AG-120, A First-in-Class Mutant IDH1 Inhibitor in Patients with Recurrent or Progressive IDH1 Mutant Glioma: Updated Results from the Phase 1 Non-Enhancing Glioma Population

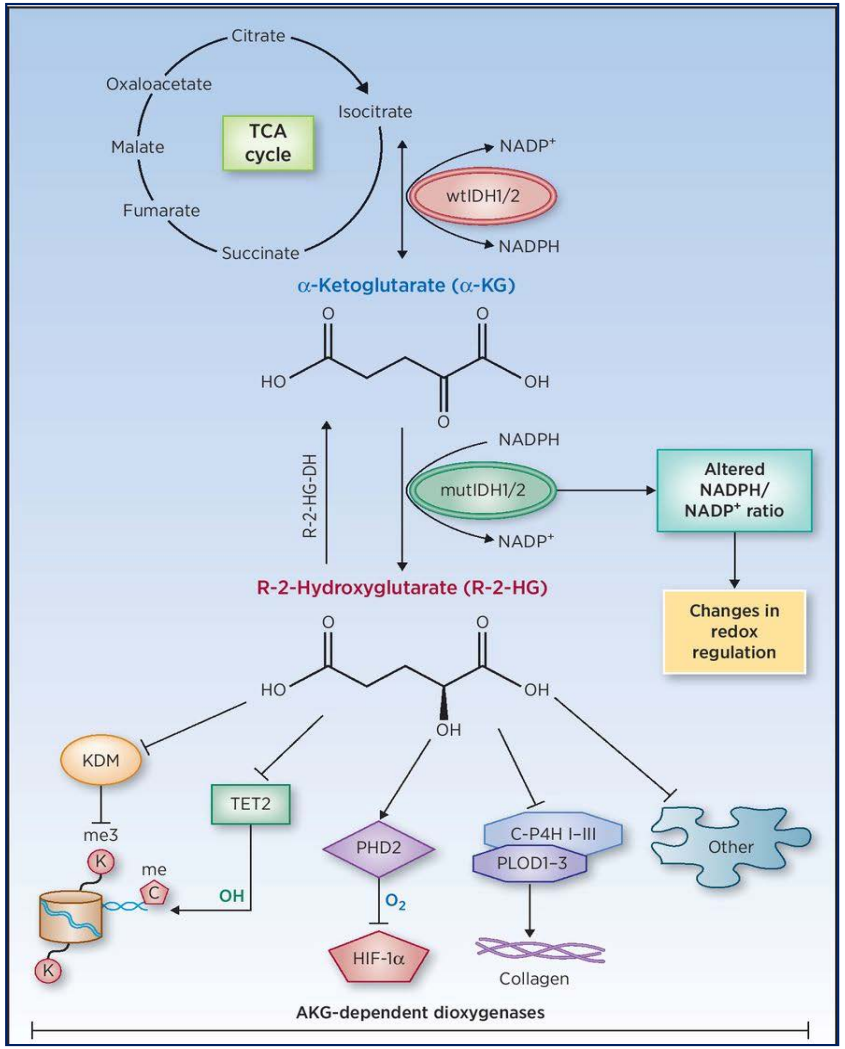
Ingo K. Mellinghoff[1], Mehdi Touat[2], Elizabeth Maher[3], Macarena I. De La Fuente[4], Timothy F. Cloughesy[5], Matthias Holdhoff[6], Gregory M. Cote[7], Howard Burris[8], Filip Janku[9], Raymond Huang[7], Robert J. Young[1], Benjamin Ellingson[5], Tara Nimkar[10], Liewen Jiang[10], Yuko Ishii[10], Sung Choe[10], Bin Fan[10], Lori Steelman[10], Katharine Yen[10], Chris Bowden[10], Susan Pandya[10] and Patrick Y. Wen[7]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Gustave Roussy, Villejuif, France; [3]University of Texas Southwestern Medical Center, Dallas, TX, USA; [4]University of Miami, Miami, FL, USA; [5]University of California, Los Angeles, CA, USA; [6]Johns Hopkins University, Baltimore, MD, USA; [7]Dana-Farber/Harvard Cancer Center, Boston, MA, USA; [8]Sarah Cannon Research Institute, Nashville, TN, USA; [9]MD Anderson Cancer Center, Houston, TX, USA; [10]Agios Pharmaceuticals, Inc., Cambridge, MA, USA

Presented at the Society for Neuro-Oncology Annual Scientific Meeting, November 16-19, 2017; San Francisco, CA , USA

Isocitrate Dehydrogenase (IDH) and Cancer

- Mutations in the metabolic enzymes IDH1 and IDH2 occur in several human malignancies, including leukemia (AML), cholangiocarcinoma, chondrosarcoma, and glioma
- IDH mutations change the function of the enzyme
  - → neomorphic production of the oncometabolite D-2HG
  - → epigenetic dysregulation and impaired cellular differentiation
  - → oncogenesis
- Recent regulatory approval for IDHIFA® (enasidenib), an IDH2 inhibitor, in relapsed/refractory AML



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

IDH Mutations and AG-120 in Glioma

- IDH mutations occur in >70% of low-grade gliomas (LGG) and ~ 5% of GBMs[1]
- **AG-120 (ivosidenib)** is a first-in-class, oral, potent, reversible, targeted inhibitor of **mutant IDH1 enzyme**
- AG-120 is under clinical evaluation in an ongoing phase 1 dose escalation and expansion study of patients with IDH1-mutant advanced solid tumors (n=168), including glioma (n=66)[a]
  - adults with previously treated WHO grade II, WHO grade III, WHO grade IV
  - contrast-enhancing (n=31) or non-enhancing (n=35) on brain MRI
  - preliminary safety and efficacy data presented previously[2]
- Here we report updated safety and efficacy data, and an exploratory volumetric growth rate analysis for the **non-enhancing** glioma patient population

[a]ClinicalTrials.gov NCT02073994

1. The Cancer Genome Atlas Research Network. *NEJM* 2015;372:2481-98; 2. Mellinghoff IK et al. *Neuro-Oncology*. 2016;18(Suppl6):vi12 ACTR-46.

AG120-C-002 Phase 1 Study Design

Dose escalation (n=60) including 20 gliomas[1]

- IDH1-mutant (local testing) advanced solid tumors, including glioma
- Recurred, progressed or not responded to standard therapy
- 9/20 enhancing glioma
- 11/20 non-enhancing glioma

Dose expansion non-enhancing gliomas (n=24)

Other dose expansion cohorts (n=84)

- Cholangiocarcinoma, chondrosarcoma, solid tumors not eligible for other cohorts
- Includes 22 enhancing gliomas

Primary study objectives:

- Evaluate safety and tolerability
- Determine MTD and/or RP2D

Secondary study objectives:

- Pharmacokinetics and pharmacodynamics
- Preliminary clinical activity (ORR, PFS)

Exploratory:

- Change in tumor volumetric growth rate in non-enhancing glioma expansion cohort
- PD evaluation of tissue and plasma

1. Burris H et al. Presented at AACR-NCI-EORTC 2015

ClinicalTrials.gov NCT02073994; RT = radiation therapy; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose

Study Status: Non-Enhancing Glioma

- Glioma enrollment complete as of 16Jan2016 (n=66)
- 500 mg QD selected as expansion dose
- 35 pts with non-enhancing gliomas (escalation, n=11; expansion, n=24)
- Study remains ongoing as of data cutoff of 12May2017; median treatment duration for the non-enhancing glioma population is 16 months

Disposition, n (%)	Dose level					Total (N=35)
	100 mg (n=0)	300 mg (n=2)	500 mg (n=28)	600 mg (n=1)	900 mg (n=4)	
On treatment	0	0	15	0	3	18 (51)
Discontinued treatment	0	2	13	1	1	17 (49)
Disease progression	0	2	13	1	1	17 (49)

Baseline Characteristics

	Total treated (N=35) n (%)
Median age, years (range)	38 (21, 71)
Gender (M/F), n	23/12
ECOG status at baseline, n (%)	
0	17 (48.6)
1	18 (51.4)
IDH1-R132H mutation[a]	28 (80.0)
WHO tumor grade	
Grade II	24 (68.6)
Grade III	8 (22.9)
Grade IV	1 (2.9)
Unknown	2 (5.7)
1p19q co-deleted, n (% of those tested)[b]	10 (34.5)

[a]All patients had IDH1 mutation; other 20% included R132C, R132S and others
[b]Missing for 6 patients (17% of total)

Prior Therapies

	Total treated (N=35) n (%)
Prior radiation therapy, n (%)	20 (57.1)
Prior systemic therapies, n (%)	24 (68.6)
Median number of prior systemic therapies, n (range)	2 (1, 5)
1 prior systemic therapy, n (%)	12 (34.3)
≥ 2 prior systemic therapies, n (%)	12 (31.4)
Type of prior systemic therapy	
Temozolomide, n (%)	22 (62.9)
Bevacizumab, n (%)	2 (5.7)
Procarbazine/CCNU/vincristine, n (%)	1 (2.9)
Median time since last systemic therapy, months (range)	7.38 (1, 139.5)
Median duration of last systemic therapy, months (range) [a]	9.59 (0, 36.0)
Anticonvulsants at baseline, n (%)	26 (74.3)
Steroid use at baseline, n (%)[b]	1 (2.9)

[a] minimum of 0 indicates missing dates for one patient and actual duration of last therapy could not be calculated

[b] Based on available clinical data and site confirmation; baseline use for one patient not confirmed due to missing data.

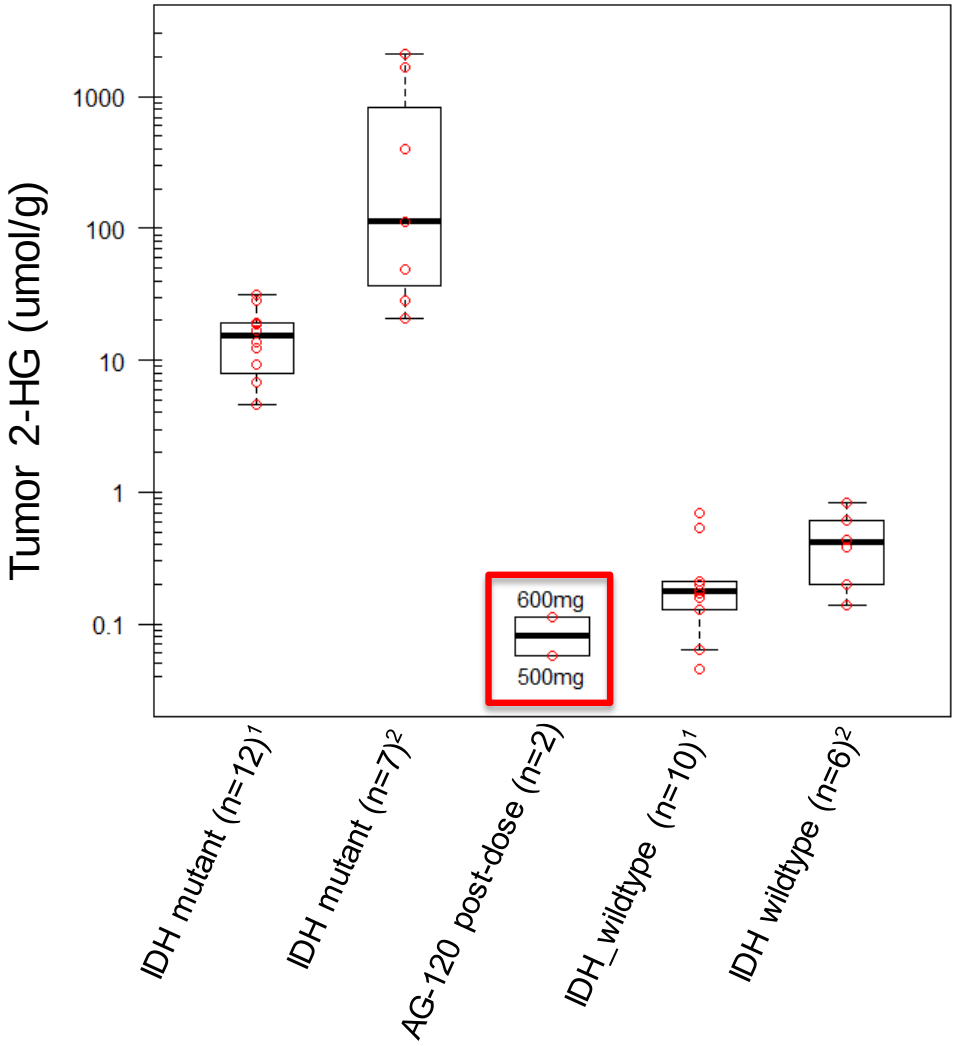
Data cutoff: 12May2017

Safety Summary

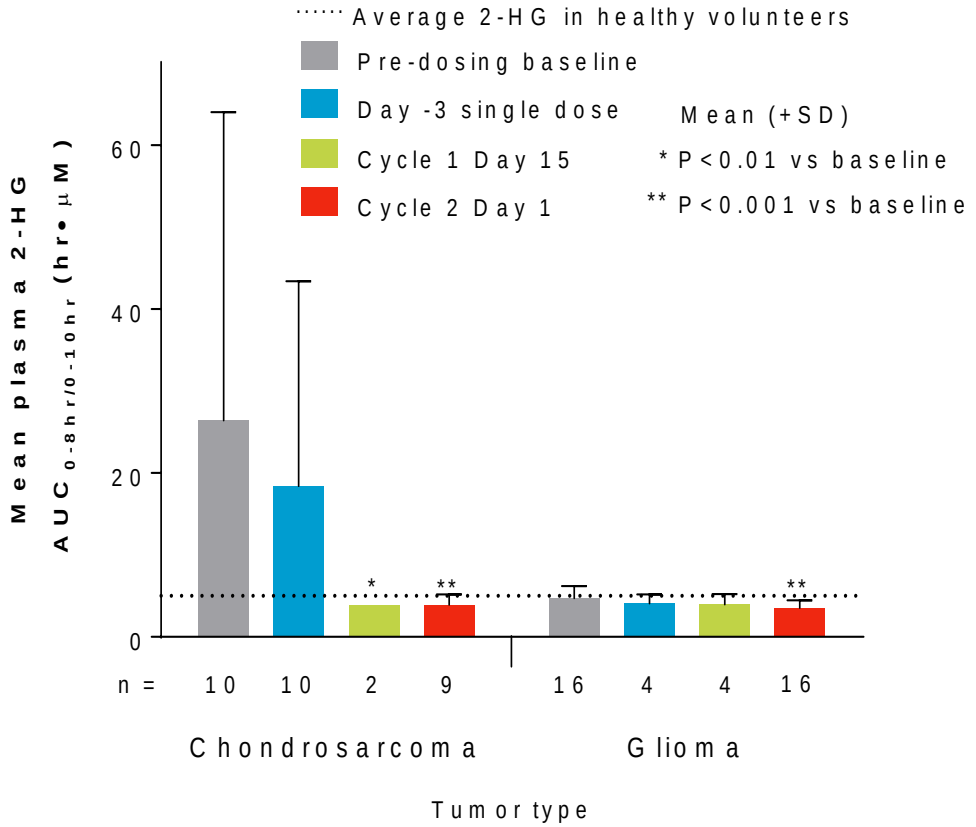
- No DLTs observed, MTD not reached
- No on-treatment deaths
- 32/35 (91%) patients experienced at least 1 AE; 7 (20%) experienced a Grade 3 or higher AE
  - Most common (>15%, all grades) AEs included headache (34%), diarrhea (26%), nausea and vomiting (each 20%), anemia, fatigue, hyperglycemia, neutrophil count decreased, seizure and upper respiratory infection (each 17%)
  - 2 patients experienced Grade 3 hypophosphatemia, no other Grade 3 or higher events were reported in more than 1 patient
- 5/35 (14%) patients experienced at least 1 SAE and all were deemed unrelated to study treatment
  - Seizure was reported in 2 patients; no other SAEs were reported in more than 1 patient

Pharmacodynamic Analysis of AG-120

Tumor 2-HG suppression by AG-120



Baseline plasma 2-HG levels not elevated in glioma[a]



[a] Plasma data presented previously: Mellinghoff IK et al. Neuro-Oncology. 2016;18(Suppl6):vi12 ACTR-46

[1] Dang *et al. Nature 2009* 462(7274): 739 ; [2] Choi et al., Nat Med 2012 18(4) 624-629

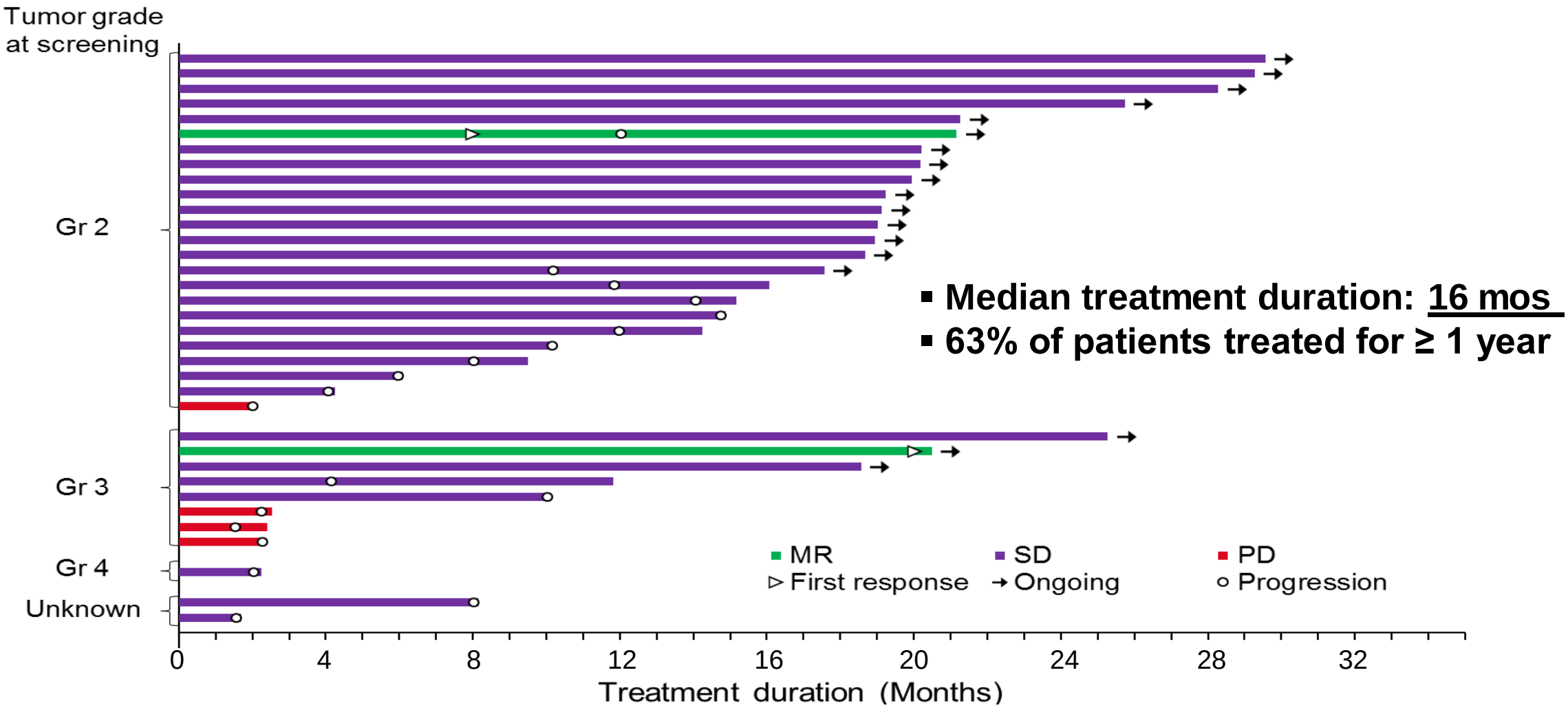
Best Overall Response by Investigator

Best Overall Response[a]	N=35 n (%)
Minor response	2 (5.7)[b]
Stable disease	29 (82.9)
Progressive disease	4 (11.4)
Overall response rate	2 (5.7)

[a]LGG patients in escalation phase assessed by RANO[1]; LGG patients in expansion phase assessed by RANO LGG[2]
[b] Minor responses (>25% but <50% decrease relative to baseline) not centrally confirmed

Data cutoff: 12May2017. [1] Wen PY et al. *J Clin Oncol* 2010;28:1963-1972; [2]van den Bent MJ et al. *Lancet Oncol* 2011;12:583-593.

Treatment Duration by Grade Including Best Overall Response



- **Median treatment duration: 16 mos**
- **63% of patients treated for ≥ 1 year**

Median PFS for ALL non-enhancing patients = 13 mos (not reached for WHO grade II subset)

Exploratory Imaging: Effects on Glioma Growth Rates

- Non-enhancing gliomas display slow but continuous growth,[1] the rate of which may correlate with transformation and survival[2,3]

Non-enhancing glioma expansion n=24

Study Inclusion Criteria

- IDH1-mutant; progression over ≤12 months
- **≥3 prior** full sets of scans **(not including screening)**, each separated by ≥2 months with ≤5 mm slice thickness and up to 1 mm interslice gap on either 2D T2 weighted image, 3D T2 weighted image, or FLAIR
- No tumor resection or RT <6 months prior to enrollment

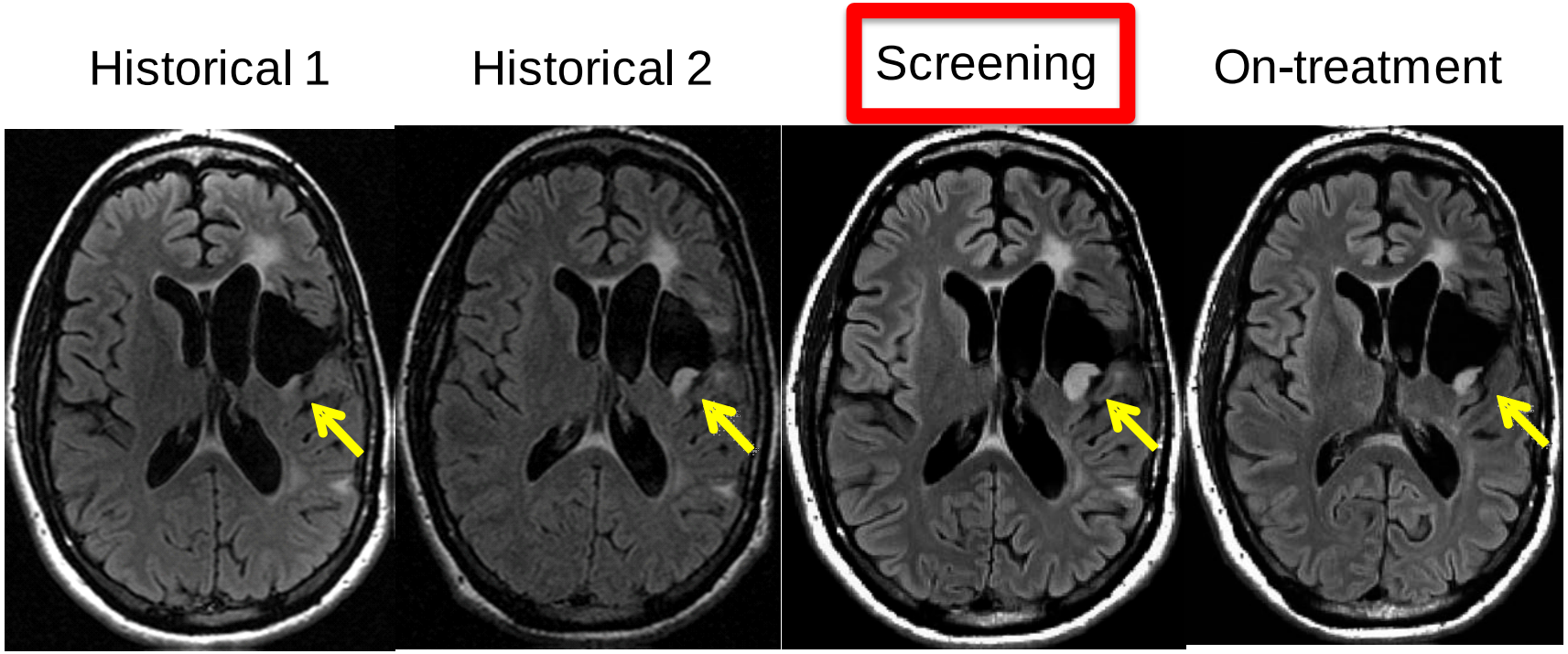
239 MRI scans from 24 patients:

- **63 historical MRIs** (prior to screening)
- **176 MRIs** (screening and on AG-120)

[1]Mandonnet E et al. *Ann Neurol* 2003;53:524-8; [2]Pallud J et al. *Ann Neurol* 2006;60:380-3; [3]Ricard D et al. *Ann Neurol* 2007;61:484-90.

Case Study #1

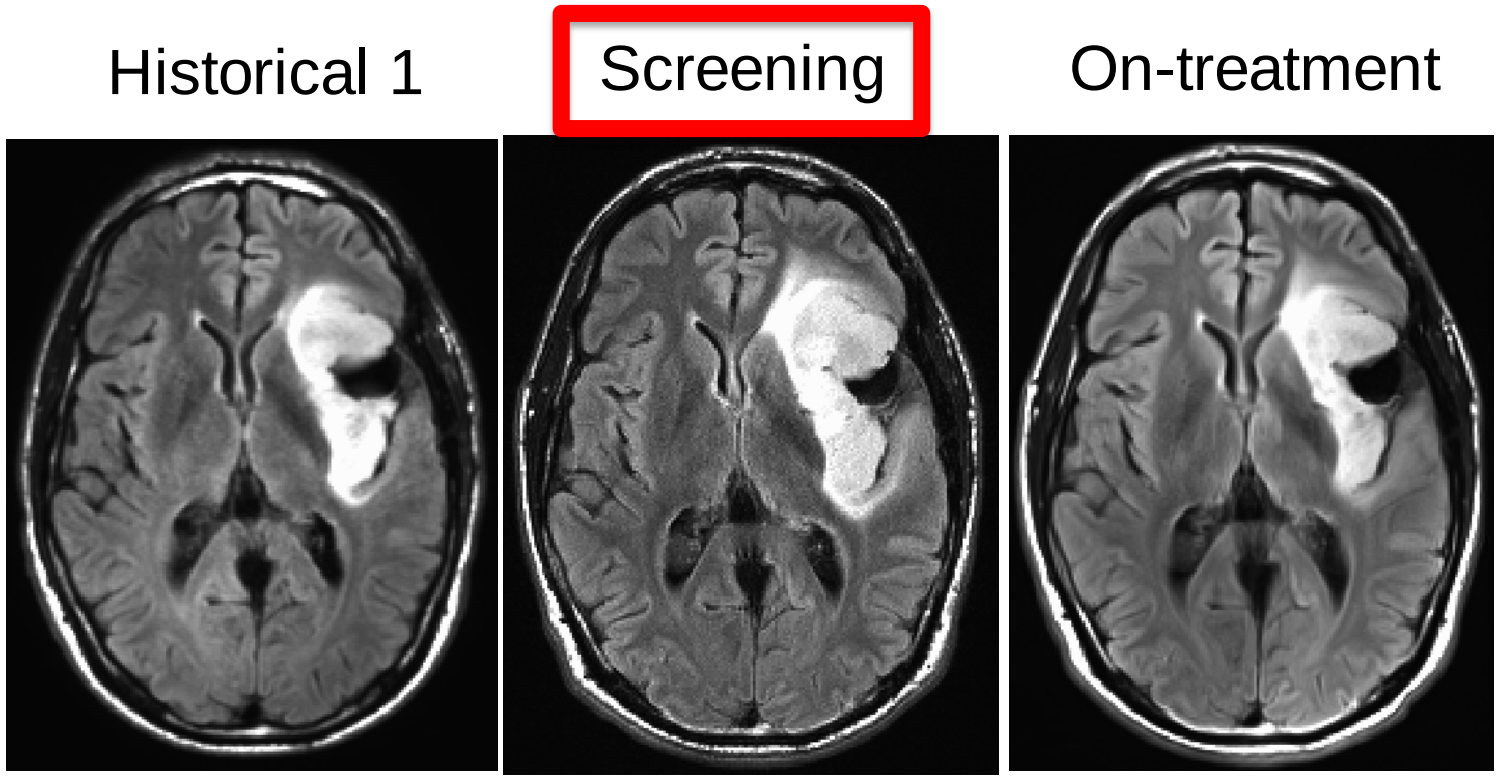
- Anapl. Oligo, 1p19q CD
- Tumor Resection 2009
- Radiation 2010
- TMZ 2010-2012
- **AG-120 Start 12/2015**
  H1 MRI: 7/2014
  H2 MRI: 5/2015
- **Remains on AG-120 (17 mos @ cutoff)**
  Best RANO response: SD



H1-H2 = historical pre-treatment scan; Screen = screening

Case Study #2

- Diffuse Astrocytoma
- Tumor Resection 2009
- No Radiation
- No other therapy
- **AG-120 Start 11/2015**
  H1 MRI: 7/2013
- **Remains on AG-120**
  (18 mos @ cutoff)
  Best RANO response: SD

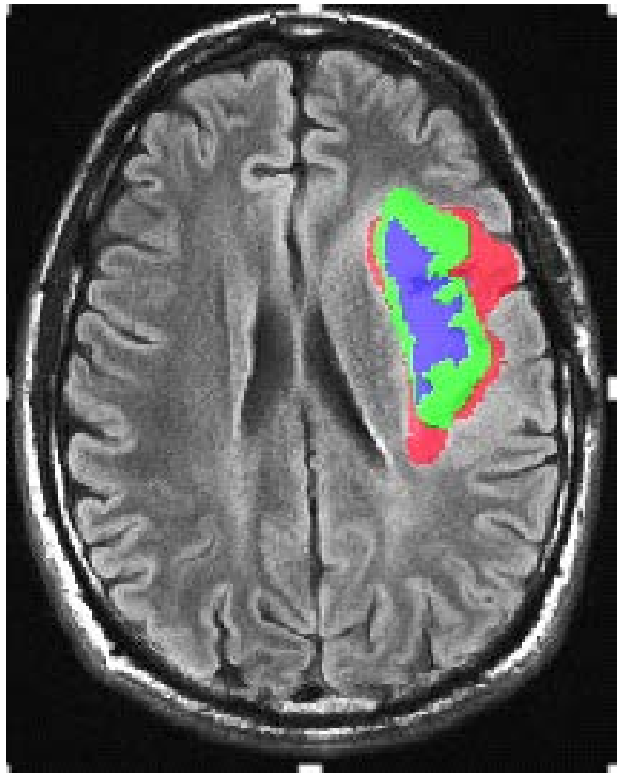


H1 = historical pre-treatment scans; Screen = screening

Case Study #2 Co-registered MRIs

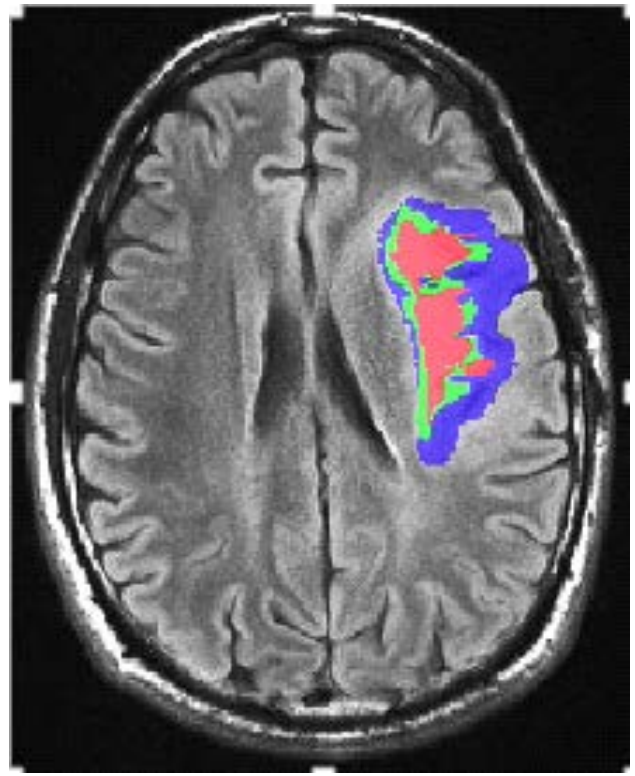
Pre-treatment changes

Historical 1
Historical 2
Screening



On-treatment changes

Screening
AG120_early cycle
AG120_later cycle



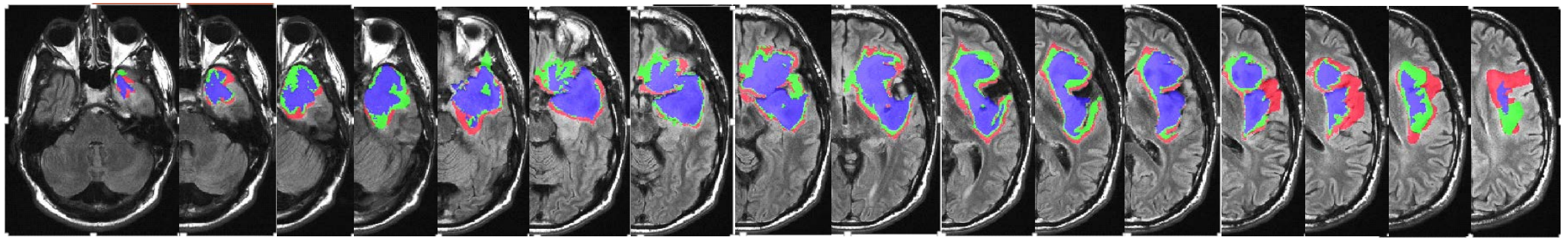
Case Study #2 Complete MRIs

Pre-treatment changes

Historical 1 -

Historical 2 -

Screening -

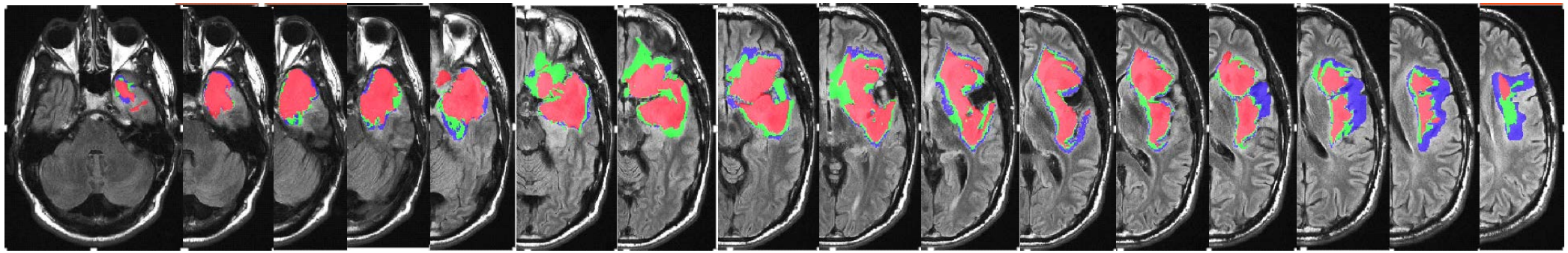


On-treatment changes

Screening -

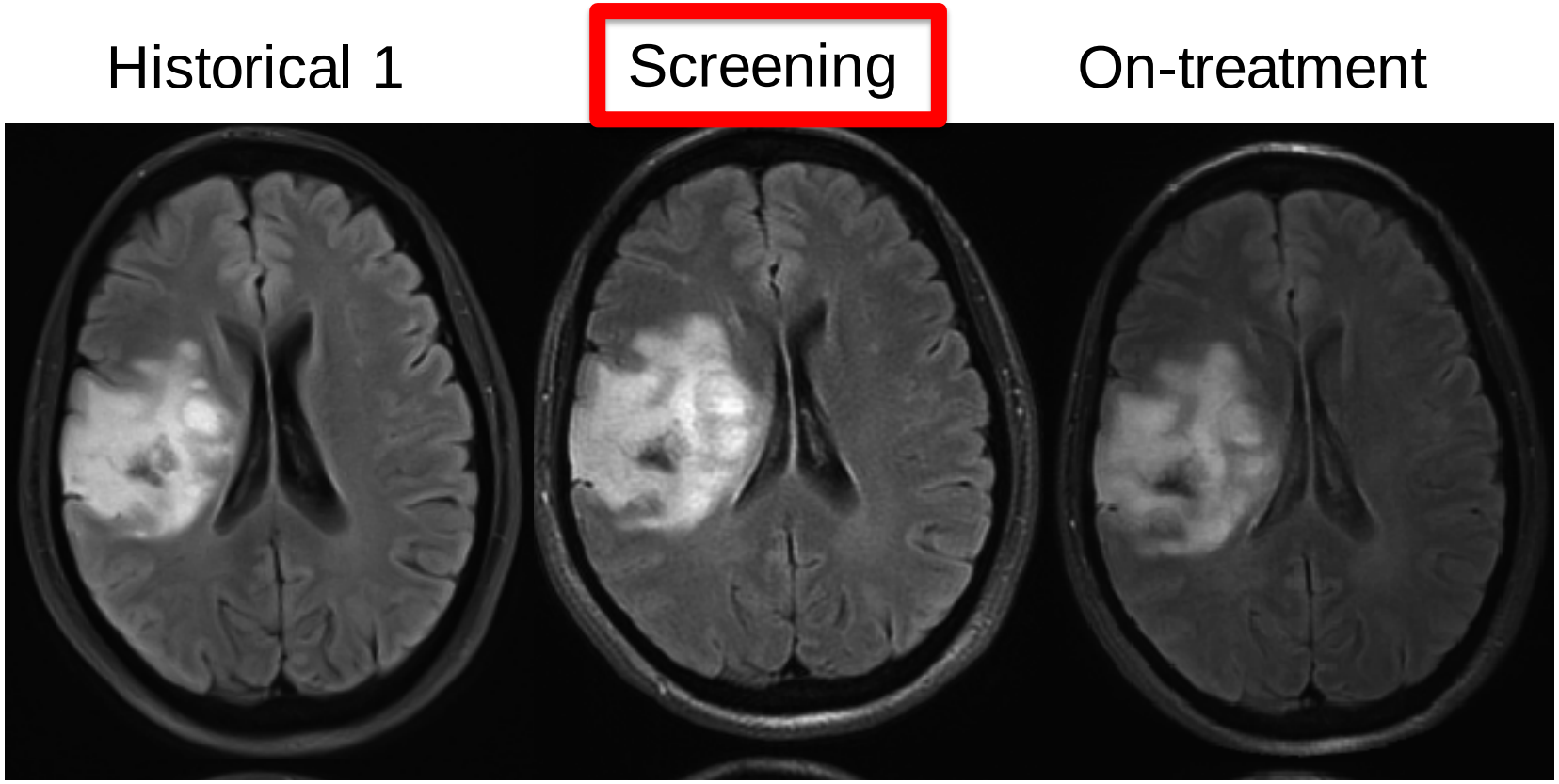
AG-120_ early cycle -

AG-120_ late cycle -



Case Study #3

- Oligodendroglioma 1p19q co-del
- Biopsy 2007
- TMZ 2007-2008
- No Radiation
- **AG-120 Start 10/2015**
  H1 MRI: 10/2014
- **Remains on treatment (18 mos @ cutoff)**
  Best RANO response: SD



H1 = historical pre-treatment scans; Screen = screening

Case Study #3 Co-registered MRIs

Pre-treatment changes

Historical 1 -

Historical 2 -

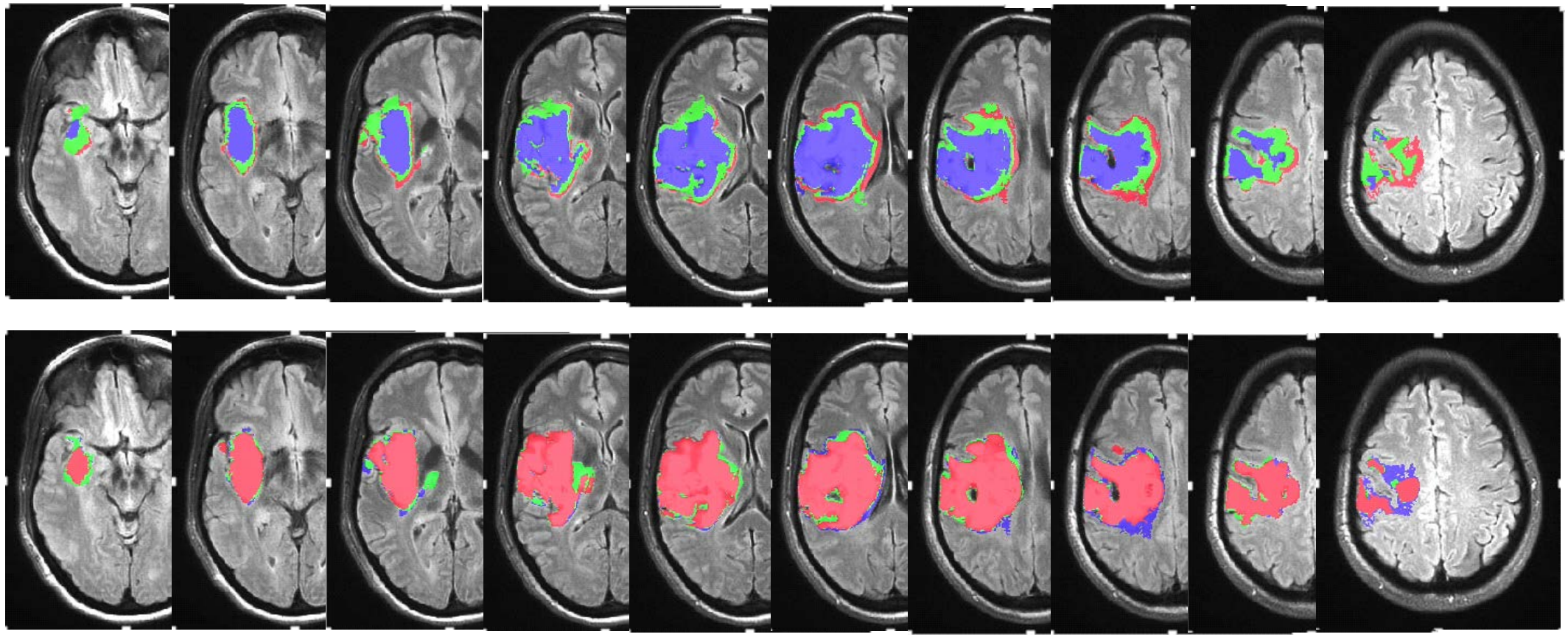
Screening -

On-treatment changes

Screening -

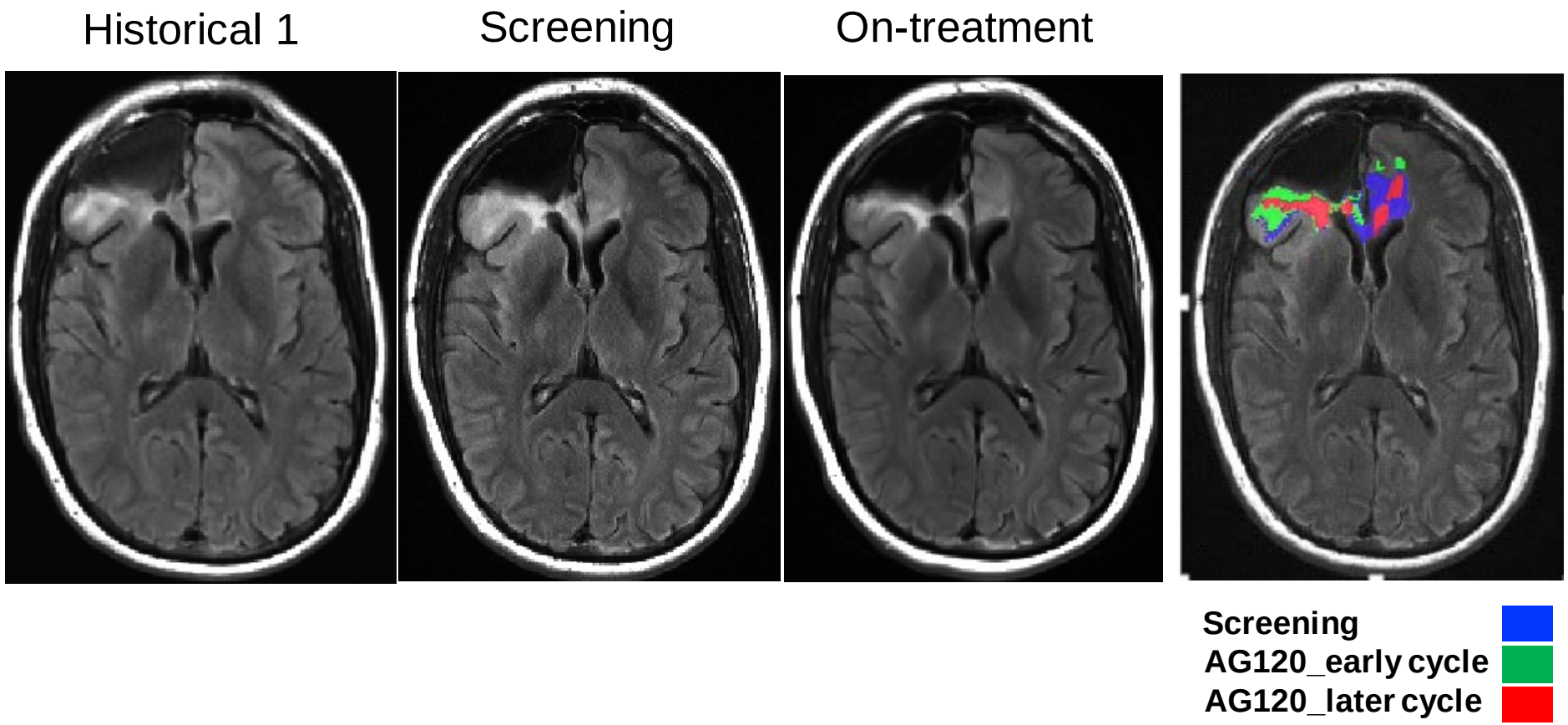
AG-120_ early cycle -

AG-120_ late cycle -



Case Study #4

- Oligodendroglioma (1p19q codel)
- Tumor Resection 2011
- No further treatment
- **AG-120 Start 12/2015**
  H1 MRI:6/2013
- **Remains on AG120 (17 mos @ cutoff)**
  Best RANO response: SD



Exploratory Imaging: Effects of AG-120 on Glioma Growth Rates

- Non-enhancing gliomas display slow but continuous growth,[1] the rate of which may correlate with transformation and survival[2,3]

Non-enhancing glioma expansion n=24

Study Inclusion Criteria

- IDH1-mutant; progression over ≤12 months
- **≥3 prior full sets of scans (not including screening), each separated by ≥2 months with ≤5 mm slice thickness and up to 1 mm interslice gap on either 2D T2 weighted image, 3D T2 weighted image, or FLAIR**
- No tumor resection or RT <6 months prior to enrollment

239 MRI scans analyzed across 24 patients
- ❖ **63 historical scans prior to Screening**
- ❖ **176 during treatment with AG-120**

Method

- Pre-segmentation 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 effect model

[1]Mandonnet E et al. *Ann Neurol* 2003;53:524-8; [2]Pallud J et al. *Ann Neurol* 2006;60:380-3; [3]Ricard D et al. *Ann Neurol* 2007;61:484-90.

Volumetric Growth Rates Pre- and Post-AG120 Treatment

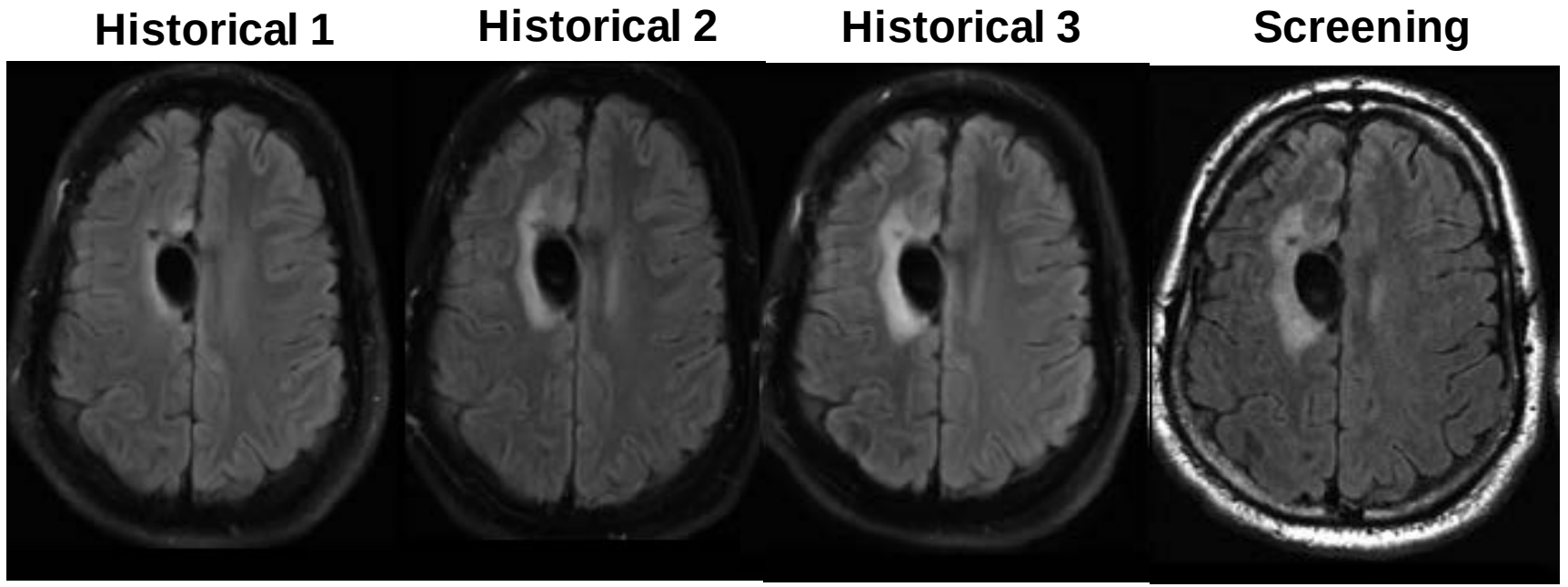
Volumetric growth rate all patients			
	Natural History Study Pre-treatment[a] (N=239[c])	Pre-AG120 (n=24)	Post-AG120 (n=24)
Mean percent change (95% CI) for every 6 months[b]	28% (24%, 32%)	24% (12%, 37%)	11% (1%, 23%)

Volumetric growth rate 1p19q intact subset			
	Natural History Study Pre-treatment[a] (N=73[c])	Pre-AG120 (n=15)	Post-AG120 (n=15)
Mean percent change (95% CI) for every 6 months[b]	34% (25%, 44%)	38% (19%, 60%)	14% (-1%, 31%)

[a]Retrospective centralized multi-center study of 239 patients with progressive non-enhancing IDH mutant LGG
Pre-treatment growth rate calculated using 3 MRI scans spanning minimum of 6 months prior to treatment using semi-automatic volumetric segmentation and mixed effect model (Presented by Huang et al. Abstract # 4809)
[b]Percent change is derived based on the slope estimate from the mixed effect model
[c]Number of subjects is indicated. Some subjects may have had more than one qualifying set of pre-treatment scans included in analysis

Confounding Effect of Prior Radiation

- Oligodendroglioma (WHO II)(1p19q intact)
- Resection: 2013
- **RT: Jun-July 2015**
- MRIs:
  H1: 4/2015
  H2: 8/2015
  H3: 11/2015
  Screen: 12/2015
- **Started AG-120 01/2016**



H1 = historical pre-treatment scan; Screen = screening

Lessons From Image Analysis

- Retrieval of historical (i.e., pre-screening) MRIs critical to establish kinetics of T2/FLAIR changes
- Review of prior treatment history (in particular, RT and surgery) critical to interpret clinical significance of T2/FLAIR changes
- Further development necessary in order to broadly implement methods for quantification and analyses of 3D tumor volumes and growth rates
- Specific imaging guidelines, methods, and study inclusion criteria are necessary for implementation of a standardized volumetric analysis approach

Summary

- AG-120 is well tolerated in patients with non-enhancing glioma
- AG-120 results in prolonged stable disease in this pretreated glioma population with a median treatment duration of 16 months and warrants further clinical evaluation
  - 51% of patients still on treatment
  - Preliminary results suggest a reduction in tumor growth rates
- Further refinement of volumetric growth rate methodology is needed
- Preliminary data suggest that AG-120 suppresses 2-HG in tumors; this will be further evaluated in a planned perioperative study

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

Editorial support was provided by Helen Varley, PhD, CCMP, Excel Scientific Solutions, Horsham, UK, and supported by Agios