
MRS = magnetic resonance spectroscopy

Inclusion Criteria

- Recurrent, WHO 2016 grade 2/3 oligodendroglioma or astrocytoma, with IDH1-R132H mutation
- Centrally confirmed measurable nonenhancing disease
  - (2D or 3D T2-weighted image or FLAIR)
- Candidate for tumor resection within 2–4 months from screening
- Adequate bone marrow, renal, and hepatic function
- No prior treatment with IDH inhibitor or bevacizumab

Study Schema



[a]All patients can opt to receive study drug postoperatively. Patients in the control group will be randomized 1:1 to either ivosidenib or vorasidenib
[b]Second doses of ivosidenib and/or vorasidenib will be tested in Cohort 2. Patients will be randomized 1:1 to either ivosidenib or vorasidenib
BID = twice daily; WT = wildtype

Biospecimen Collection and Analysis

- **Blood samples**
  - Day 1/8/15: predose: 2-HG and drug concentration
  - Day 22: pre- and postdose (up to 8hr): 2-HG and drug concentration
  - Within 30 minutes of tumor resection: 2-HG and drug concentration
- **Tumor samples** (fresh frozen):
  - H&E staining for confirmation of histological diagnosis
  - 2-HG and drug concentration
  - Quantification of cell density and m*IDH* variant allele frequency (VAF) for 2-HG normalization to tumor cell content
- **CSF samples** (optional)
  - Day 1: predose
  - Day of surgery: predose
  - 2-HG and drug concentration

Study Status

Disposition	Presurgery treatment N=27			Postsurgery treatment[a] N=27	
	Vorasidenib 50 mg QD n=12	Ivosidenib 500 mg QD n=10	Untreated n=5	Vorasidenib 50 mg QD n=14	Ivosidenib 500 mg QD n=13
On treatment, n (%)	11 (92)	10 (100)	5 (100)	13 (93)	13 (100)

- All patients proceeded to surgery without unplanned delays
- All patients were treated following surgery
  - Untreated patients were re-randomized 1:1 to ivosidenib (n=3) or vorasidenib (n=2)
- Study initiated March 2018: median (range) treatment duration is 6.2 months (1.8–10.1) for ivosidenib and 6.8 months (2.3–10.1) for vorasidenib
- 26 of 27 patients remain on treatment as of the March 1, 2019 data cutoff
  - 1 patient discontinued vorasidenib postoperatively due to disease progression

[a]Includes untreated subjects who were re-randomized postoperatively

Baseline Characteristics

	Vorasidenib 50 mg QD n=14	Ivosidenib 500 mg QD n=13
Median age, years (range)	48.5 (31–61)	37.0 (24–57)
Male/female, n	10/4	8/5
KPS status at baseline, n (%) 100% 90% 80%	 4 (28.6) 8 (57.1) 2 (14.3)	 6 (46.2) 6 (46.2) 1 (7.7)
WHO tumor grade, n (%) Grade 2 Grade 3	 13 (92.9) 1 (7.1)	 12 (92.3) 1 (7.7)
Histological subtype, n (%) Oligodendroglioma Astrocytoma Anaplastic oligodendroglioma	 8 (57.1) 6 (2.9) 0	 7 (53.8) 5 (38.5) 1 (7.7)
1p19q status (if known), n (%) Intact Co-deleted	 5 (35.7) 8 (57.1)	 3 (23.1) 7 (53.8)
Prior surgery, n (%)	14 (100)	13 (100)
Prior radiation therapy, n (%)	4 (28.6)	5 (38.5)
Prior systemic therapy, n (%)	6 (42.9)	8 (61.5)

KPS = Karnofsky performance status

AEs in ≥10% of Patients Treated With Vorasidenib (all Causalities)

All patients, N (%)[a]	All grades N=14
Patients with at least 1 AE	13 (92.9)
Diarrhea	5 (35.7)
Constipation	3 (21.4)
Nausea	3 (21.4)
Fatigue	3 (21.4)
Headache	2 (14.3)
Alanine aminotransferase increased	2 (14.3)
Memory impairment	2 (14.3)
Abdominal pain	2 (14.3)
Insomnia	2 (14.3)
Muscular weakness	2 (14.3)
Tinea pedis	2 (14.3)

- Safety profile consistent with phase 1 data in patients with glioma[1]
- Grade 3 or higher events occurred in 5 (35.7%) patients, with majority related to postoperative complications
- AEs of transaminase elevations occurred in 2 patients and were considered related to study drug
  - Grade 1 ALT elevation during presurgery treatment which remains ongoing and without dose modification
  - Grade 3 ALT elevation occurred during post-surgery treatment and resolved to grade 1 with dose interruption
- No patients discontinued treatment due to an AE

[a]Includes all subjects who received at least 1 dose of vorasidenib in pre- or postsurgery treatment period. Only AEs occurring on or after the first dose of study drug are included.

1. Mellinghoff I et al. 2018 SNO Annual Meeting: Presentation ACTR-31. AE = adverse event; ALT = alanine aminotransferase

AEs in ≥10% of Patients Treated With Ivosidenib (all Causalities)

All patients, N (%)[a]	All grades N=13
Patients with at least 1 AE	13 (100)
Diarrhea	5 (38.5)
Hypocalcemia	4 (30.8)
Anemia	3 (23.1)
Hyperglycemia	3 (23.1)
Pruritus	3 (23.1)
Constipation	2 (15.4)
Nausea	2 (15.4)
Headache	2 (15.4)
Cough	2 (15.4)
Dysarthria	2 (15.4)
Hypokalemia	2 (15.4)
Upper respiratory infection	2 (15.4)
Dysphagia	2 (15.4)
Rash	2 (15.4)
Seizure	2 (15.4)
Tremor	2 (15.4)
White blood cell decreased	2 (15.4)

- Safety profile consistent with phase 1 data in patients with glioma[1]
- Grade 3 or higher events occurred in 3 (23.1%) patients, none related to study drug, with majority related to postoperative complications
  - No grade 3 or higher event occurred in 2 or more patients
- No patient discontinued treatment due to an AE

[a]Includes all subjects who received at least 1 dose of ivosidenib in pre- or postsurgery treatment period. Only AEs occurring on or after the first dose of study drug are included. **1.** Mellinghoff I et al. 2017 SNO Annual Meeting: Presentation ACTR-46.

PK in Tumor and Plasma

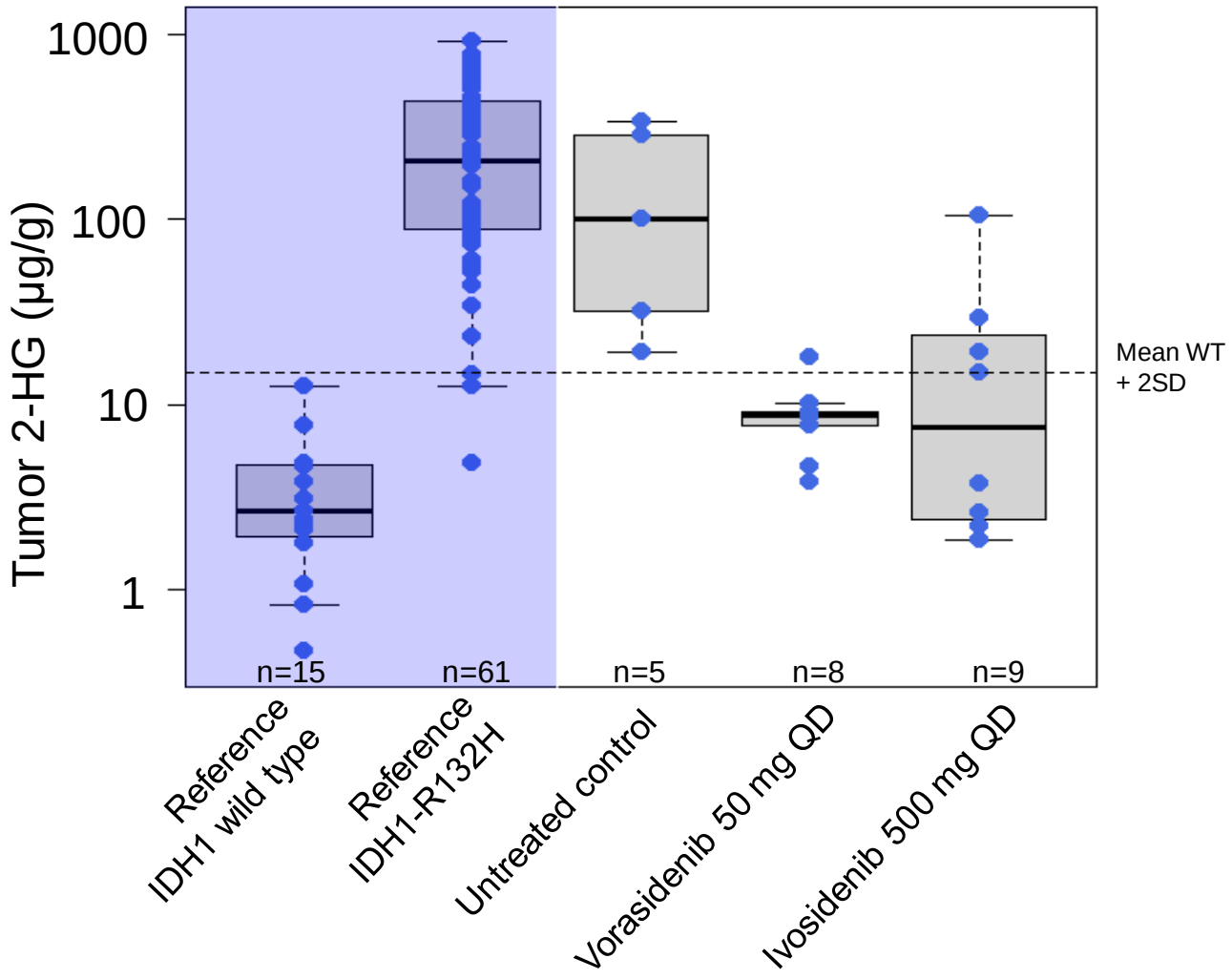
	Vorasidenib 50 mg QD		Ivosidenib 500 mg QD	
Time of surgery sample	**Plasma (C_{avg}) ng/mL n=10**	**Tumor ng/g n=9**	**Plasma (C_{avg}) ng/mL n=10**	**Tumor ng/g n=8**
Drug concentration geo-mean (range) ng/g or ng/mL	70 (31.6–144)	110 (59.8–190)	2640 (1760–3500)	299 (106–604)

- Tumors obtained from 26 of 27 randomized patients, with 22 evaluable (8 ivosidenib, 9 vorasidenib, 5 controls)
- Vorasidenib and ivosidenib demonstrate brain penetrance with geo-mean (range) brain:plasma ratios of 1.59 (0.69–2.4) and 0.13 (0.047–0.17), respectively

C_{avg} = average plasma concentration

2-HG Concentrations in Tumors

	Tumor 2-HG	
	Geo-mean (range) µg/g	Mean % reduction (95% CI) relative to untreated[a]
Reference wild type n=15	2.7 (0.5–12.5)	
Reference mIDH1-R132H n=61	173.9 (4.8–909)	
Untreated control patients n=5	90.3 (29.3–335)	
Vorasidenib n=9	7.9 (3.9–18.1)	92.5 (78.1, 97.7)
Ivosidenib n=8	8.5 (1.8–104)	92.0 (73.2, 97.4)



Box plots represent median with 25th and 75th percentiles

Summary and Conclusions

- Ivosidenib 500 mg QD and vorasidenib 50 mg QD demonstrate brain penetrance
- Ivosidenib 500 mg QD and vorasidenib 50 mg QD suppress 2-HG in resected mIDH1 gliomas by >90% compared to untreated controls; vorasidenib is associated with more consistent 2-HG suppression
- Ivosidenib 500 mg QD and vorasidenib 50 mg QD continue to have a favorable safety profile
- Cohort 2 testing ivosidenib 250 mg BID and vorasidenib 10 mg QD has completed enrollment
- Additional tumor biomarker analyses are ongoing
- Vorasidenib has been selected as the molecule for a planned phase 3 study in mIDH low-grade glioma

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