Phase 1 study of AG-881, an inhibitor of mutant IDH1 and IDH2: results from the recurrent/progressive glioma population

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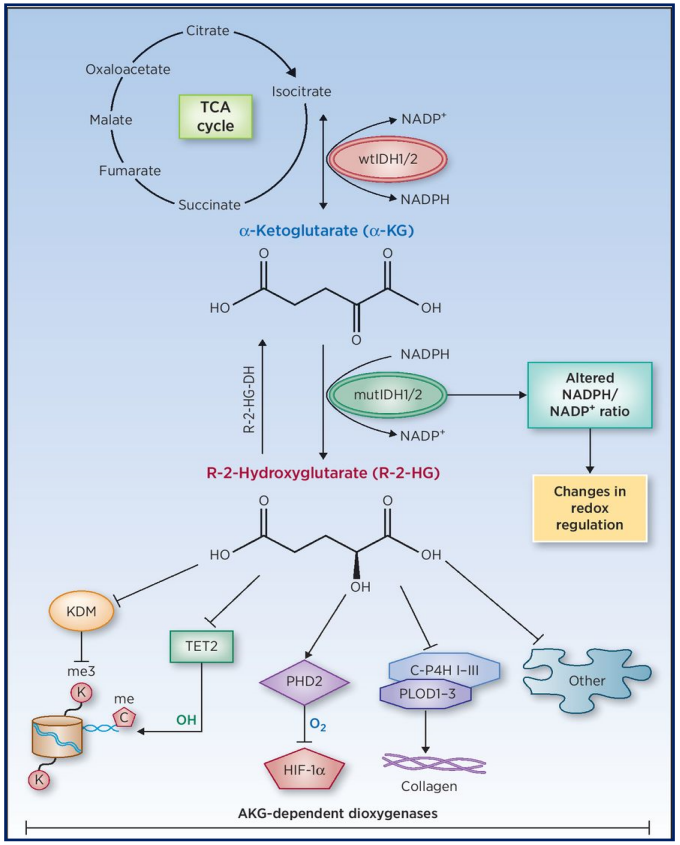
Isocitrate Dehydrogenase (IDH) in Cancer

- Mutations in IDH1/2 occur in several human malignancies, including cholangiocarcinoma, chondrosarcoma, acute myeloid leukemia (AML), glioblastoma, and lower grade glioma (~70%)
- Neomorphic production of the oncometabolite 2-HG, leading to epigenetic dysregulation and impaired differentiation, promoting tumorigenesis
- IDHIFA® (enasidenib), an IDH2 inhibitor, approved in Aug 2017 in mIDH2 relapsed/refractory AML
- TIBSOVO® (ivosidenib), an IDH1 inhibitor, approved in Aug 2018 in mIDH1 relapsed/refractory AML



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

mIDH1 = mutant IDH1; mIDH2 = mutant IDH2

AG-881

- Oral, potent, reversible, brain-penetrant inhibitor of mutant IDH1/2:
  - IC_{50} ranges from <1 nM (IDH1-R132H) to 32 nM (IDH2-R140Q)[1]
  - In an orthotopic glioma model, AG-881 showed growth inhibition and brain penetrance (brain:plasma ratio of 1.33; 98% suppression of tumor 2-HG)[2]
- Under clinical evaluation in an ongoing phase 1 study of patients with mIDH1 and mIDH2 advanced solid tumors (N=93), including glioma (n=52)[3]
- Here we report updated safety and efficacy data, and an exploratory volumetric growth rate analysis, in the glioma patient population as of Jul 20, 2018

2-HG = D-2-hydroxyglutarate

1. Yen K et al. *AACR-NCI-EORTC Meeting* 2017: Poster B126. 2. Nicolay B et al. *2017 SNO Annual Meeting*: Poster EXTH-34. 3. Mellinghoff IK et al. *2018 ASCO Annual Meeting*: Oral presentation 2002

Study Objectives

- **Primary** objectives
  - Safety and tolerability
  - Determine MTD and/or RP2D
- **Secondary** objectives
  - Pharmacokinetics and pharmacodynamics
  - Preliminary clinical activity (ORR, PFS)
- **Exploratory** objectives
  - Change in tumor volumetric growth rate in patients with nonenhancing glioma
  - Pharmacodynamic evaluation of tissue and plasma

MTD = maximum tolerated dose; ORR = objective response rate; PFS = progression-free survival; RP2D = recommended phase 2 dose

Study Design

- Single-arm, open-label, multicenter, dose escalation study
- Bayesian model to predict MTD/RP2D
- Inclusion criteria:
  - mIDH1 or mIDH2 tumors
  - Recurrent, progressed, or not responded to standard therapy
- Tumor response assessed locally by RANO or RANO-LGG

Dose level	Glioma (N=52)
10 mg QD	6
25 mg QD (DL1)	6
50 mg QD	11
100 mg QD	10
200 mg QD	14
300 mg QD	5

DL1 = dose level 1 (initial dose level tested)

Study Status

Disposition	Enhancing glioma (n=30)	Nonenhancing glioma (n=22)	Total glioma (N=52)
On treatment, n (%)	1 (3.3)	13 (59.1)	14 (26.9)
Discontinued treatment, n (%)	29 (96.7)	9 (40.9)	38 (73.1)

- Enrollment completed in June 2017
- Study ongoing as of July 20, 2018 data cutoff; 14 glioma patients remain on AG-881 (13/14 with nonenhancing disease)
- Median treatment duration of 15 months for the nonenhancing glioma population
- Of the 38 glioma patients who discontinued treatment: 29 (76.3%) discontinued for disease progression, 2 (5.2%) discontinued due to an AE

Baseline Characteristics – Glioma

	Total treated (N=52)
Median age, years (range)	42.5 (16–73)
Male/female, n	26/26
ECOG status at baseline, n (%) 0 1 2	 22 (42.3) 29 (55.8) 1 (1.9)
IDH1 mutation, n (%)[a] IDH2 mutation, n (%)	48 (92.3) 3 (5.8)
Enhancing, n (%) Nonenhancing, n (%)	30 (57.7) 22 (42.3)
WHO tumor grade, n (%) Grade II Grade III Grade IV Unknown	 25 (48.1) 22 (42.3) 4 (7.7) 1 (1.9)
Prior radiation therapy, n (%)	30 (57.7)
Prior systemic therapy, n (%)	39 (75.0)
Number of prior systemic therapies, median (range)	2 (1–6)
Type of prior systemic therapy, n (%) Temozolomide Procarbazine/CCNU/vincristine	 38 (73.1) 4 (7.7)

[a]One patient did not have biopsy, presumed IDH mutation by the investigator as evidenced by consistent 2-HG elevation by MRS

AEs ≥10% (All Patients, All Causalities)

All patients, n (%)	All grades (N=52)	Grade 3 or higher (N=52)
Patients with at least 1 AE	52 (100)	10 (19.2)
Alanine aminotransferase increased	23 (44.2)	3 (5.8)
Aspartate aminotransferase increased	21 (40.4)	2 (3.8)
Headache	19 (36.5)	0
Fatigue	17 (32.7)	1 (1.9)
Nausea	15 (28.8)	1 (1.9)
Seizure	13 (25.0)	4 (7.7)
Hyperglycemia	19 (19.2)	0
Dizziness	9 (17.3)	0
Vomiting	9 (17.3)	1 (1.9)
Constipation	8 (15.4)	0
Diarrhea	8 (15.4)	0
Neutrophil count decreased	8 (15.4)	1 (1.9)
Cough	7 (13.5)	0
White blood cell decreased	7 (13.5)	0
Aphasia	6 (11.5)	0
Hypoglycemia	6 (11.5)	0

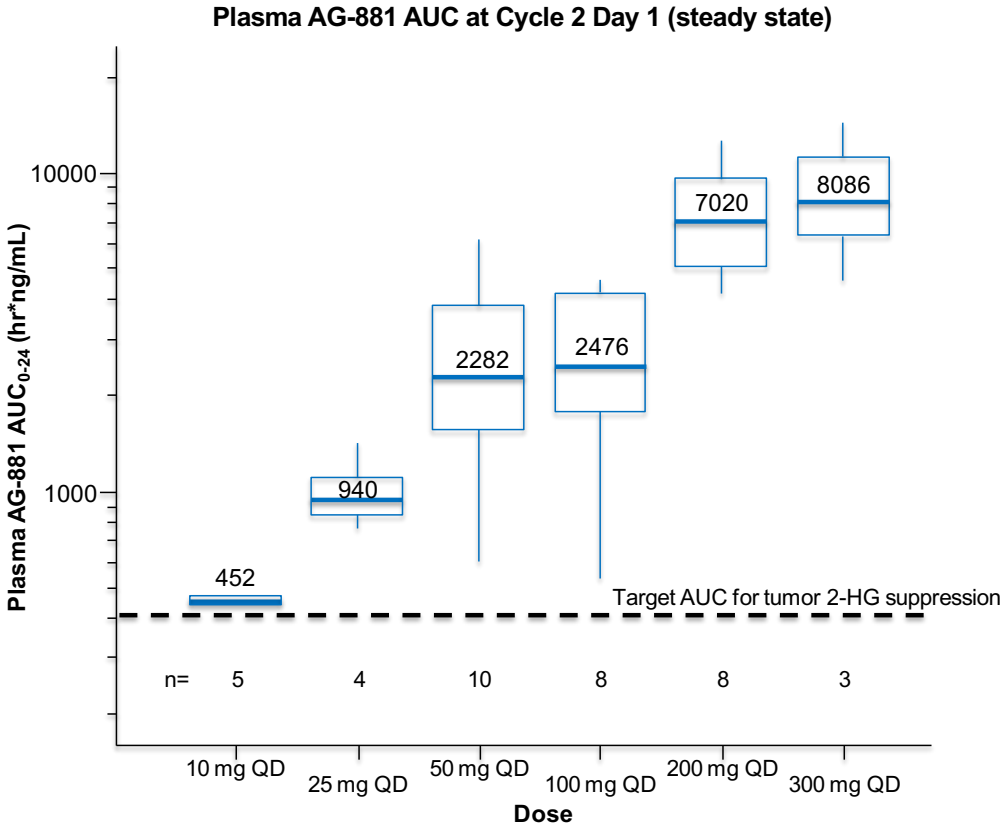
Transaminase Elevation Is Dose Dependent in Glioma Patients

New or worsening AE at actual dose, n (%)[a]	10 mg QD (n=6)[b]	25 mg QD (n=8)	50 mg QD (n=20)	100 mg QD (n=19)	200 mg QD (n=24)	300 mg QD (n=5)	Total (N=52)
No AE	6 (100.0)	7 (87.5)	13 (65.0)	6 (31.6)	11 (45.8)	2 (40.0)	28 (53.8)
Grade 1	0	0	7 (35.0)	6 (31.6)	7 (29.2)	1 (20.0)	14 (26.9)
Grade 2	0	1 (12.5)	0	6 (31.6)	4 (16.7)	1 (20.0)	6 (11.5)
Grade 3	0	0	0	0	2 (8.3)	1 (20.0)	3 (5.8)
Grade 4	0	0	0	1 (5.3)	0	0	1 (1.9)

- DLT defined as any grade ≥3 AE during Cycle 1 and related to study treatment, or by sponsor designation
- Transaminase AEs were not associated with elevated bilirubin
- Exposure safety analysis indicated a trend of increased probability of elevated transaminase with increased plasma exposure of AG-881
- No apparent concomitant drug interaction or underlying etiology associated with elevated transaminases

[a]Within 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
[b]N-value for each dose level indicates the number of patients who received that dose at any time during the study

Pharmacokinetics in Glioma Population



- Plasma exposure increases linearly with dose between 10 mg and 200 mg; less-than-dose proportional >200 mg
- Long, effective half-life (mean ± SE: 67.2 ± 9.5 hr, n=35)
- Plasma drug exposure at all doses tested in patients with glioma is predicted to be sufficient for tumor 2-HG suppression based on the TS-603 orthotopic glioma model[1]

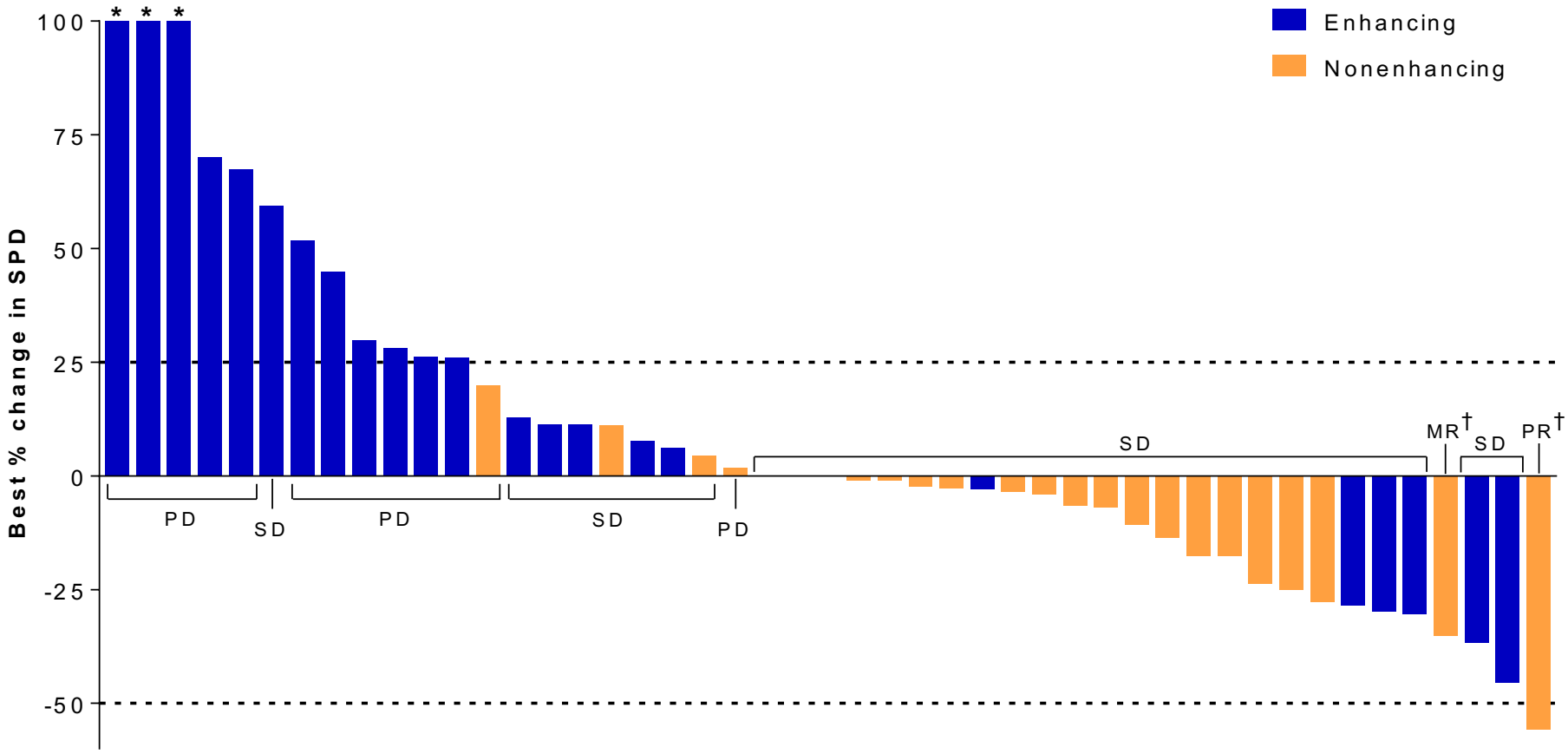
Box plots represent median with 25th and 75th percentiles. Median values indicated. Whiskers extend to 1.5 × interquartile range (IQR) from the quartiles. Outliers (>3 x IQR above or below quartiles) not shown
AUC = area under curve
1. Agios internal data on file

Best Response by the Investigator: Glioma

RANO response, n (%)	Nonenhancing (n=22)	Enhancing (n=30)	Total evaluable patients (N=52)
Partial response (PR)	1 (4.5)[a]	0	1 (1.9)
Minor response (MR)	1 (4.5)[a]	NA	1 (1.9)
Stable disease (SD)	18 (81.8)	18 (60.0)	36 (69.2)
Progressive disease (PD)	2 (9.1)	11 (36.7)	13 (25.0)
Not assessed[b]	0	1 (3.3)	1 (1.9)
Objective Response Rate (ORR)	2 (9.1)	0	2 (3.8)

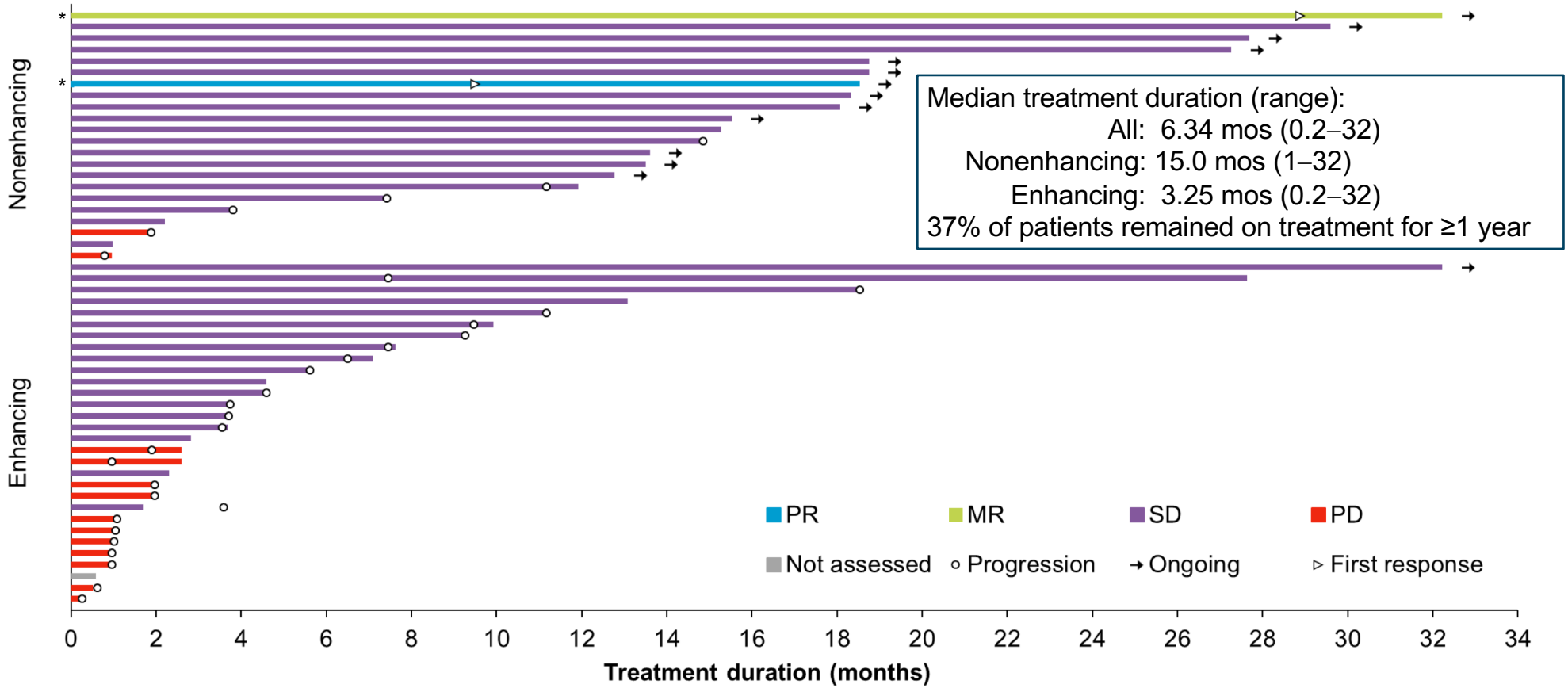
Response assessed by RANO (Wen PY et al. *J Clin Oncol.* 2010;28:1963-72) or RANO-LGG (van den Bent M et al. *Lancet Oncol.* 2011;12:583-93)
MR defined as ≥25% but <50% decrease in tumor measurements compared with baseline; applicable to RANO-LGG criteria only
[a]Lesion measurements for the PR and MR were correct but the response indicated was incorrect at the time of the data transfer. This was updated and the correct response is included in the table
[b]Discontinued treatment prior to first response assessment

Best Percent Change from Baseline by the Investigator: Glioma



*Indicates change >100%
†Lesion measurements for the PR and MR were correct but the response indicated was incorrect at the time of the data transfer. This was updated and the correct response is included in the figure
MR defined as ≥25% but <50% decrease in tumor measurements compared with baseline; applicable to RANO-LGG criteria only
MR = minor response; PD = progressive disease; PR = partial response; SD = stable disease; SPD = sum of product of diameters

Treatment Duration and Best Response: Glioma



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MR defined as ≥25% but <50% decrease in tumor measurements compared to baseline; applicable to RANO-LGG criteria only
Not assessed = patient discontinued treatment prior to first response assessment

Exploratory Imaging: Effect on Tumor Volume Growth Rates

- We previously reported post treatment reduction in volumetric growth rate with an IDH1 inhibitor (ivosidenib) in nonenhancing gliomas[1]
- Using similar methodology we analyzed 172 MRI scans across 18 patients with nonenhancing gliomas

Nonenhancing glioma (n=18)

Study inclusion and imaging criteria

- IDH1 or IDH2 mutant that has progressed
- No anticancer therapy or RT <21 days prior to first dose
- **On-treatment MRI scans every 2 months with 3–5 mm slice thickness and 1 mm interslice gap on either 2D T2-weighted image, 3D T2-weighted image, or FLAIR**

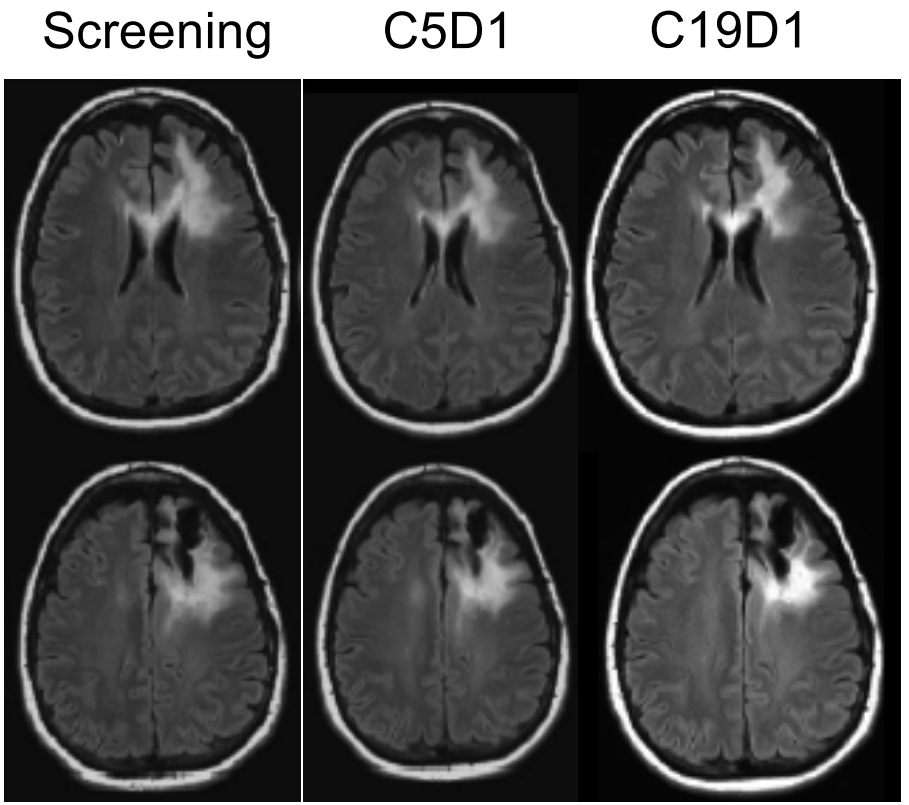
Volumetric imaging method

- Presegmentation of T2/FLAIR
- Quantification of T2/FLAIR hyperintense volume
- Automatic calculation of bidimensional product
- Application of LGG RANO criteria and volumetric assessments
- Tumor growth rate estimates produced using mixed effects model

1. Mellinghoff et al. *2017 SNO Annual Meeting*: Oral presentation ACTR-46

Case Study 1: Glioma Patient With a Partial Response

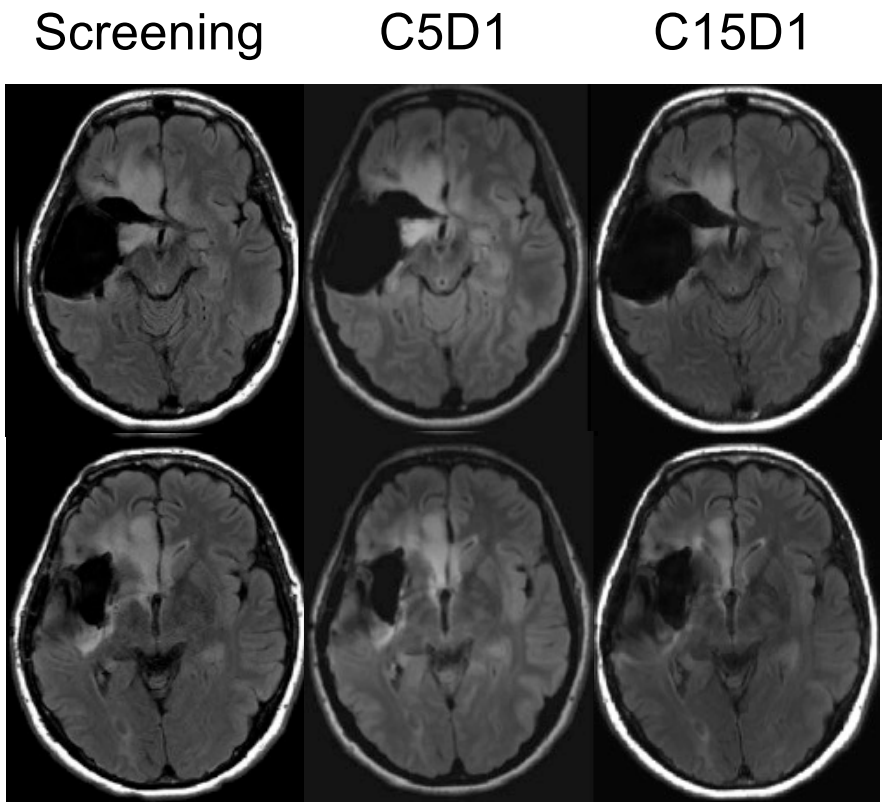
- Oligo (WHO II), 1p19q co-del
- Resection: 2013
- No other treatment
- Screen: Dec 2016
- Started AG-881 100 mg Jan 2017; decreased to 50 mg May 2017 (Grade 2 ALT/AST)
- **Sustained MR Oct 2017; PR as of Apr 2018[a]**
- **Remains on AG-881 (19 mos as of Jul 2018)**



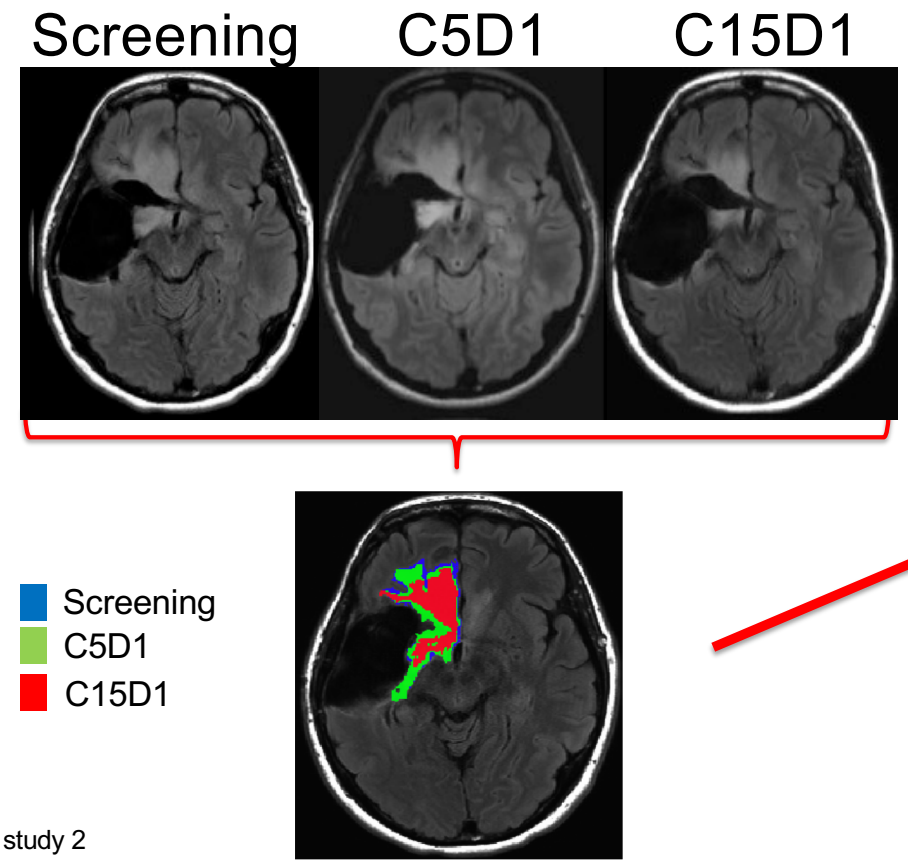
[a]Lesion measurements for the PR were correct but the response indicated was incorrect at the time of the data transfer. This was updated and the correct response is included in the slide

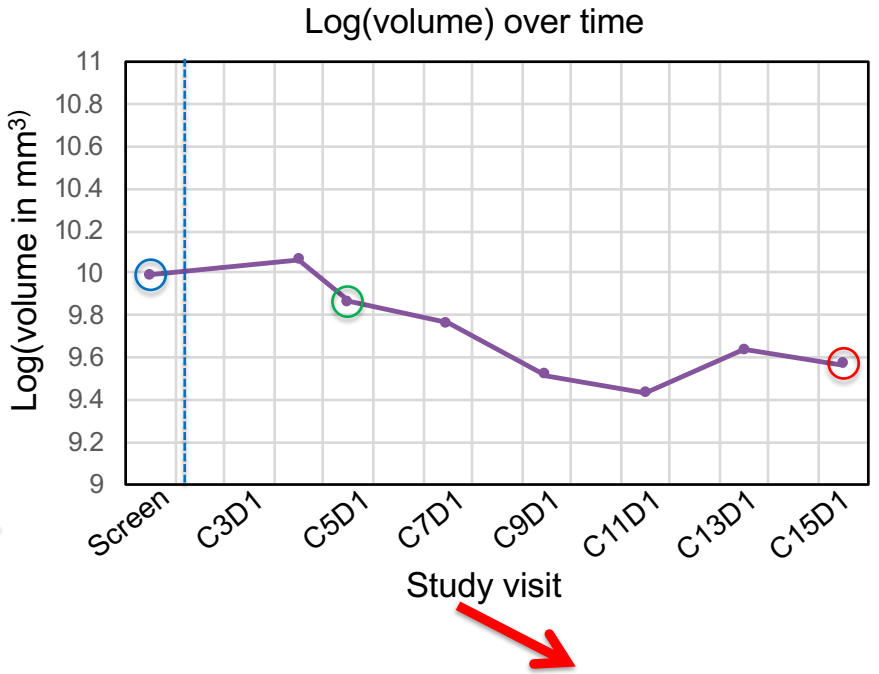
Case Study 2: Glioma Patient at 10 mg QD

- Diffuse astrocytoma (WHO II), 1p19q intact
- Resection: 2004 and Feb 2017
- No other treatment
- Screen: May 2017
- Started AG-881 10 mg Jun 2017
- Best RANO response: SD
- **Remains on AG-881 (14 mos as of Jul 2018)**



Determining Tumor Volume Growth Rates





Calculated Tumor Volume Growth Rate on AG-881:
–16.6% over 6 months

Case study 2

Post-Treatment Tumor Growth Rate with AG-881 Based on Volume

Study	N[a]	Mean percent change (95% CI) every 6 months based on volume	
		Pre-treatment	Post-treatment
NHS	143	24.5 (20.3, 28.9)	NA
AG120-002	24	26.5 (9.2, 46.5)	9.0 (–0.8, 19.7)
AG881-002	18	NA	6.8 (–0.7, 14.9)

- The tumor volume growth rate is derived based on the slope estimate from the linear mixed effects model
- Pre- and post treatment growth rates for AG-120 (ivosidenib) and the Natural History Study were presented previously[1]

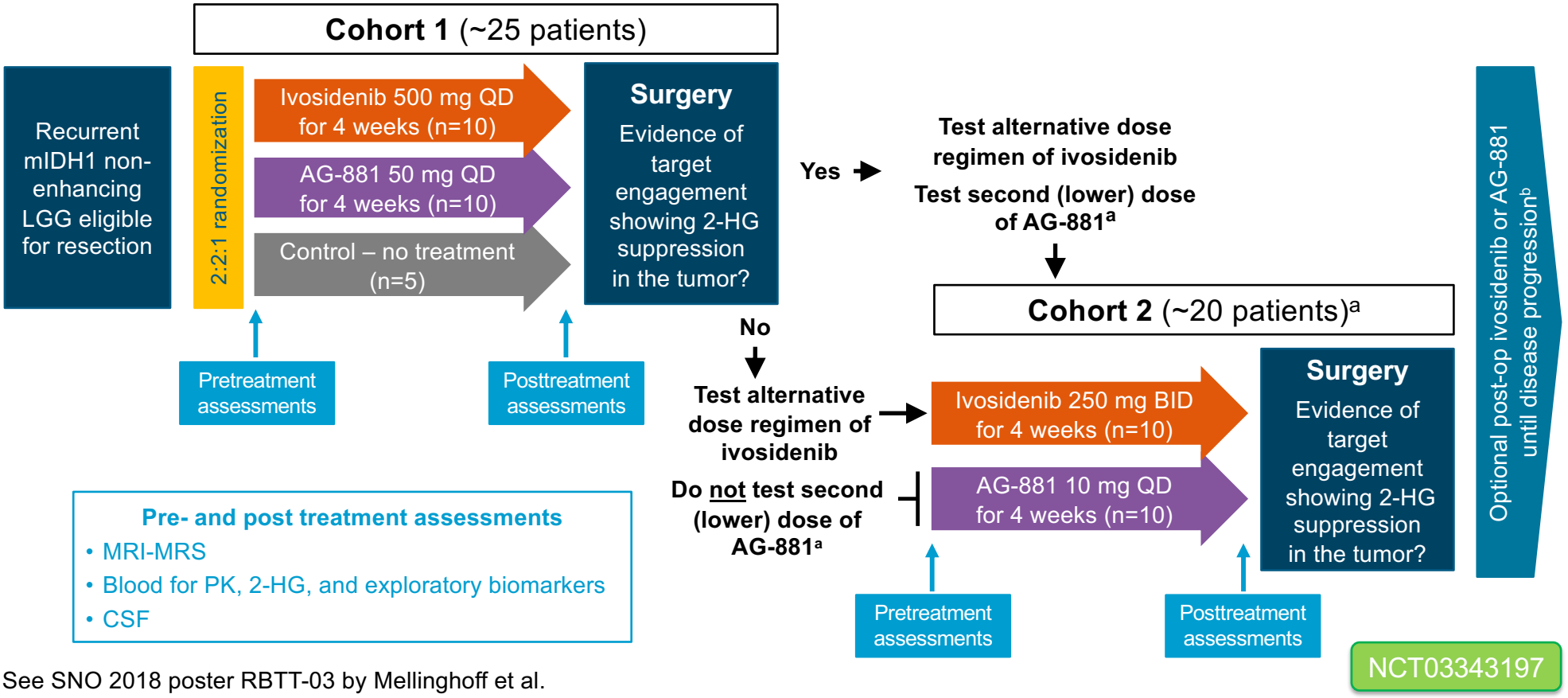
[a]N indicates the number of patients with mIDH Grade 2/3 nonenhancing glioma with data

1. Mellinghoff et al. *2017 SNO Annual Meeting*: Oral presentation ACTR-46

Summary and Conclusions

- AG-881 has a favorable safety profile at dose levels <100 mg
- Five DLTs of elevated transaminases occurred in patients with glioma at the higher dose levels (≥100 mg) and were reversible
- Plasma drug exposure at all doses tested in patients with glioma is predicted to be sufficient for tumor 2-HG suppression based on preclinical model
- AG-881 was associated with prolonged disease control in the nonenhancing glioma population (median treatment duration of 15 mos, with 59% of these patients ongoing)
- AG-881 (10 mg and 50 mg) and AG-120 (ivosidenib) are under evaluation in an ongoing perioperative study to confirm CNS penetration and tumor 2-HG suppression in Grade 2/3 nonenhancing glioma (NCT03343197)

Perioperative Study Schema



See SNO 2018 poster RBTT-03 by Mellinghoff et al.

[a]Second doses of ivosidenib and/or AG-881 may be tested in cohort 2. In the event that for both are tested, patients will be randomized 1:1 to either ivosidenib or AG-881
[b]Control patients can opt to be randomized to either ivosidenib or AG-881 postoperatively
LGG = low-grade glioma (WHO 2016-classified grade 2 or 3 oligodendroglioma or astrocytoma); MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy

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