Determination of IDH1 mutational burden and clearance via next-generation sequencing in patients with IDH1 mutation-positive hematologic malignancies receiving AG-120, a first-in-class inhibitor of mutant IDH1

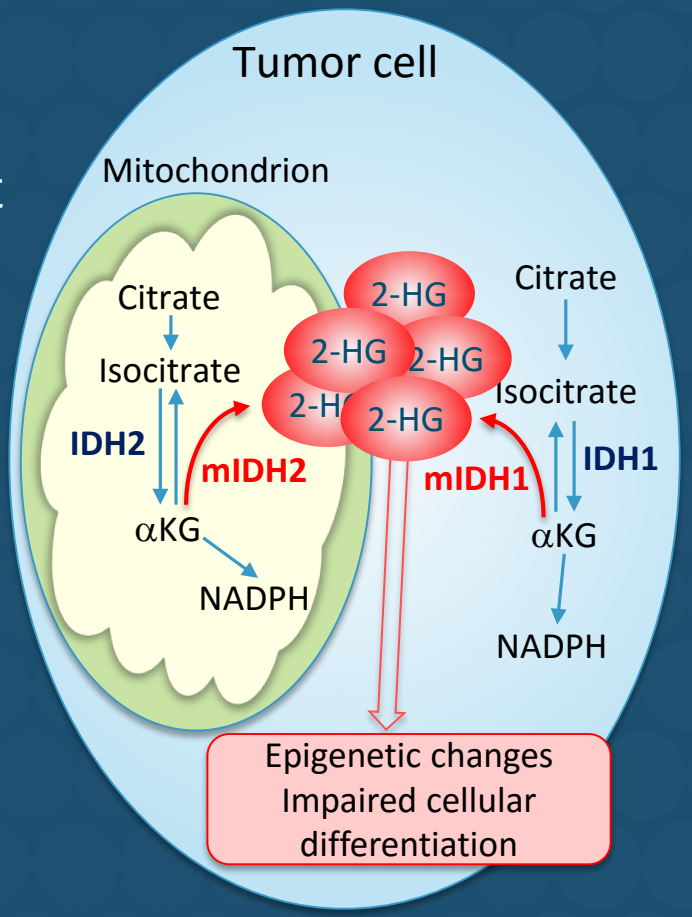
Courtney DiNardo[1], Stéphane de Botton[2], Eytan M Stein[3], Gail J Roboz[4], Ronan T Swords[5], Daniel A Pollyea[6], Amir T Fathi[7], Robert Collins[8], Jessica K Altman[9], Ian W Flinn[10], Gabriel N Mannis[11], Alice S Mims[12], James M Foran[13], Arnaud Pigneux[14], Gabrielle T Prince[15], Geoffrey L Uy[16], Martin S Tallman[3], Hagop Kantarjian[1], Hua Liu[17], Eyal C Attar[17], Jennifer Sacolick[17], Katharine Yen[17], Jonathan B Hurov[17], Sung Choe[17], Bin Wu[17], Richard M Stone[18]

[1]MD Anderson Cancer Center, Houston, TX; [2]Institut Gustave Roussy, Villejuif, France; [3]Memorial Sloan Kettering Cancer Center, New York, NY; [4]Weill Cornell Medical College, New York, NY; [5]Sylvester Comprehensive Cancer Center, Miami, FL; [6]University of Colorado Cancer Center, Aurora, CO; [7]Massachusetts General Hospital, Boston, MA; [8]University of Texas Southwestern Medical Center, Dallas, TX; [9]Robert H Lurie Comprehensive Cancer Center, Chicago, IL; [10]Sarah Cannon Research Institute, Nashville, TN; [11]University of California San Francisco School of Medicine, San Francisco, CA; [12]Ohio State University, Columbus, OH; [13]Mayo Clinic, Jacksonville, FL; [14]Hôpitaux du Haut Lévéque CHU Bordeaux, Pessac, France; [15]Johns Hopkins Hospital, Baltimore, MD; [16]Washington University School of Medicine, St. Louis, MO; [17]Agios Pharmaceuticals, Inc., Cambridge, MA; [18]Dana-Farber Cancer Institute, Boston, MA

Presented at the 58th American Society of Hematology Annual Meeting and Exposition, December 5, 2016, San Diego, CA

Introduction

- Somatic IDH1 and IDH2 mutations result in accumulation of oncometabolite 2-HG
  - → epigenetic changes, impaired cellular differentiation



- mIDH identified in multiple solid and hematologic tumors

	mIDH1	mIDH2
% of AML cases	~6–10%	~9–13%

- AG-120: a first-in-class, oral, potent, reversible, selective inhibitor of mIDH1 enzyme
  - under evaluation in multiple clinical trials as a single agent and in combinations

2-HG = D-2-hydroxyglutarate; IDH = isocitrate dehydrogenase; mIDH = mutant IDH

Study design

Single-arm, open-label, phase 1, multicenter study
ClinicalTrials.gov NCT02074839

Dose escalation
Enrollment complete

Patients with mIDH1+ advanced hematologic malignancies

Oral AG-120 daily in continuous 28-day cycles

Doses included 100 mg BID, 300, 500, 800, 1200 mg QD

Dose expansion
Ongoing: 500 mg QD in continuous 28-day cycles

- **R/R AML in 2nd+ relapse, relapse after SCT, refractory to induction or reinduction, or relapse within 1 year, n=125**
- **Untreated AML not eligible for SOC, n=25**
- **Other non-AML mIDH1 R/R advanced hematologic malignancies, n=25**
- **Other R/R AML, n=25**

Dose escalation objectives

Primary	Safety and tolerability, identification of maximum tolerated dose (MTD) and/or recommended phase 2 dose
Secondary	Assessment of clinical activity by investigators using modified 2003 International Working Group criteria in AML
Exploratory	Determination of mIDH1 variant allele frequency (VAF) by next-generation sequencing (NGS)

R/R = relapsed or refractory; SCT = stem cell transplant; SOC = standard of care

Disposition and demographics

- As of 1 August 2016, 78 patients in dose escalation have been treated and 71 patients discontinued treatment:
  - PD (n=37)
  - transplant (n=9)
  - death (n=9)
  - adverse event (n=7)
  - withdrawal of consent (n=4)
  - investigator decision (n=3)
  - other (n=2)

	Dose escalation n=78
Age in years, median (range)	68 (36–89)
Men/women, n	41/37
Diagnosis, n (%)	
R/R AML	63 (81)
Untreated AML	9 (12)
MDS	4 (5)
Other[a]	2 (3)
ECOG performance status, n (%)	
0	18 (23)
1	44 (56)
2	16 (21)
No. of prior chemotherapy regimens, median (range)	2 (0–5)
Prior transplant, n (%)	16 (21)
Abnormal cytogenetics at screening,[b] n (%)	48 (62)

[a]Myelofibrosis, essential thrombocythemia
[b]Missing in 9 patients

ECOG = Eastern Cooperative Oncology Group; PD = progressive disease

Safety summary 1

- AG-120 was well tolerated up to a dose of 1200 mg QD; MTD was not reached
- No indication of differences in AEs at different doses
  - All-cause mortality: 30-day, 9 (12%) and 60-day, 16 (21%)

Safety summary for dose escalation phase (regardless of causality)

AE	Patients n=78	Details
Dose-limiting toxicities, n (%)	2 (3)	One grade 3 QT prolongation at 800 mg QD, one grade 3 rash at 1200 mg QD
At least one treatment-related AE, n (%)	47 (60)	In ≥5% of patients: nausea 13 (17), fatigue 12 (15), diarrhea 9 (12), vomiting 9 (12), ECG prolonged QT 7 (9), decreased appetite 6 (8), rash 6 (8), leukocytosis 5 (6), asthenia 4 (5)
At least one serious AE, n (%)	53 (68)	In ≥5% of patients: febrile neutropenia 13 (17), pneumonia 9 (12), pyrexia 6 (8), leukocytosis 5 (6), sepsis 5 (6)
AEs leading to discontinuation, n (%)	4 (5)	Three events (rash, posterior reversible encephalopathy syndrome, pulmonary edema) considered possibly related to AG-120
Deaths due to AEs, n (%)	18 (23)	AE considered possibly related to AG-120 in one patient (pericardial and pleural effusion)

AE = adverse event

Safety summary 2

Most common AEs regardless of causality (≥15%; all treated patients, N=78)	All grades, n (%)	Grade ≥3, n (%)
Any AE, n (%)	78 (100)	65 (83)
Fatigue	28 (36)	6 (8)
Nausea	26 (33)	3 (4)
Diarrhea	25 (32)	2 (3)
Pyrexia	21 (27)	2 (3)
Edema peripheral	20 (26)	-
Vomiting	19 (24)	2 (3)
Leukocytosis	17 (22)	11 (14)
Anemia	16 (21)	14 (18)
Cough	16 (21)	-
Decreased appetite	16 (21)	1 (1)
Dyspnea	16 (21)	4 (5)
Febrile neutropenia	16 (21)	16 (21)
Arthralgia	15 (19)	1 (1)
Constipation	14 (18)	1 (1)
Electrocardiogram QT prolonged	14 (18)	3 (4)
Rash	14 (18)	2 (3)
Asthenia	13 (17)	-
Pneumonia	13 (17)	11 (14)
Hypotension	12 (15)	4 (5)

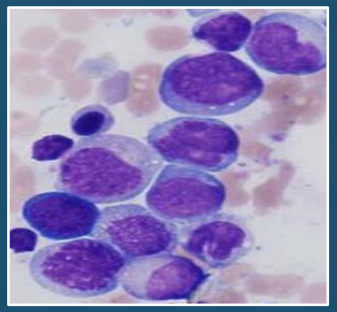
Additional grade ≥3 AEs in ≥5% of patients: tumor lysis syndrome 7 (9%), thrombocytopenia 6 (8%), hypoxia 5 (6%), neutropenia 5 (6%), respiratory failure 5 (6%), sepsis 5 (6%)

Incidence of reported IDH differentiation syndrome (coded term APL differentiation syndrome): all grades = 5%, grade ≥3 = 1%

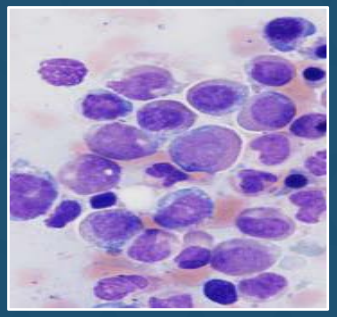
Clinical activity

CR at end of Cycle 1

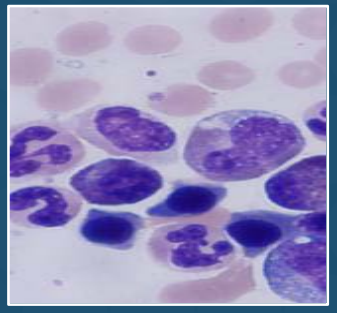
Screening
44% blasts



Cycle 1
Day 15
3% blasts



Cycle 1
Day 28
2% blasts

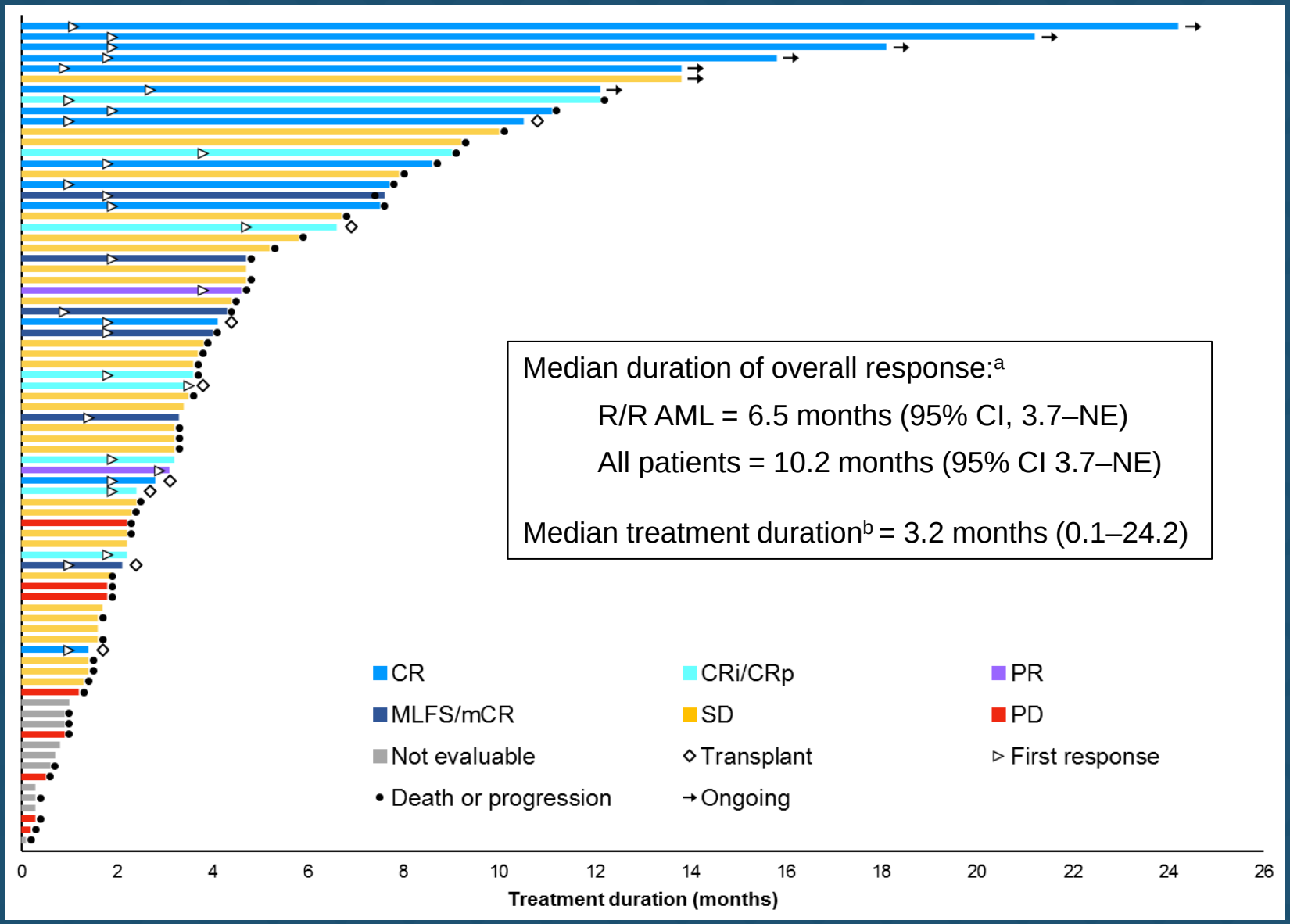


	Dose escalation	
	R/R AML n=63	Overall N=78
CR, n (%)	10 (16)	14 (18)
CRi/CRp, n (%)	8 (13)	8 (10)
PR, n (%)	1 (2)	2 (3)
mCR/MLFS, n (%)	2 (3)	6 (8)
SD, n (%)	27 (43)	30 (38)
PD, n (%)	8 (13)	8 (10)
NE, n (%)	7 (11)	10 (13)
ORR, n (%) [95% CI]	21 (33) [22, 46]	30 (38) [28, 50]

Data cut off date 1 August 2016

CR = complete response; CRi = CR with incomplete neutrophil recovery; CRp = CR with incomplete platelet recovery; PR = partial response; mCR/MLFS (marrow CR/morphologic leukemia-free state) = <5% blasts in bone marrow, no hematologic recovery; SD = stable disease; NE = not evaluable; ORR = overall response rate (CR + CRi + CRp + PR + mCR/MLFS)

Duration of treatment and best overall response (dose escalation patients, n=78)



A patient with CRi/CRp discontinued treatment to proceed with transplant, but the date was unavailable at time of data cut

[a]Defined as time from 1st response to disease progression or death among responders. [b]Among all 78 treated patients

Data cut-off date 1 August 2016. NE = not estimable

Determination of mIDH1 mutation clearance by NGS

Mutation clearance defined as:
- mIDH1 positive at screening (VAF >1% from any sample type), AND
- no mIDH1 detected at ≥1 on-study time point (VAF cut off 1%)

Genomic DNA extracted for NGS analysis of mIDH1 VAF from samples:
- Whole PB/BM
- PB/BM mononuclear cells

→ 67 subjects with mIDH1 VAF data at screening and at least one on-study time point

→ mIDH1 mutation clearance analyzed

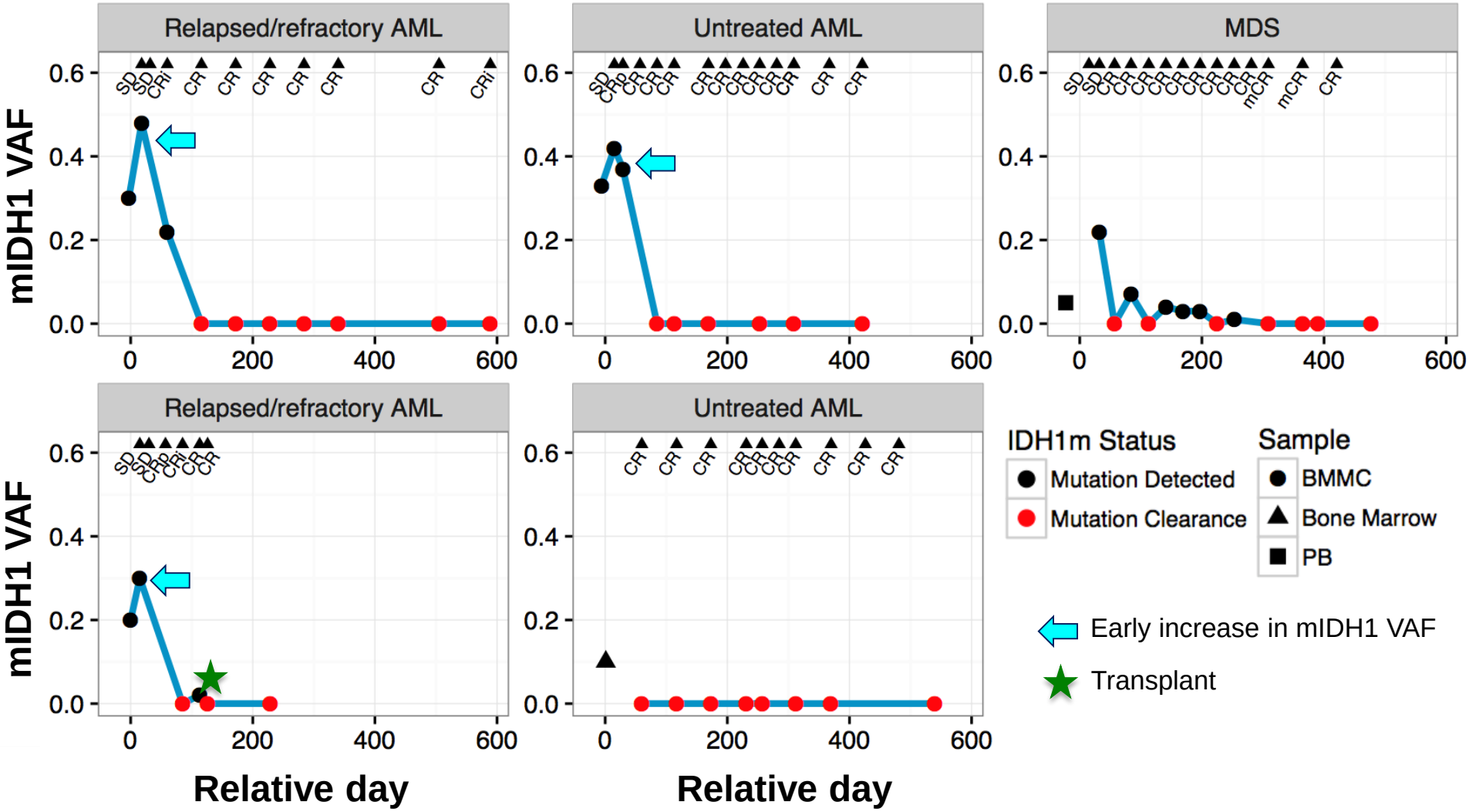
Best response	Number of subjects with longitudinal VAF	Number of subjects with mutation clearance
CR	14	5
Non-CR	53	2
Total	**67**	**7**

p=.003*

*Fisher's exact test

NGS = next-generation sequencing by FoundationOne Heme Panel; Non-CR = CRi/CRp, PR, mCR/MLFS, SD, PD, NE; PB/BM = peripheral blood/bone marrow; VAF = variant allele frequency

AG-120: IDH1 mutation clearance in patients with CR



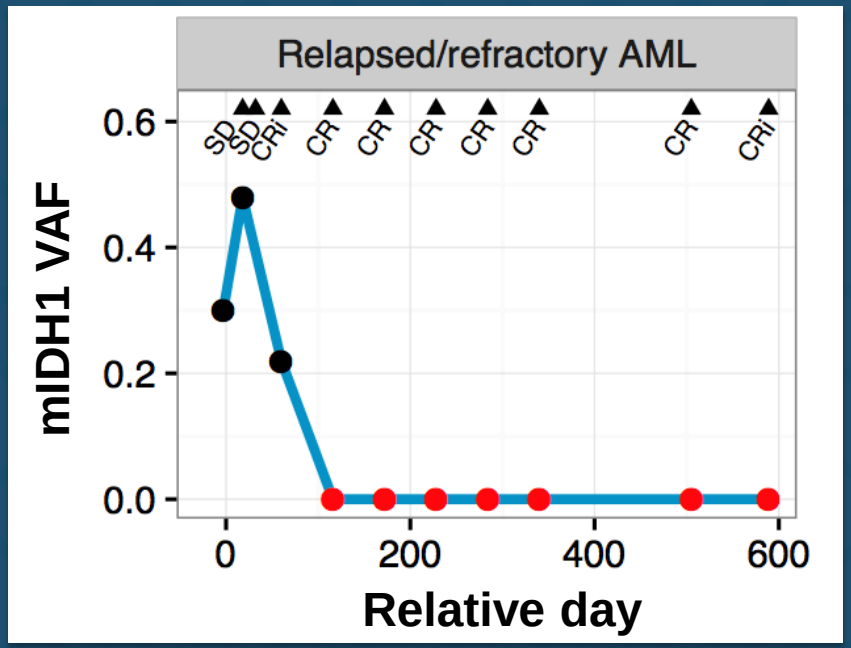
In subjects for whom the mIDH1 VAF could not be obtained from mononuclear cells at baseline due to technical limitations, whole BM or whole PB was utilized

Subjects for whom results from a non-BMMC sample were used at baseline in this analysis also had confirmed detection of mIDH1 from a baseline BM sample using the site's local test

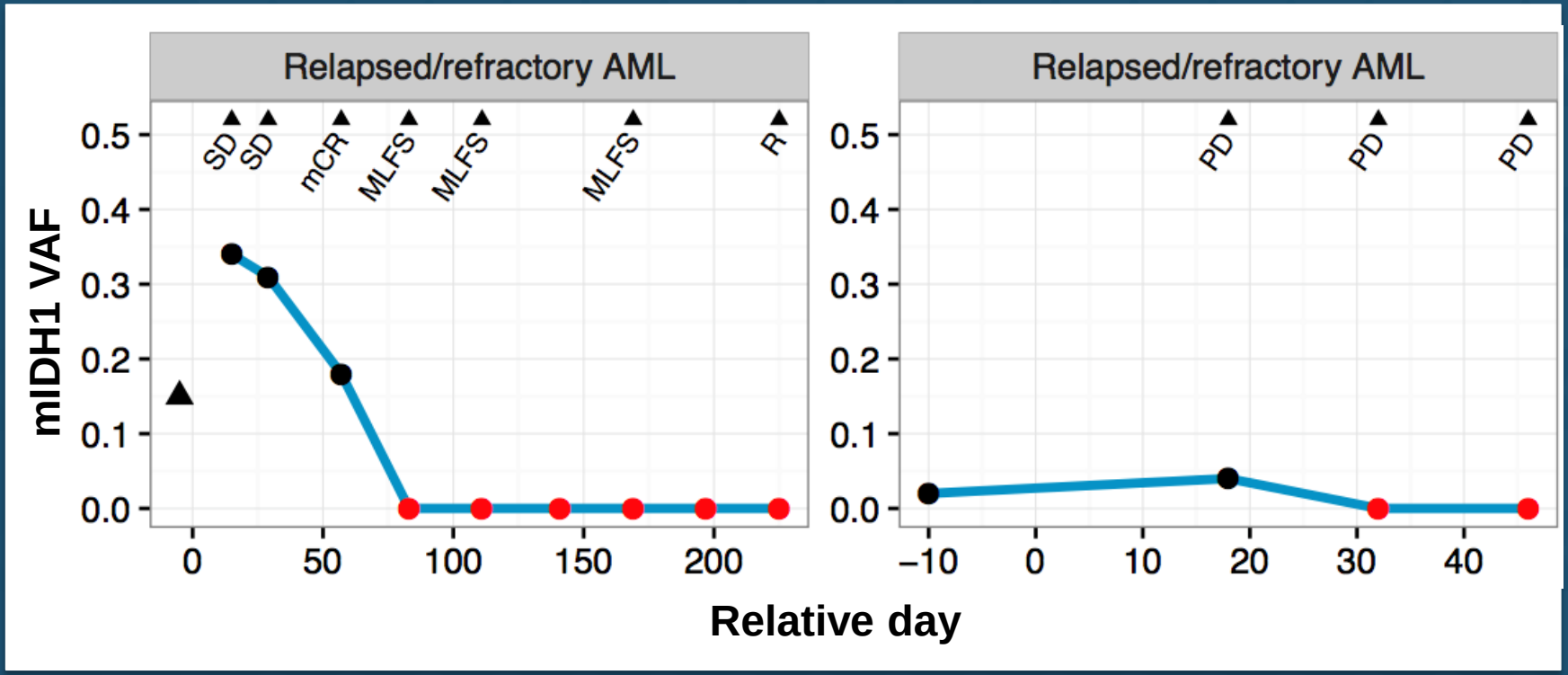
BMMC = bone marrow mononuclear cell

Case study of mutation clearance: R/R AML

- 77-year-old man
- 5/27/14: Diagnosis MDS with excess blasts
- 6/16/14: AML 63% blasts. Complex karyotype (der5, t(5;?7), del7p13, del13q, IDH1 R132C
- No response to 4 cycles decitabine D1-5



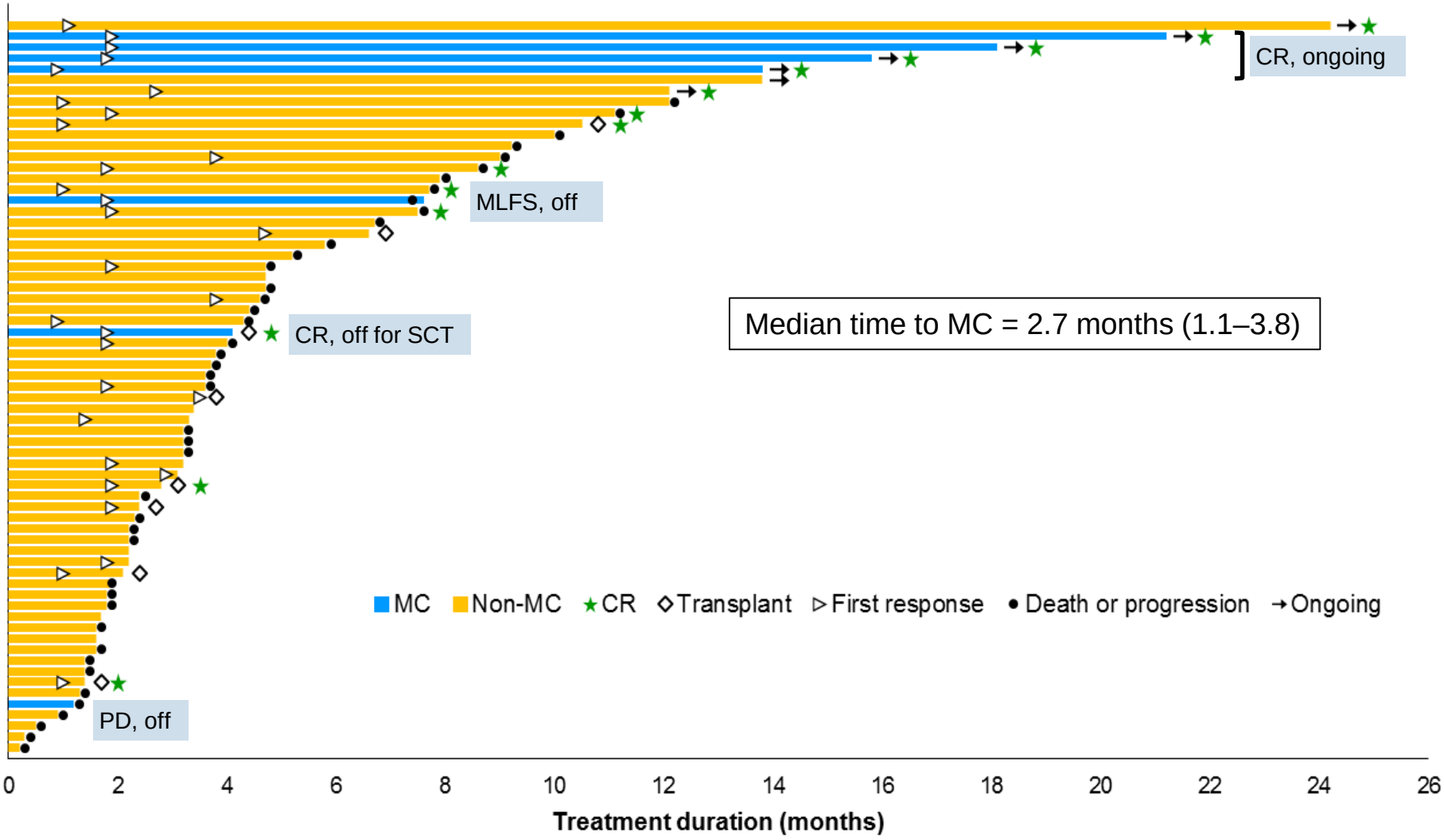
AG-120: IDH1 mutation clearance in subjects without CR



In subjects for whom the mIDH1 VAF could not be obtained from mononuclear cells at baseline due to technical limitations, whole BM or whole PB was utilized

Subjects for whom results from a non-BMMC sample were used at baseline in this analysis also had confirmed detection of mIDH1 from a baseline BM sample using the site's local test

Duration of treatment according to mutation clearance (dose escalation patients with available VAF, n=67)



MC = mutation clearance

Conclusions

- AG-120 is well tolerated to date; MTD was not reached
- Overall response rate of 38% including 18% CR, with a duration of study treatment of up to 24.2 months
  - R/R AML: overall response rate 33%, CR rate 16%
- This is the first demonstration that treatment with single agent AG-120 can result in mIDH1 clearance as determined by NGS
- MC is associated with CR, with mIDH1-MC observed in 36% (5/14) of CRs versus 4% (2/53) of non-CRs (p=.003)

Acknowledgments

- We would like to thank the patients who volunteered to take part in this study, the principal investigators, and their institutions

Editorial assistance was provided by Helen Varley, PhD, CMPP, Excel Scientific Solutions, Horsham, UK, and supported by Agios.