ACTR-46

AG-120, a first-in-class mutant IDH1 inhibitor in patients with recurrent or progressive IDH1 mutant glioma: results from the phase 1 glioma expansion cohorts

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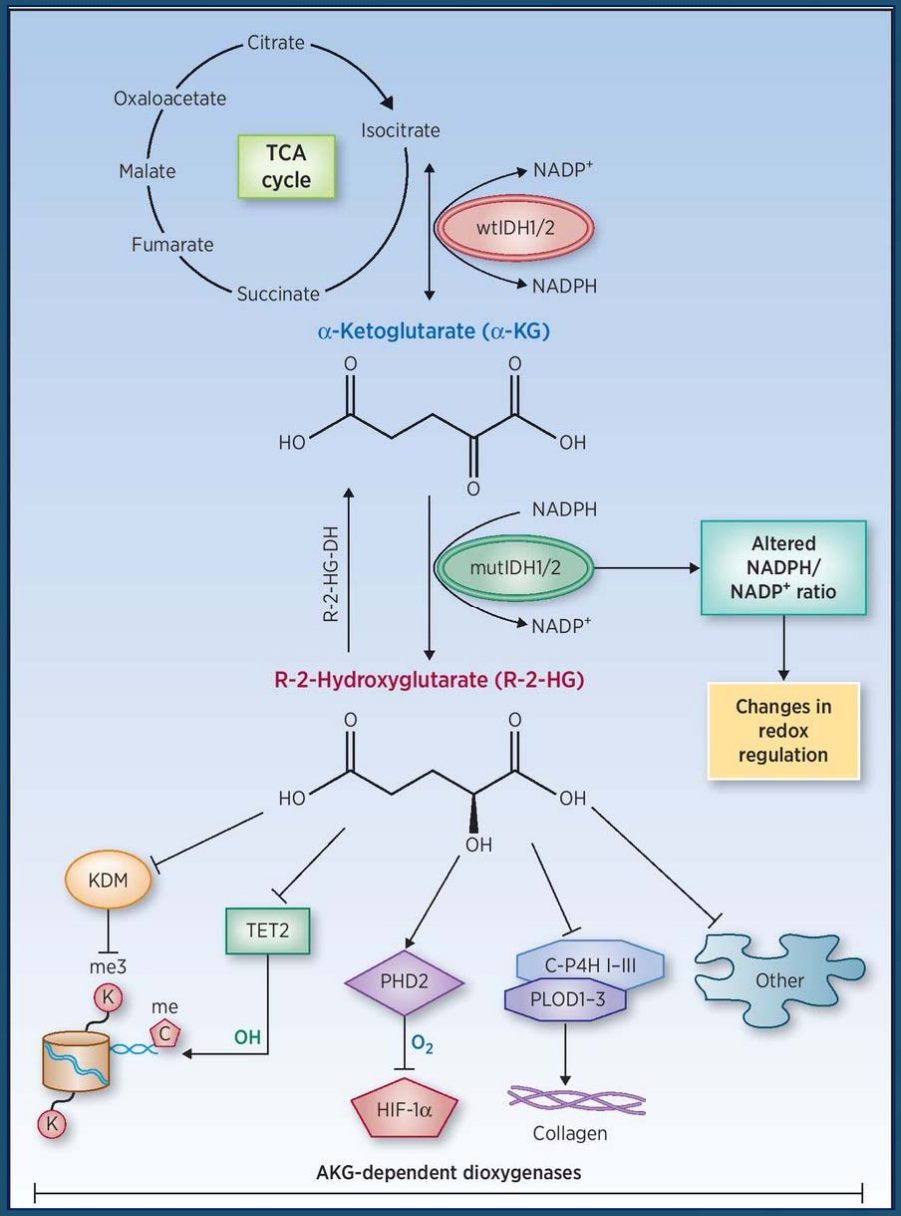
IDH and cancer

- IDH mutations (IDH1 or IDH2) occur in many human cancers
- IDH mutations change the function of the enzyme → neomorphic production of the oncometabolite 2-HG
- Inhibiting the function of the mutant enzyme in patients with IDH1-mutant advanced hematologic malignancies results in objective responses in 36% of patients[1]



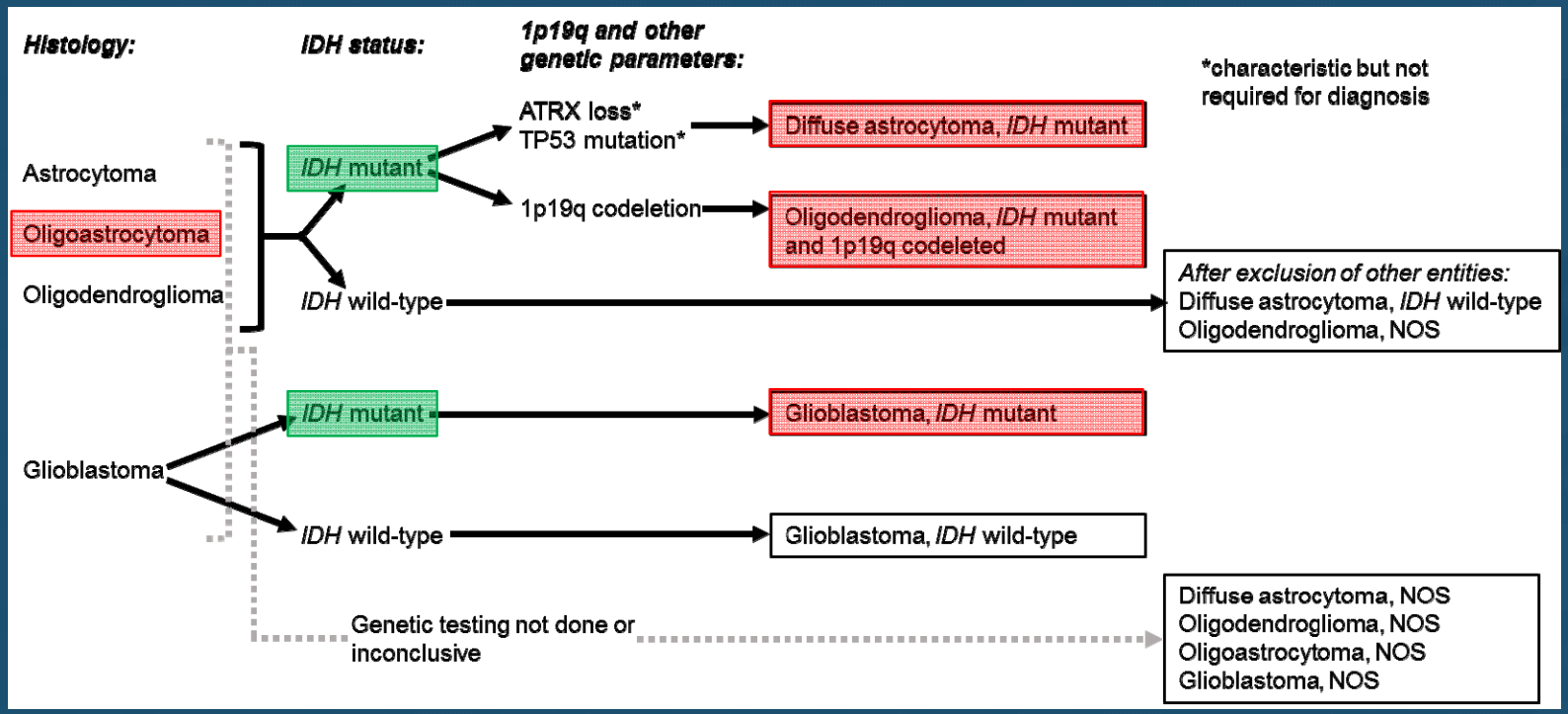
Clark O, Yen K, Mellinghoff IK. *Clin Cancer Res* 2016;22:1837

[1]DiNardo CD et al. Blood 2015;126:Abstract 1306, presented at the *57th ASH Annual Meeting* 2015

IDH mutations in glioma

- 5% GBMs; ~80% of WHO grade II/III gliomas, mostly IDH1*[1,2]

2016 WHO classification[3]



- AG-120: oral, selective, first-in-class, potent inhibitor of mutant IDH1; reduces intracellular 2-HG in primary human IDH1-mutant hematological cancer cells[4]

*Estimates evolving with availability of new data. [1]The Cancer Genome Atlas Research Network. *NEJM* 2015;372:2481-98; [2]Yan H et al. *NEJM* 2009;360:765-73; [3]Adapted from Louis DN et al. *Acta Neuropathol* 2016;131:803-20; [4]Hansen E et al. Poster 3734, presented at the *56th ASH Annual Meeting* 2014

NOS = not otherwise specified

Study design

- Single-arm, open-label, multicenter, dose escalation and expansion study

Dose escalation[1]
Glioma n=20

- IDH1-mutant (local testing) advanced solid tumors, including glioma
- Recurred, progressed or not responded to standard therapy

Non-enhancing glioma expansion*
n=24

- 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

'Basket' expansion*
Glioma n=22

- IDH1-mutant progressive tumors not meeting other cohort criteria (includes enhancing glioma)

*Other expansions: cholangiocarcinoma and chondrosarcoma, to be reported elsewhere

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

ClinicalTrials.gov NCT02073994; RT = radiation therapy

Key objectives

- Safety and tolerability
  - Escalation dosing: 100 mg BID, 300, 400, 500, 600, 800, 900, 1200 mg QD
- Identify the maximum tolerated dose and/or recommended phase 2 dose
- Characterize pharmacokinetic/pharmacodynamic relationship
- Characterize preliminary clinical activity
  - Escalation phase, and for enhancing glioma in expansion phase:
    - RANO criteria (local investigators)
  - Non-enhancing glioma in expansion phase:
    - RANO LGG criteria (local investigators and central review)

ClinicalTrials.gov NCT02073994.

BID = twice daily; QD = once daily; RANO = response assessment in neuro-oncology; LGG = low grade glioma

Study status

- Glioma enrollment complete as of 13 Jan 2016, N=66
  - Escalation, n=20
  - Expansion, n=46
- Expansion dosing: 500 mg QD selected
- Study ongoing as of 1 Aug 2016; 28 of 66 (42%) subjects remain on treatment

Reasons for discontinuation, n=38	
Progressive disease	34 (52%)
Physician decision	3 (5%)[a]
Adverse event	1 (2%)[a]

[a]Evidence of clinical progression

Patient demographics

	Total treated glioma N=66
Median age, years (range)	41 (21–71)
Gender (M/F)	41/25
ECOG status at baseline, n (%)	
0	29 (44)
1	37 (56)
Tumor type and grade at screening, n (%)	
Oligodendroglioma[a]	23 (35)
Grade II	14 (21)
Grade III	8 (12)
Astrocytoma[a]	19 (29)
Grade II	12 (18)
Grade III	6 (9)
Oligoastrocytoma	12 (18)
Grade II	8 (12)
Grade III	4 (6)
Glioblastoma	12 (18)
1p19q co-deletion, n (% of those tested)[b]	17 (31)
ATRX mutation, n (% of those tested)[c]	24 (92)

[a]Grade missing for one patient
[b]11 (17% of total) unknown
[c]40 (61% of total) unknown

ECOG = Eastern cooperative oncology group

Prior and concomitant therapy

	Total treated glioma N=66
Prior therapies	
Median number of prior systemic therapies (range)	2 (1–6)
Temozolomide, n (%)	47 (71)
PCV, n (%)	9 (14)
Bevacizumab, n (%)	8 (12)
Radiotherapy, n (%)	49 (74)
Concomitant therapies	
Baseline anticonvulsant use, n (%)	54 (82)
Baseline steroid use, n (%)	7 (11)

PCV includes Procarbazine, CCNU (lomustine), and Vincristine given as a single regimen

Safety summary

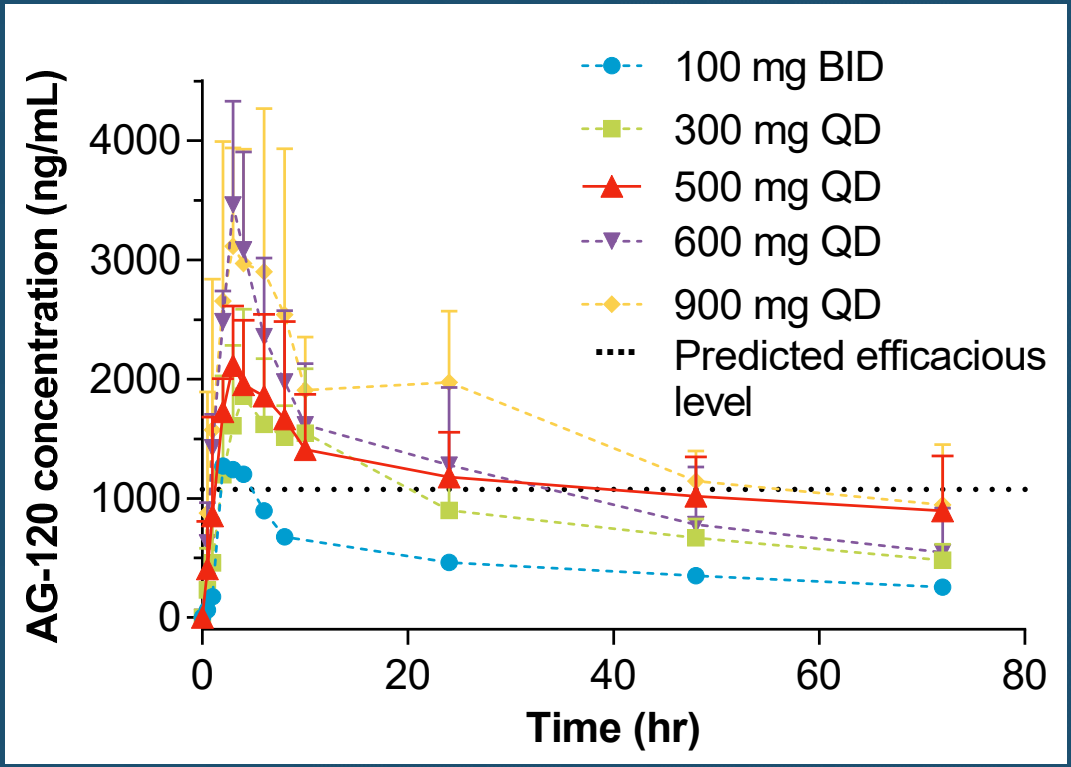
- No DLTs observed; no on-treatment deaths
- MTD not reached
- Patients experiencing at least one serious treatment-emergent AE: 11 of 66 (17%)
  - All deemed unrelated to treatment

AEs in glioma patients (regardless of relationship), N=66	All grades, n (%)	Grade ≥3, n (%)
Patients experiencing ≥1 AE	62 (94)	14 (21)
Most frequent AEs (in ≥10% of patients)		
Headache	17 (26)	3 (5)
Nausea	14 (21)	-
Diarrhea	10 (15)	-
Vomiting	9 (14)	-
Neutrophil count decreased	8 (12)	-
Aphasia	7 (11)	-
Fatigue	7 (11)	-
Hypophosphatemia	7 (11)	2 (3)

Assessed with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03
DLT = dose-limiting toxicity; MTD = maximum tolerated dose

Pharmacokinetic profile

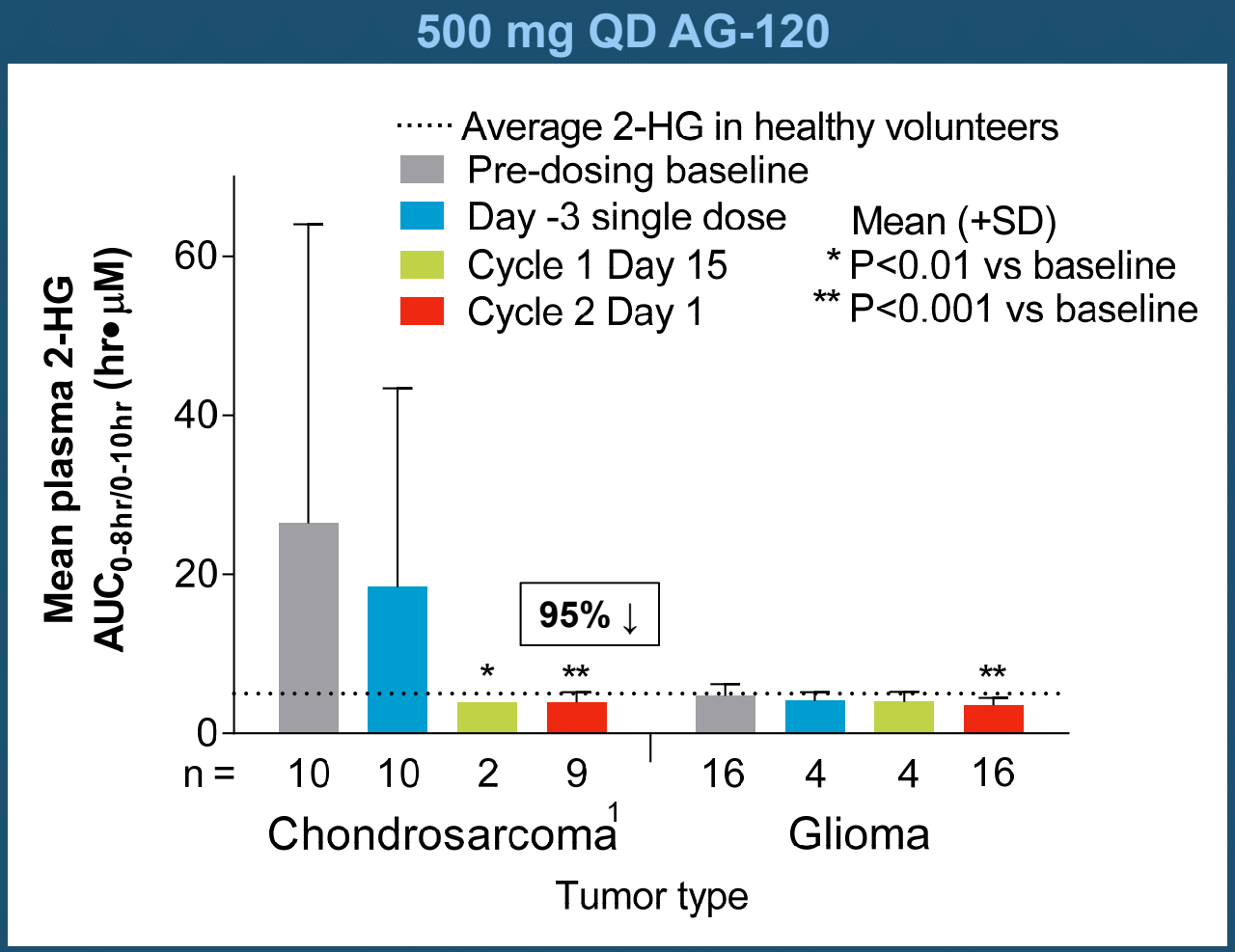
Plasma AG-120 after single dose (mean + SD)



- Plasma AG-120 steady state achieved in Cycle 1; exposure at 500 mg above efficacious level predicted by a subcutaneous xenograft mouse model
- Increases in plasma exposure above 500 mg QD are not proportional
- Mean terminal half-life: 33.6–71.5 hr
- 500 mg QD selected for expansion based on the observed clinical activity, safety, and PK/PD data

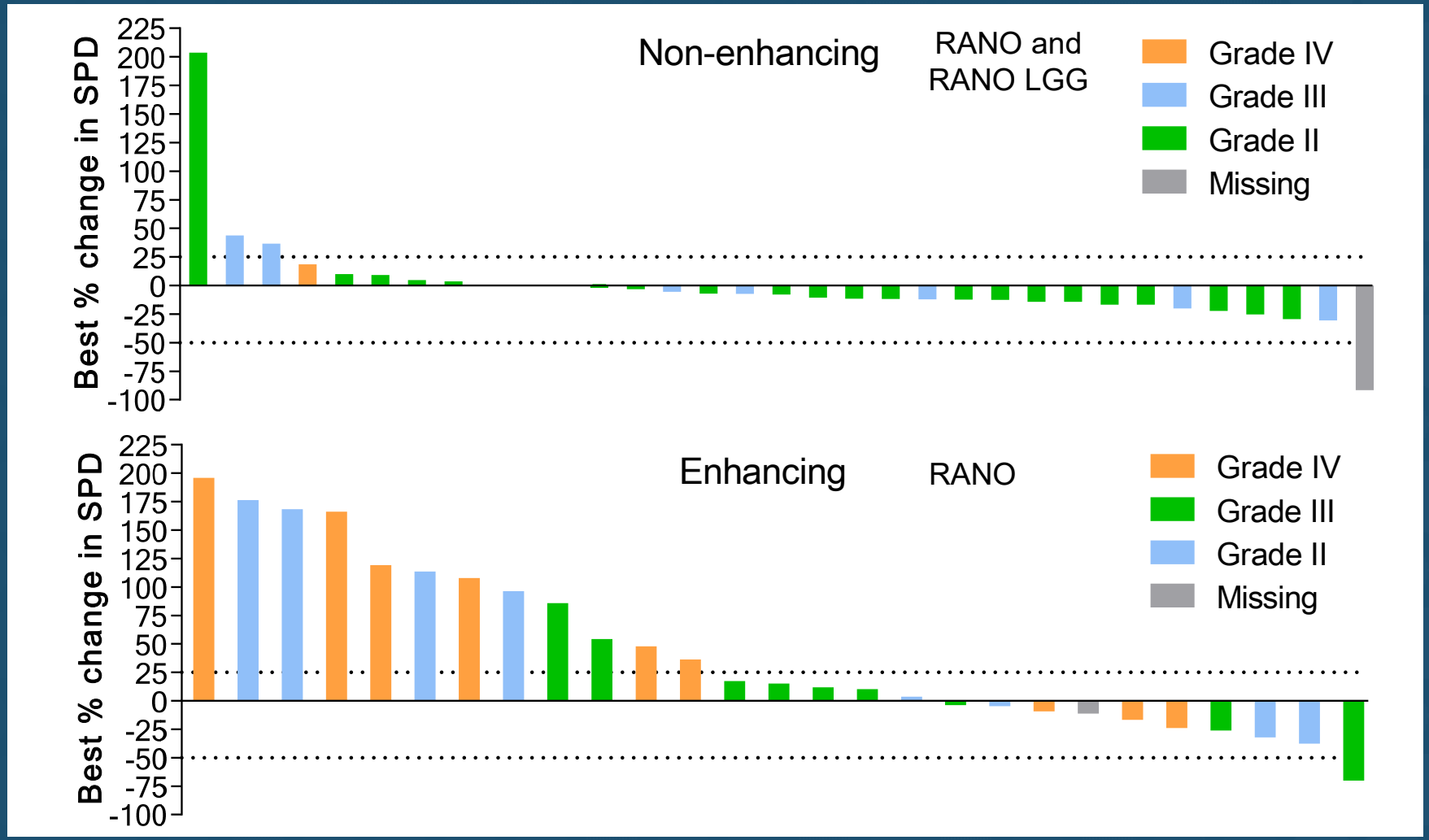
SD = standard deviation; PK/PD = pharmacokinetics/pharmacodynamics

Baseline plasma 2-HG levels in glioma are not elevated beyond the healthy volunteer range



[1]Tap W et al. Poster 138, presented at the *CTOS Annual Meeting* 2016

Best % change in sum of the product of diameters



By investigator; patients with ≥1 post-baseline tumor assessment shown, n=60

One additional subject not shown here had best change in SPD of 839% due to merged lesions

25% change is the RANO threshold for progressive disease and –50% change the RANO threshold for partial response

Graph shows best response at any single time point

SPD = sum of the product of diameters

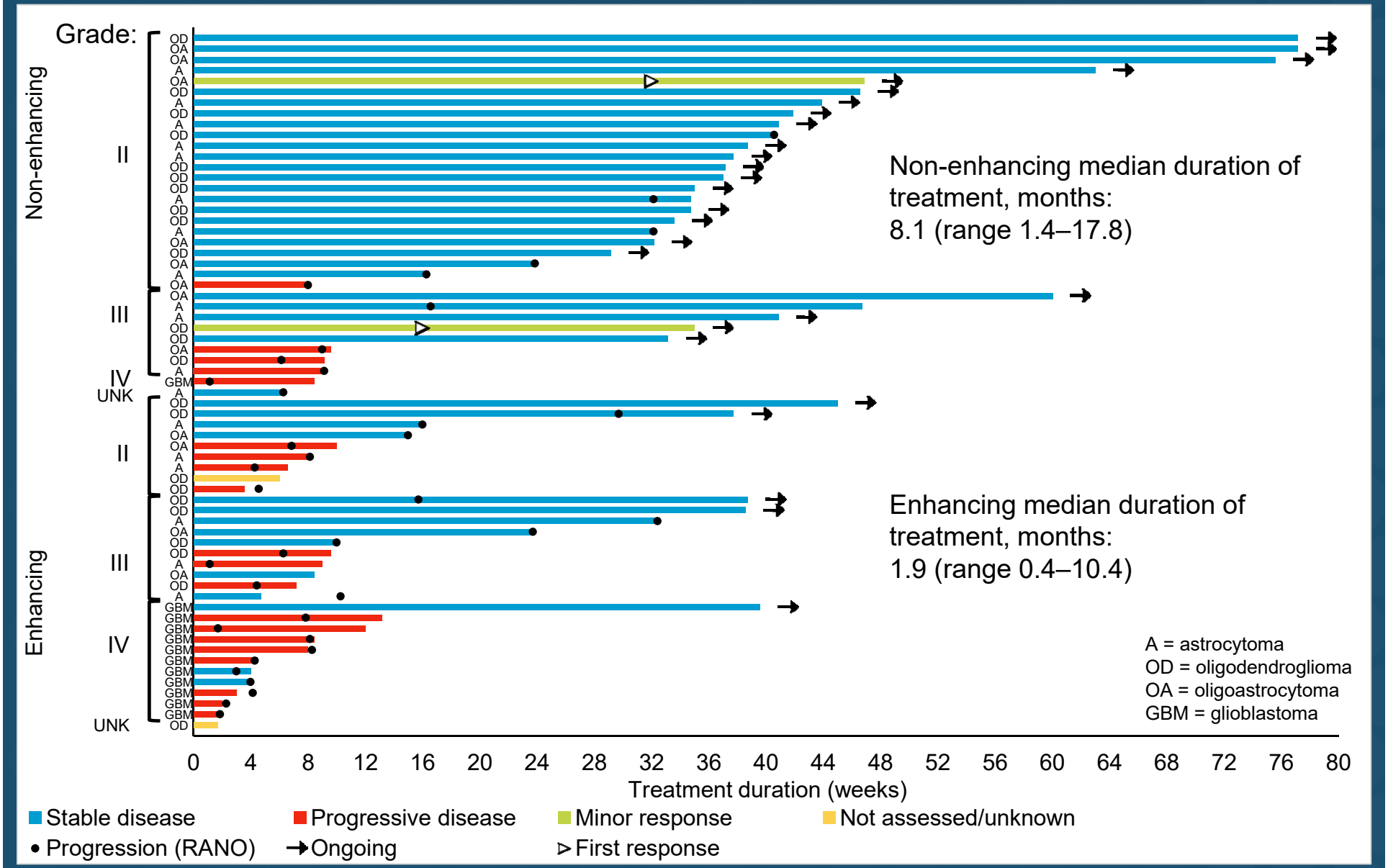
Best overall response by RANO/RANO LGG criteria
(by investigator; efficacy evaluable subjects[a])

	RANO		RANO LGG	Overall
	Enhancing n=31	Non-enhancing escalation n=11	Non-enhancing expansion n=23	Total glioma N=65
Best response, n (%)				
Minor response	-	-	2 (9)	2 (3)
Stable disease	14 (45)	8 (73)	19 (83)	41 (63)
Progressive disease	15 (48)	3 (27)	2 (9)	20 (31)
Unknown/not assessed	2 (6)	-	-	2 (3)
Overall response rate[b], n (%) [95% CI]	-	-	2 (9) [1.1–28.0]	2 (3) [0.4–10.7]

RANO and RANO LGG evaluated by local investigators

[a]Includes subjects who had baseline and post-baseline response assessments or discontinued prematurely
[b]Defined as complete or minor or partial response

Duration on treatment and best overall response



By investigator; efficacy evaluable patients as of data cut-off 1 Aug 2016

Exploratory imaging: glioma growth rates

- Gliomas display slow but continuous growth,[1] the rate of which may correlate with transformation and survival[2,3]
- Exploratory goal: measurement of effects on tumor growth rates

Non-enhancing glioma expansion n=24

- 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

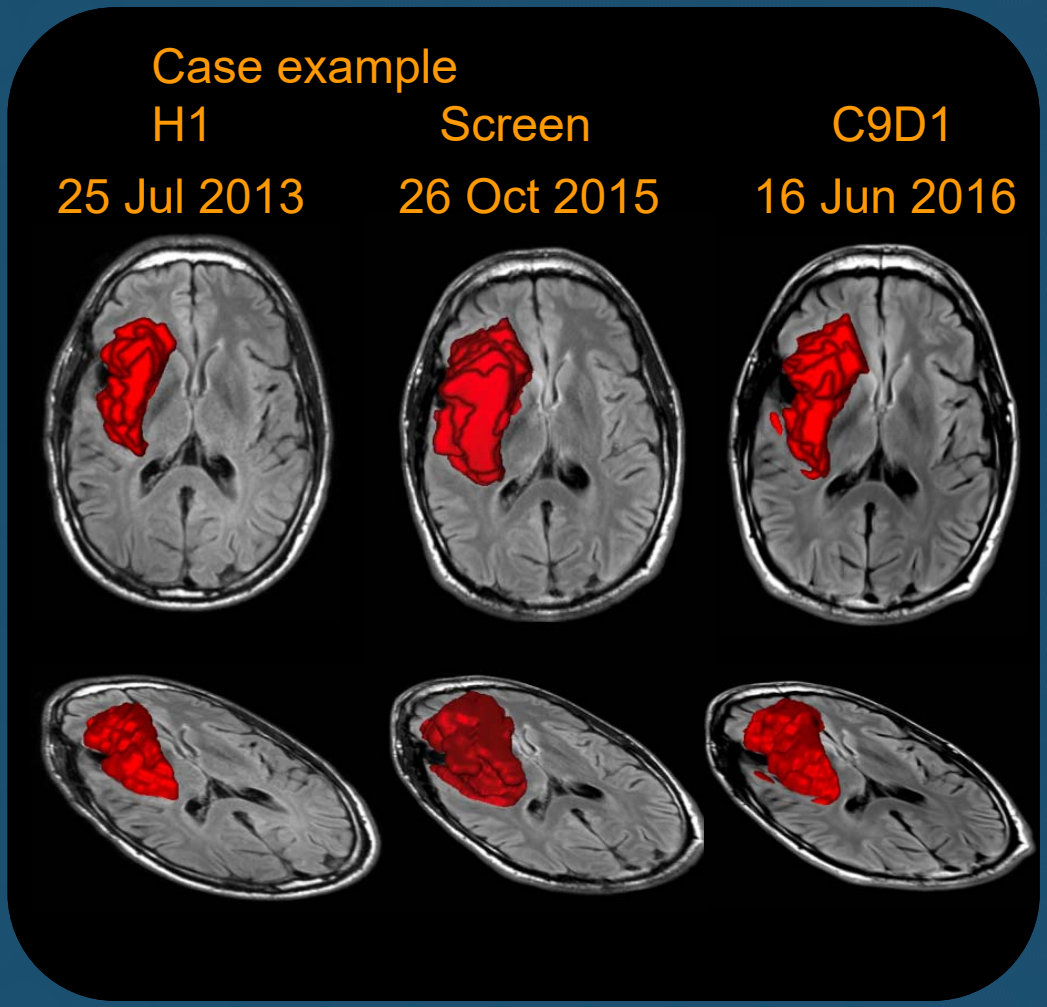
174 MRI scans (n=63 historical scans, n=111 protocol MRIs)

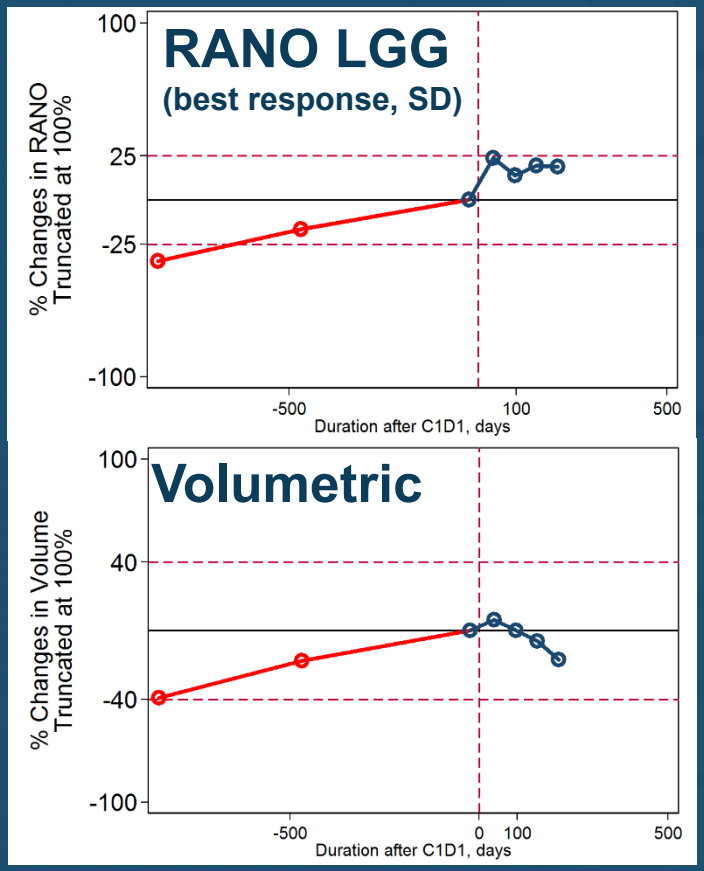
Methods

- Pre-segmentation of T2/FLAIR
- Editing and sign-off by 3 neuroradiologists
- Quantification of T2/FLAIR hyperintense volume
- Automatic calculation of bidimensional product
- Application of LGG RANO criteria and volumetric assessments

[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

Example: volumetric analysis





Tumor imaging summary

- Non-enhancing expansion subgroup with centralized, computer-assisted analysis (n=24*)
- Patients with stable or decreasing tumor slope on AG-120 compared to historic scans:
  - 14 of 22 (64%) by volumetric
  - 12 of 22 (55%) by bi-dimensional

*Two patients did not have historical scans

Study summary

- AG-120 is well tolerated in patients with IDH1-mutated glioma (as of 1 Aug 2016)
- 42% of patients remain on AG-120 (as of 1 Aug 2016)
- In non-enhancing expansion cohort (efficacy evaluable, n=23), 9% (n=2) with minor response and 83% (n=19) with stable disease
- Volumetric analysis demonstrated decrease in tumor growth rate compared to pre-treatment rate in 64% (n=14 of 22) of non-enhancing expansion patients receiving AG-120 and requires further development as a response evaluation tool
- 2-HG MRS could not be adequately assessed in this study and future efforts will incorporate a standardized methodology
- Further evaluation of mutant IDH inhibitors in glioma is warranted; AG-881, a brain-penetrant pan-IDH inhibitor, is under phase 1 evaluation in patients with IDH1- and/or IDH2-mutated gliomas or other solid tumors (ClinicalTrials.gov NCT02481154)

MRS, magnetic resonance spectroscopy

Acknowledgments

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