Phase 1 study of AG-881, an inhibitor of mutant IDH1/IDH2, in patients with advanced IDH mutant solid tumors, including glioma

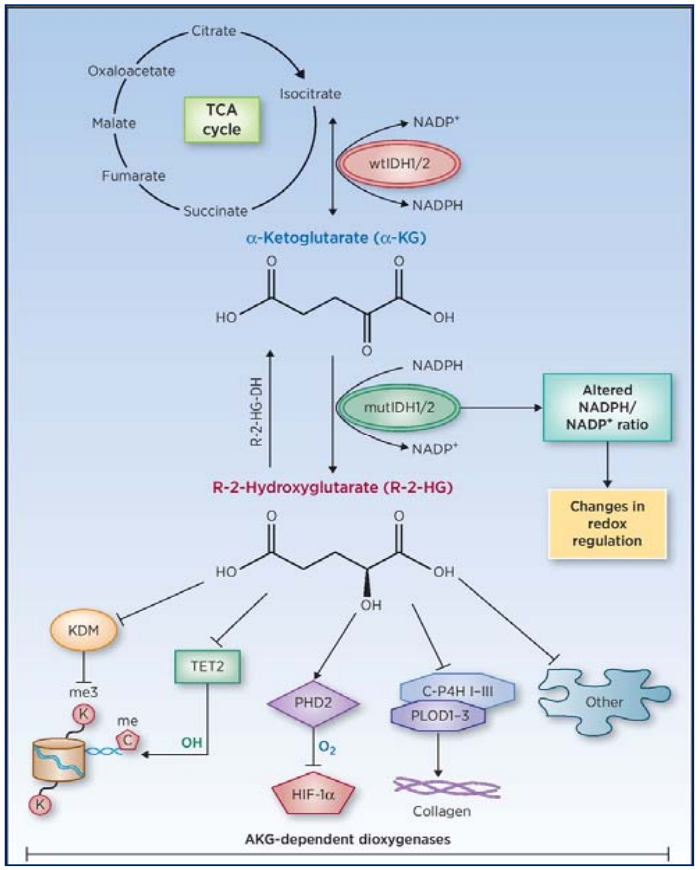
Ingo K Mellinghoff[1], Marta Penas-Prado[2], Katherine B Peters[3], Timothy F Cloughesy[4], Howard A Burris III[5], Elizabeth A Maher[6], Filip Janku[2], Gregory M Cote[7], Macarena I De La Fuente[8], Jennifer Clarke[9], Lori Steelman[10], Kha Le[10], Yanwei Zhang[10], Alison Sonderfan[10], Diana Hummel[10], Steven Schoenfeld[10], Katharine Yen[10], Shuchi S Pandya[10], Patrick Y Wen[11]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Duke University Medical Center, Durham, NC; [4]University of California Los Angeles, Los Angeles, CA; [5]Sarah Cannon Research Institute, Nashville, TN; [6]The University of Texas Southwestern Medical Center, Dallas, TX; [7]Massachusetts General Hospital, Boston, MA; [8]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; [9]University of California San Francisco, San Francisco, CA; [10]Agios Pharmaceuticals, Inc., Cambridge, MA; [11]Dana-Farber/Harvard Cancer Center, Boston, MA

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, June 1–5, 2018, Chicago, IL, USA

Background

- Mutations in the metabolic enzymes isocitrate dehydrogenase (IDH) 1 and IDH2 occur in several human malignancies, including cholangiocarcinoma, chondro-sarcoma, glioma, and acute myeloid leukemia (AML)
- IDH mutations change the function of the enzyme:
  - → neomorphic production of the oncometabolite 2-HG, leading to epigenetic dysregulation and impaired cellular differentiation, promoting tumorigenesis
- IDHIFA® (enasidenib), an IDH2 inhibitor, approved in Aug 2017 in mIDH2 relapsed/refractory AML
- Tibsovo (ivosidenib), an IDH1 inhibitor, under regulatory review in mIDH1 relapsed/refractory AML



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

AG-881

- **AG-881** is an oral, potent, reversible, brain-penetrant inhibitor of the mutant IDH1/2 enzymes:
  - 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)

- We report the **first results** of AG-881 **in patients with advanced solid tumors**, including gliomas (NCT02481154), as of 29 Mar 2018

[1]Yen K et al. *AACR-NCI-EORTC 2017 Meeting*: Poster B126

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 non-enhancing glioma
  - Pharmacodynamic evaluation of tissue and plasma

MTD = maximum tolerated dose; RP2D = recommended phase 2 dose

Study Design

- Single-arm, open-label, multicenter, dose escalation study
- Bayesian model to predict MTD/RP2D
- Inclusion criteria:
  - IDH1 or IDH2 mutant tumors
  - Recurrent, progressed, or not responded to standard therapy
- Tumor response assessed locally by RANO-RANO LGG or RECIST

Dose level	Glioma (n=52)	Other solid tumors (n=41)
10 mg QD	6	NA
25 mg QD (DL1)	6	4
50 mg QD	11	7
100 mg QD	10	11
200 mg QD	14	8
200 mg BID	NA	5
300 mg QD	5	NA
400 mg QD	NA	6

DL1 = dose level 1 (initial dose level tested)

Study Status

Disposition	Glioma (n=52)	Non-glioma solid tumors (n=41)	Total (N=93)
On treatment, n (%)	17 (32.7)	1 (2.4)	18 (19.4)
Discontinued treatment, n (%)	35 (67.3)	40 (97.6)	75 (80.6)

- Enrollment completed in Jun 2017
- Study remains ongoing as of 29 Mar 2018
- 18 patients remain on AG-881: 17 (94%) glioma and 1 (6%) non-glioma
- Of the 75 patients who discontinued treatment: 55 (73%) discontinued for disease progression, 4 (5.4%) discontinued due to an AE at doses of 100 mg and above
- Non-glioma solid tumor enrollment stopped in Oct 2016 in favor of continued development in glioma

Baseline Characteristics – Non-Glioma Solid Tumors

	Total treated (n=41)
Median age, years (range)	57.0 (28–89)
Male/female, n	14/27
ECOG status at baseline, n (%) 0 1 2	 10 (24.4) 28 (68.3) 3 (7.3)
IDH1 mutation, n (%)[a] IDH2 mutation, n (%)	27 (65.9) 14 (34.1)
Diagnosis, n (%) Cholangiocarcinoma Chondrosarcoma Other[b]	 24 (58.5) 9 (22.0) 8 (19.5)
Median number prior systemic therapies (range) 1 prior regimen, n (%) ≥2 prior regimens, n (%)	2.5 (1–7) 9 (22.0) 29 (70.7)
Prior mIDH inhibitor, n (%)	3 (7.3)

[a]IDH status missing for 1 patient and mis-categorized for 3 other patients due to data entry errors at time of data cut; all were confirmed post data cut and are corrected in table. [b]Other: colon (n=1), colorectal (n=1), NSCLC (n=3), pancreatic (n=1), rectal carcinoma (n=1), signet cell adenocarcinoma (n=1)

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	 19 (36.5) 32 (61.5) 1 (1.9)
IDH1 mutation, n (%)[a] IDH2 mutation, n (%)	48 (92.3) 3 (5.8)
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 mIDH inhibitor	 38 (73.1) 4 (7.7) 1 (1.9)

[a]One patient did not have biopsy, presumed IDH mutation by the investigator as evidenced by consistent 2-HG elevation by MRS. Two patients mis-categorized as IDH1/2-mutant due to data entry error at time of data cut; status was confirmed post data cut and is corrected in the table

AEs ≥ 10% (All Patients, All Causalities)

All patients	All Grades (N=93)	Grade 3 or higher (N=93)
Patients with at least 1 AE	92 (98.9)	31 (33.3)
Fatigue	36 (38.7)	3 (3.2)
Nausea	33 (35.5)	2 (2.2)
Alanine aminotransferase increased[a]	32 (34.4)	4 (4.3)
Aspartate aminotransferase increased	31 (33.3)	2 (2.2)
Headache	24 (25.8)	0
Vomiting	24 (25.8)	2 (2.2)
Constipation	23 (24.7)	0
Decreased appetite	17 (18.3)	1 (1.1)
Dyspnea	17 (18.3)	2 (2.2)
Diarrhea	15 (16.1)	0
Abdominal pain	13 (14.0)	1 (1.1)
Cough	12 (12.9)	0
Dizziness	12 (12.9)	0
Seizure	12 (12.9)	5 (5.4)
Anemia	11 (11.8)	2 (2.2)
Hyperglycemia	11 (11.8)	1 (1.1)
Hypertension	10 (10.8)	0

[a]Includes 1 patient with uncoded event of Grade 3 alanine aminotransferase increased

Transaminase Elevation Is Dose Dependent in Glioma Patients

Worst post-baseline grade[a]	10 mg QD (n=6)	25 mg QD (n=3)	50 mg QD (n=12)	100 mg QD (n=7)	200 mg QD (n=19)	300 mg QD (n=5)	Total (n=52)
No AE	6 (100.0)	2 (66.7)	7 (58.3)	1 (14.3)	10 (52.6)	2 (40.0)	28 (53.8)
Grade 1	0	0	5 (41.7)	4 (57.1)	4 (21.1)	1 (20.0)	13 (25.0)
Grade 2	0	1 (33.3)	0[b]	1 (14.3)	3 (15.8)	1 (20.0)	7 (13.5)
Grade 3	0	0	0	0	2 (10.5)	1 (20.0)	3 (5.8)
Grade 4	0	0	0	1 (14.3)	0	0	1 (1.9)

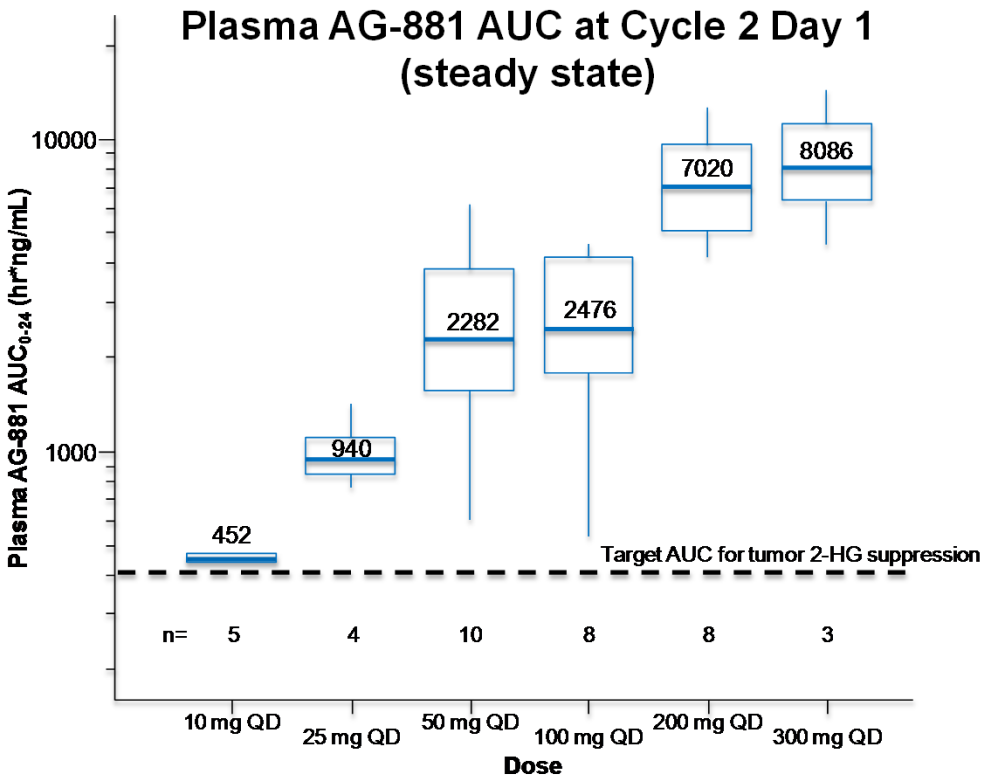
- DLT defined as any grade ≥3 AE during Cycle 1 and related to study treatment, or by Sponsor designation
- Transaminase AEs were not associated with elevated bilirubin
- Exposure safety analysis indicated trend of increased probability of elevated transaminase with increased plasma exposure of AG-881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

[a]Patients who did not have any ALT/AST AE are counted within the highest dose ever received. Patients with ALT/AST AE are counted at the actual dose received at the time of the first occurrence of the worst grade AE
[b]One Grade 1 event captured as Grade 2 due to data entry error; data corrected following the data cut and this event is counted as Grade 1 in this table

Safety Summary

- Five AEs of Grade 2 or higher elevated transaminases without bilirubin increase in glioma patients at 100 mg and above designated as DLTs by Sponsor; no DLT observed in non-glioma solid tumor patients
- MTD not reached by Bayesian model; clinical study team recommended exploration of doses <100 mg
- DLTs resolved to Grade ≤1 with dose modification or discontinuation
- No related on-treatment deaths

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 glioma patients 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: Non-Glioma Solid Tumors

Response, n (%)	Cholangio-carcinoma (n=24)	Chondro-sarcoma (n=9)	Other indications (n=8)	Total (n=41)
Partial response	1 (4.2)	0	0	1 (2.4)
Stable disease	7 (29.2)	4 (44.4)	4 (50.0)	15 (36.6)
Progressive disease	10 (41.7)	4 (44.4)	4 (50.0)	18 (43.9)
Not assessed[a]	6 (25.0)	1 (11.1)	0	7 (17.1)

- Median treatment duration = 2.0 months (range 0–18)
- 3 patients remained on treatment for ≥1 year

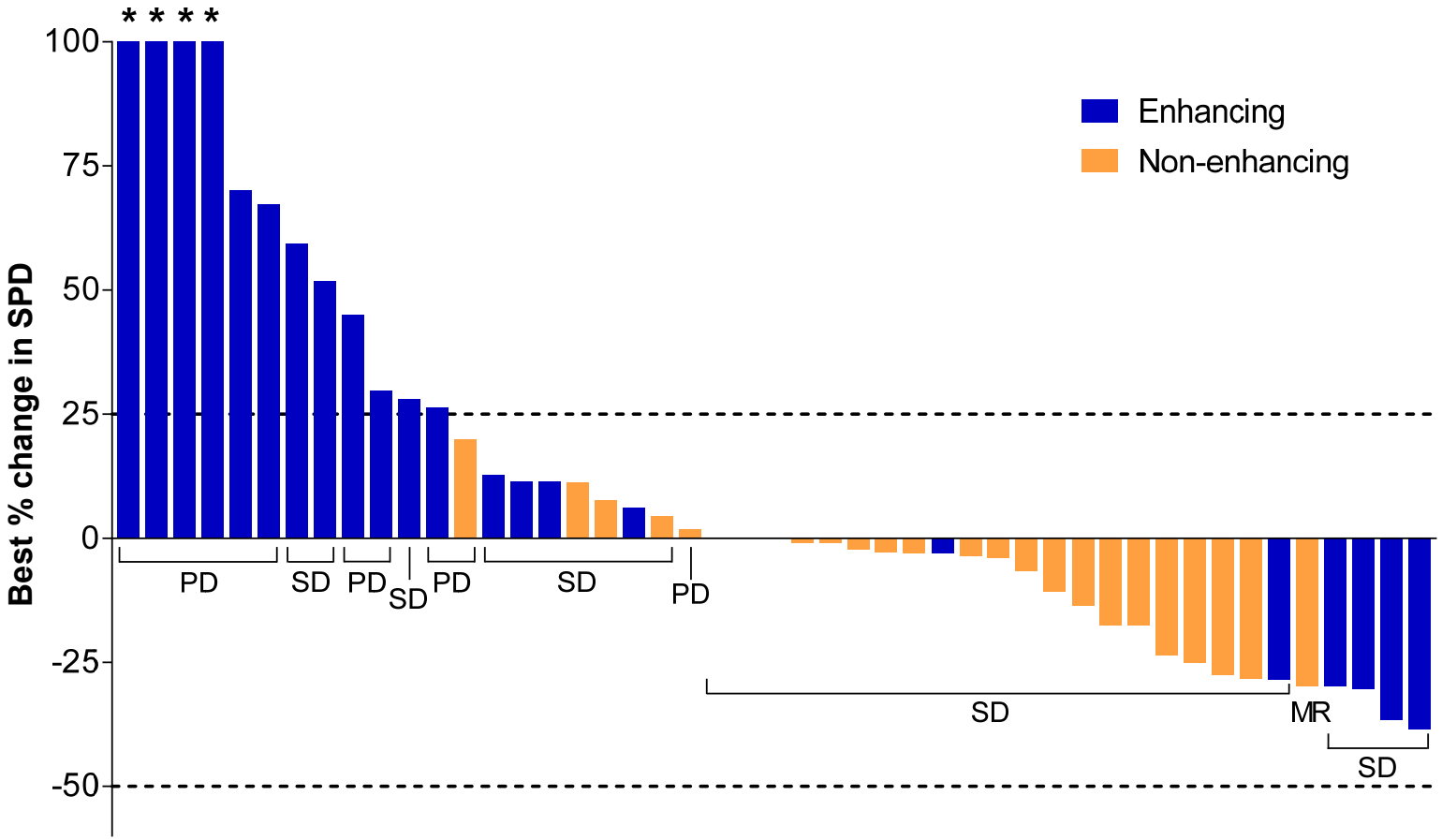
Disease response assessment per RECIST v1.1 (Eisenhauer EA et al. *Eur J Cancer.* 2009;45:228-47)
[a]Discontinued prior to first response assessment

Best Response: Glioma

Response, n (%)	Non-enhancing (n=23)	Enhancing (n=29)	Total evaluable patients (n=52)
Minor response	1 (4.3)	NA	1 (1.9)
Stable disease	20 (87.0)	19 (65.5)	39 (75.0)
Progressive disease	2 (8.7)	9 (31.0)	11 (21.2)
Not assessed[a]	0	1 (3.4)	1 (1.9)

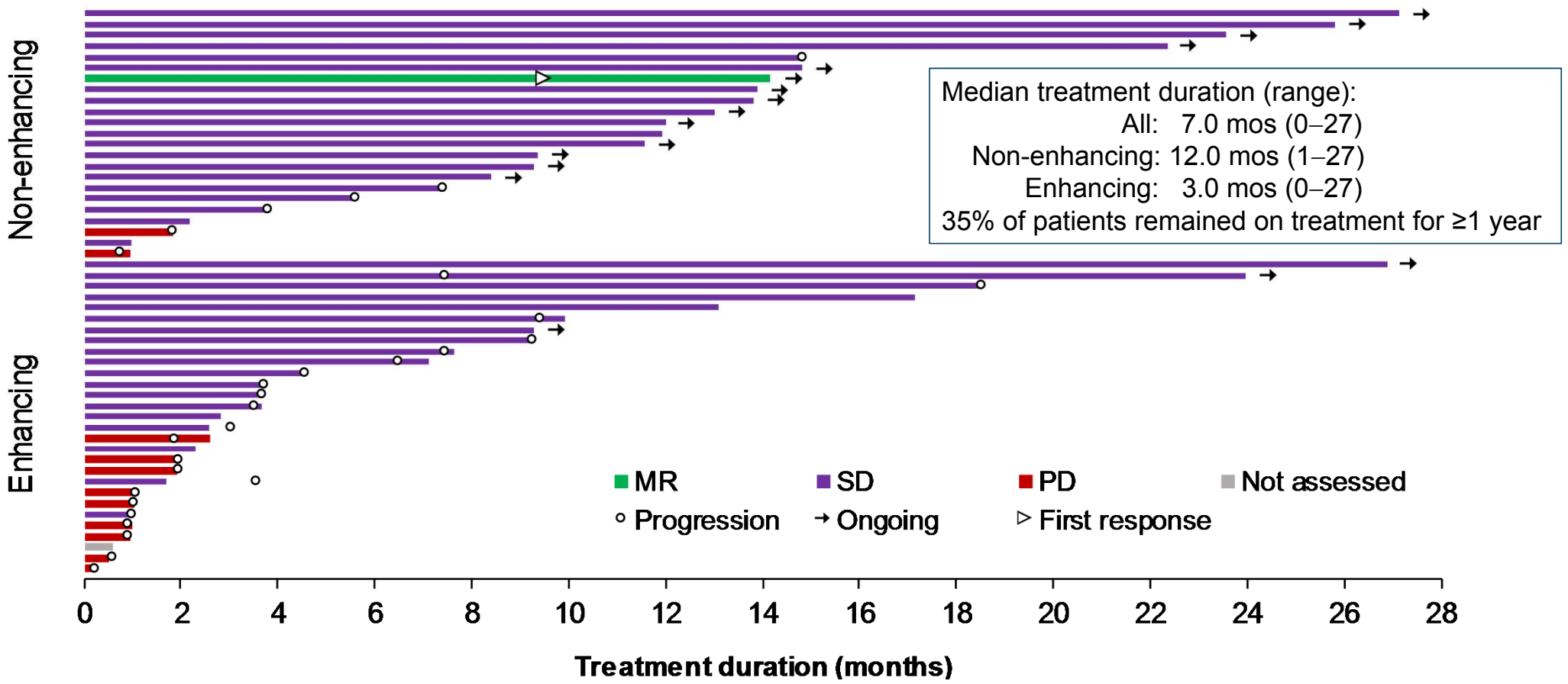
Response assessed by RANO (Wen PY et al. *J Clin Oncol.* 2010;28:1963-72) or RANO-LGG (van den Bent M et al. *Lancet Oncol.* 2011;12:583-93)
Minor response: ≥25% but <50% decrease in tumor measurements compared with baseline; applicable to RANO-LGG criteria only
[a]Discontinued treatment prior to first response assessment

Best Percent Change from Baseline: Glioma



*Indicates change >100%
MR defined as ≥25% but <50% decrease in tumor measurements compared to baseline; applicable to RANO-LGG criteria only
MR = minor response; PD = progressive disease; SD = stable disease; SPD = sum of product of diameters

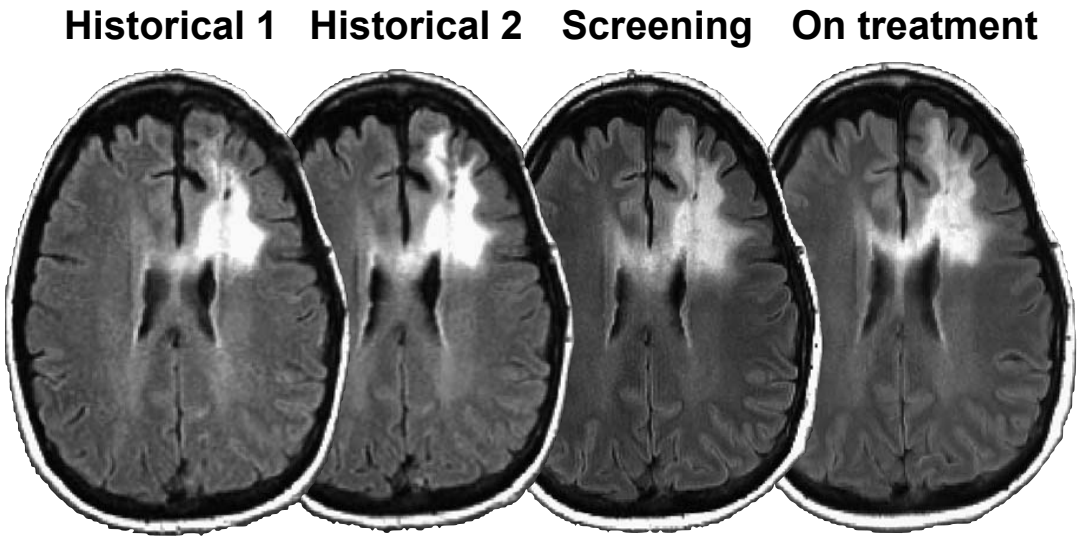
Treatment Duration and Best Response: Glioma



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

Case Study: Glioma Patient with Minor Response

- 49 y/o F diagnosed in 2013 with Grade 2 oligodendroglioma; 1p19q co-deleted
- Resection 2013; no other treatment
- H1: Jun 2014; H2: Jun 2015; Screening: Dec 2016
- Started AG-881 100 mg Jan 2017; dose decreased to 50 mg May 2017
- Sustained MR Oct 2017
- Remains on treatment (Cycle 15) with MR as of 29 Mar 2018



Courtesy of B. Ellingson & T. Cloughesy, UCLA

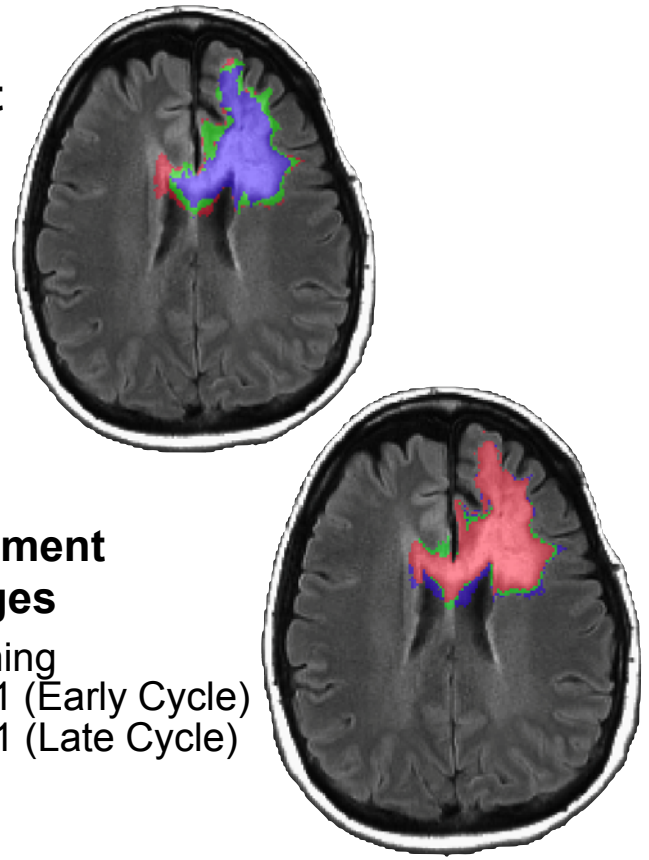
Case Study: Glioma Patient with Minor Response – Volumetric Imaging

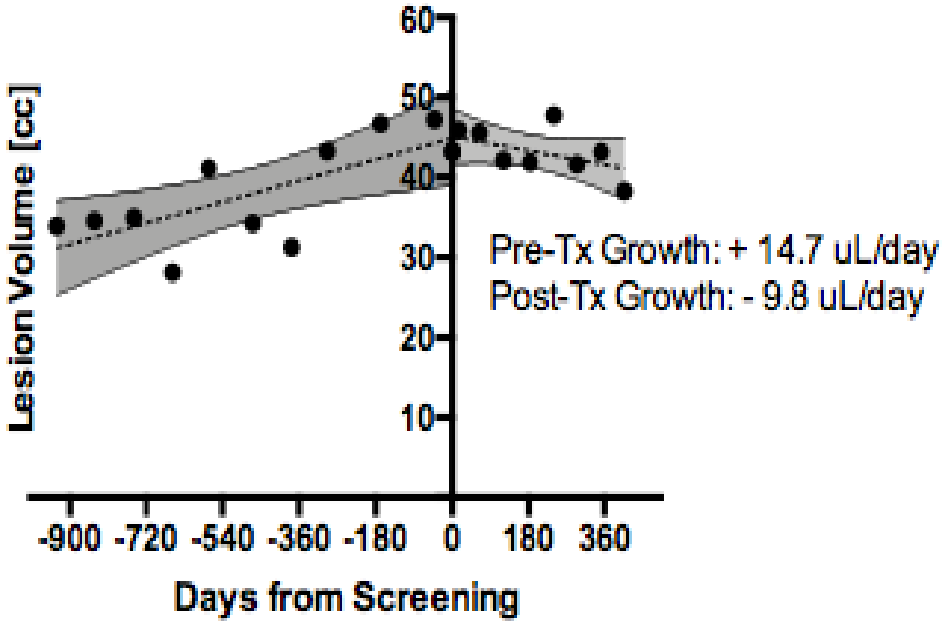
Pre-treatment changes

- Historical 1
- Historical 2
- Screening

On-treatment changes

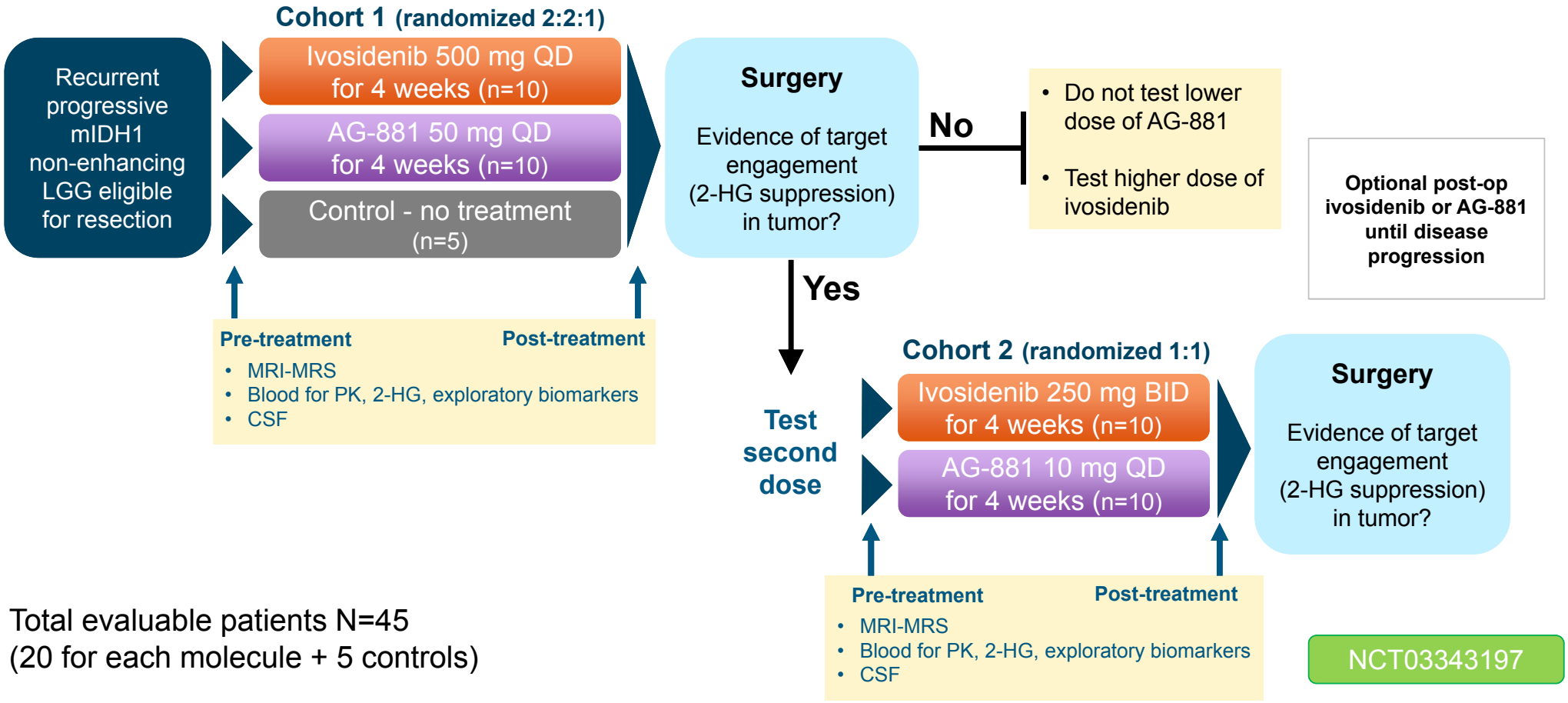
- Screening
- AG-881 (Early Cycle)
- AG-881 (Late Cycle)





Courtesy of B. Ellingson & T. Cloughesy, UCLA

Perioperative Study Schema



Total evaluable patients N=45
(20 for each molecule + 5 controls)

NCT03343197

LGG = low-grade glioma (WHO 2016-classified Grade 2 or 3 oligodendroglioma or astrocytoma)

Summary and Conclusions

- AG-881 has a favorable safety profile at dose levels <100 mg
  - 50 mg and 10 mg are under ongoing clinical investigation in glioma
- DLTs of elevated transaminases occurred in glioma patients at the higher dose levels (≥100 mg) and were reversible
- Plasma drug exposure at all doses tested in glioma patients is predicted to be sufficient for tumor 2-HG suppression based on preclinical model
- AG-881 resulted in prolonged disease control in the non-enhancing glioma population (median treatment duration of 1 year, with 61% 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 non-enhancing glioma (NCT03343197)

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 Helen Varley, PhD, CMPP, Excel Medical Affairs, Horsham, UK, and supported by Agios