Ivosidenib (AG-120) in Mutant IDH1 AML and Advanced Hematologic Malignancies: Results of a Phase 1 Dose Escalation and Expansion Study

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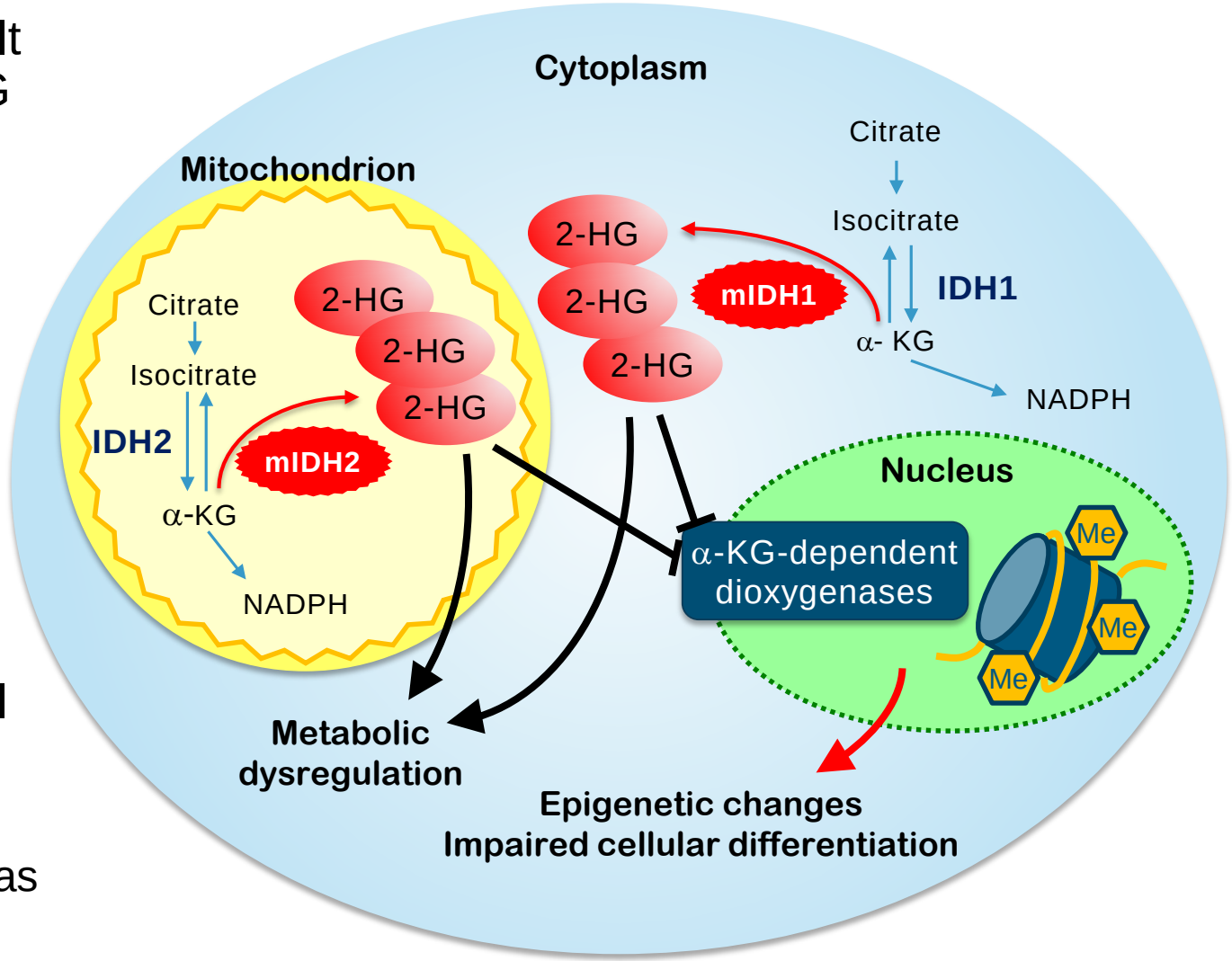
Isocitrate Dehydrogenase (IDH) Mutations as a Target in AML

- 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 patients	~6–10%	~9–13%

- **Ivosidenib (AG-120):** an investigational first-in-class, oral, potent, reversible, targeted inhibitor of mIDH1 enzyme
  - under evaluation in multiple clinical trials as a single agent and in combinations



Study Design and Objectives

Single-arm, open-label, phase 1, multicenter trial

Dose escalation (n=78)

Enrollment complete

Patients with mIDH1+ advanced hematologic malignancies

Oral ivosidenib daily in continuous 28-day cycles

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

Dose expansion (n=180)

Enrollment complete: 500 mg QD in continuous 28-day cycles

1. R/R AML in 2nd+ relapse, relapse after SCT, refractory to induction or reinduction, or relapse within 1 year, **n=126**
2. Untreated AML not eligible for SOC, **n=25**
3. Other non-AML mIDH1 R/R advanced hematologic malignancies, **n=11**
4. Other R/R AML not eligible for Arm 1, **n=18**

Study objectives

Primary	Safety and tolerability, MTD and/or RP2D, clinical activity in mIDH1 R/R AML enrolled in expansion Arm 1
Secondary	DLTs, pharmacokinetics and pharmacodynamics (including 2-HG), preliminary clinical activity in advanced hematologic malignancies
Exploratory	Determination of comutations and mIDH1 variant allele frequency (VAF)

Primary Efficacy Endpoint and Analysis Sets

Key analysis sets

- Safety Analysis Set (N=258): All treated patients
- Primary R/R AML Analysis Set (n=125):
  - The first 125 treated patients from Arm 1 of expansion (n=92) and eligible dose escalation patients (n=33) treated at 500 mg QD who were enrolled ≥ 6 months prior to the primary analysis cutoff date of 12 May 2017

Primary efficacy endpoint for R/R AML: CR+CRh rate

Response	Bone marrow blasts (%)	ANC	Platelets
CR[1]	< 5	> 1000	> 100,000
CRh	< 5	> 500	> 50,000

IWG responses, including CR, reported by Investigator. CRh derived by Sponsor

1. Modified IWG 2003 criteria. Cheson B et al. *J Clin Oncol* 2013;21:4642-4649.

Disposition and Treatment Duration

	All treated patients (N=258)	Primary R/R AML Set (n=125)
Ongoing treatment, n (%)	62 (24.0)	12 (9.6)
Discontinued treatment, n (%)	196 (76.0)	113 (90.4)
Progressive disease	104 (40.3)	66 (52.8)
Adverse event	33 (12.8)	17 (13.6)
Bone marrow transplant	22 (8.5)	12 (9.6)
Death	16 (6.2)	8 (6.4)
Withdrawal of consent	12 (4.7)	4 (3.2)
Investigator decision	7 (2.7)	5 (4.0)
Other	2 (0.8)	1 (0.8)
Discontinued study, n (%)	159 (61.6)	92 (73.6)
In post-transplant follow-up	8 (3.1)	4 (3.2)
In survival follow-up	29 (11.2)	17 (13.6)

- Median treatment duration: Primary R/R AML Set, 3.9 months (range 0.1–25.8)

Baseline Characteristics (n=125)

Characteristic	Primary R/R AML Set (n=125)
Women / men, n	60 / 65
Age in years, median (range)	67.0 (18–87)
ECOG PS at screening, n (%)	
0	27 (21.6)
1	64 (51.2)
De novo AML, n (%)	83 (66.4)
Secondary AML, n (%)	42 (33.6)
History of MDS	18 (14.4)
Therapy-related AML	14 (11.2)
No. of prior therapies, median (range)	2.0 (1–6)
Prior AML therapy outcomes[a], n (%)	
Relapsed after transplant	36 (28.8)
In 2nd or later relapse	20 (16.0)
Refractory to initial induction/reinduction therapy	86 (68.8)
Relapsed ≤ 1 year of initial therapy	13 (10.4)

Characteristic	Primary R/R AML Set (n=125)
Cytogenetic risk status by investigator, n (%)	
Favorable	0
Intermediate	66 (52.8)
Poor	38 (30.4)
Unknown	4 (3.2)
Missing	17 (13.6)
Co-mutation rates[b], n (%)	
FLT3	10 (8.1)
ITD	3 (2.4)
TKD	7 (5.6)
NPM1	24 (19.4)
CEBPA	3 (2.4)

[a]Not mutually exclusive, patients may be in more than one category; [b]Assessed in 124 patients

Most Common AEs Regardless of Causality (≥ 15%) (N=258)

All treated patients, N=258	Any grade, n (%)	Grade ≥ 3, n (%)
Any AE	255 (98.8)	200 (77.5)
Diarrhea	86 (33.3)	6 (2.3)
Leukocytosis	78 (30.2)	17 (6.6)
Nausea	76 (29.5)	3 (1.2)
Fatigue	74 (28.7)	8 (3.1)
Febrile neutropenia	65 (25.2)	64 (24.8)
Dyspnea	61 (23.6)	9 (3.5)
Anemia	60 (23.3)	49 (19.0)
Electrocardiogram QT prolonged	58 (22.5)	23 (8.9)
Edema peripheral	56 (21.7)	0 (0.0)
Pyrexia	53 (20.5)	4 (1.6)
Decreased appetite	51 (19.8)	4 (1.6)
Constipation	48 (18.6)	2 (0.8)
Cough	48 (18.6)	1 (0.4)
Hypokalemia	45 (17.4)	7 (2.7)
Vomiting	45 (17.4)	3 (1.2)
Arthralgia	41 (15.9)	5 (1.9)
Thrombocytopenia	41 (15.9)	35 (13.6)
Dizziness	40 (15.5)	1 (0.4)
Epistaxis	39 (15.1)	2 (0.8)

Data cutoff: 12May2017. AE, adverse event

AEs of Interest: Primary R/R AML Set (n=125)

- **Leukocytosis**
  - Grade ≥ 3 leukocytosis reported in 10/125 patients (8%)
  - Managed with hydroxyurea
  - None were fatal
- **ECG QT prolongation**
  - Grade 3 QT prolongation reported in 10/125 patients (8%)
  - Study drug was reduced in 1 patient and held in 5 patients (all grades)
  - None were Grade 4 or fatal
- **IDH-differentiation syndrome (IDH-DS)**
  - All grade reported in 12/125 patients (9.6%)
  - 4/12 IDH-DS patients had co-occurring leukocytosis
  - Managed with corticosteroids and diuretics, and hydroxyurea if accompanied by leukocytosis
  - None were Grade 4 or fatal
  - Best response for the 12 patients with IDH-DS:

Best Response	CR	CRh	CRi/CRp	MLFS	SD
n=12	2	0	3	1	6

- These events were managed using standard of care treatments and ivosidenib dose modifications as required

Grade 3 = WBC > 100,000/mm^3; Grade 4 = clinical manifestations of leukostasis, urgent intervention indicated

Data cutoff: 12May2017. AE, adverse event; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; SD, stable disease

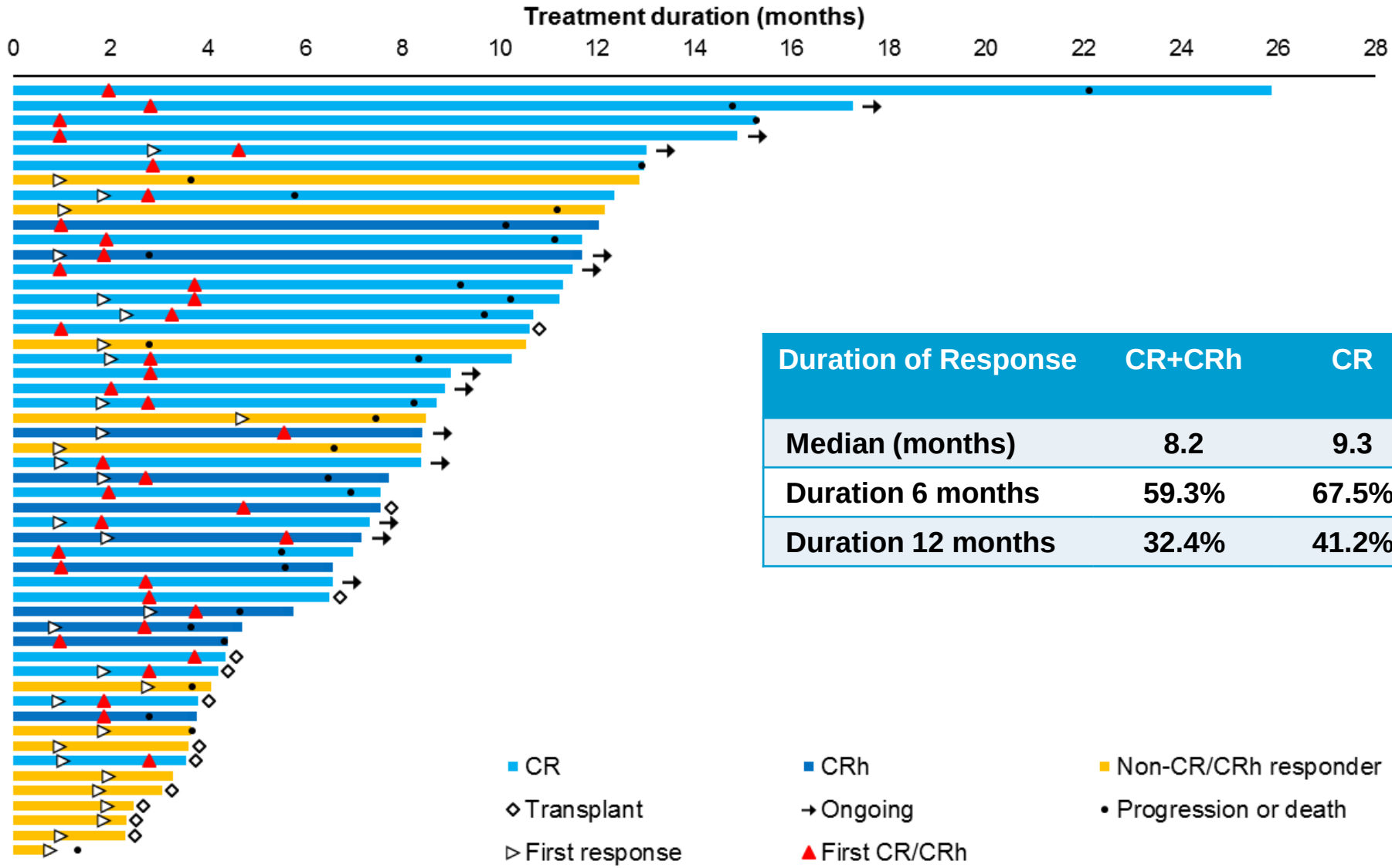
Response in R/R AML (n=125)

	Primary R/R AML Set (n=125)
CR+CRh rate, n (%) [95% CI]	**38 (30.4%) [22.5, 39.3]**
Time to CR/CRh, median (range) months	2.7 (0.9, 5.6)
Duration of CR/CRh, median [95% CI] months	8.2 [5.5, 12.0]
CR rate, n (%) [95% CI]	27 (21.6%) [14.7, 29.8]
Time to CR, median (range) months	2.8 (0.9, 8.3)
Duration of CR, median [95% CI] months	9.3 [5.6, 18.3]
CRh rate, n (%)	11 (8.8%)
Overall Response Rate, n (%) [95% CI]	**52 (41.6%) [32.9, 50.8]**
Time to first response, median (range) months	1.9 (0.8, 4.7)
Duration of response, median [95% CI] months	6.5 [4.6, 9.3]
Best response, n (%)	
CR	27 (21.6)
CRi or CRp	16 (12.8)
MLFS	9 (7.2)
SD	44 (35.2)
PD	13 (10.4)
NA	16 (12.8)

- CRh = 6 patients with investigator assessed responses of CRi/CRp and 5 with MLFS

Data cutoff: 12May2017. CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; NA, not assessed; PD, progressive disease; SD, stable disease

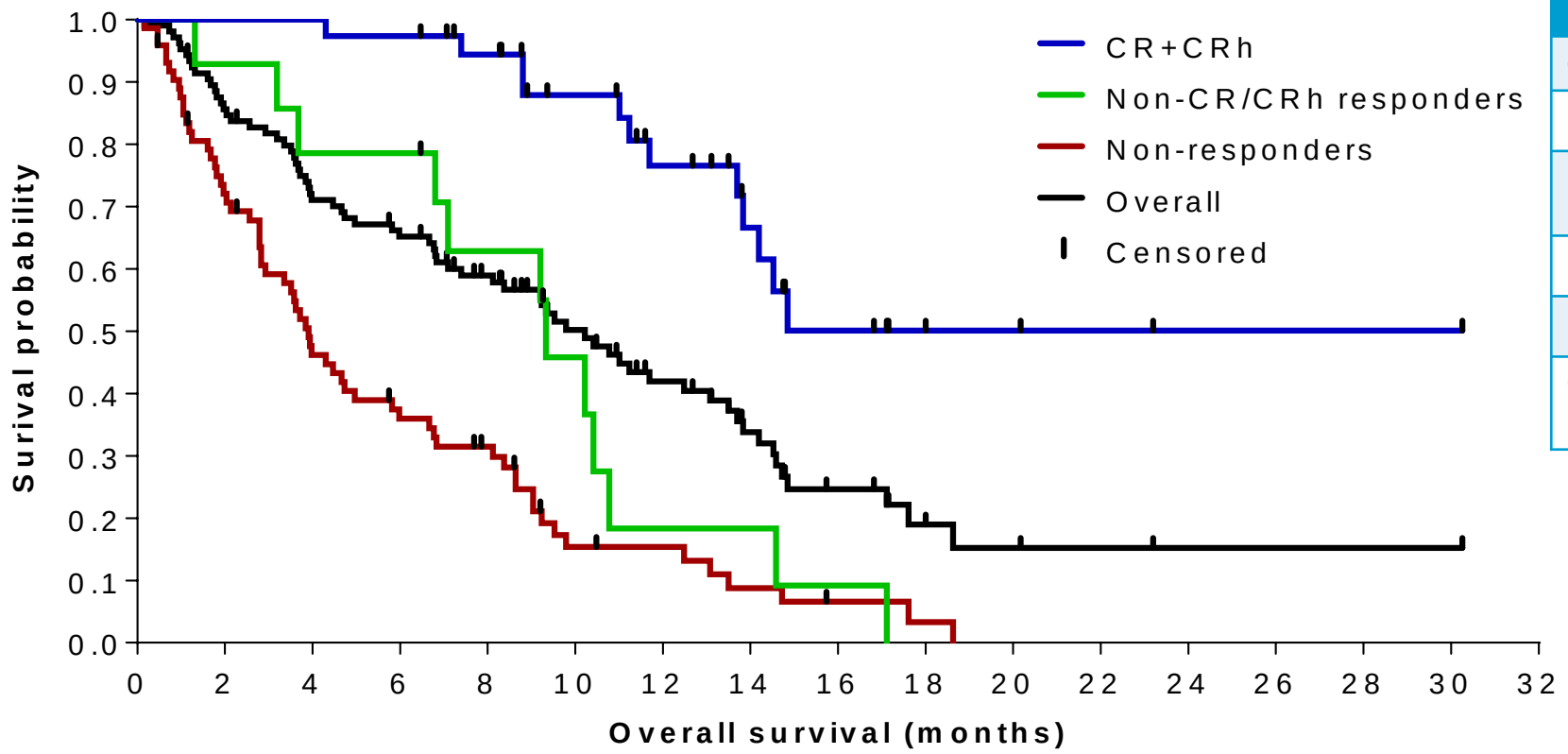
Duration of Treatment and Best Overall Response in Responders Primary R/R AML Set (n=52)



Duration of Response	CR+CRh	CR	Overall Response
Median (months)	8.2	9.3	6.5
Duration 6 months	59.3%	67.5%	55.0%
Duration 12 months	32.4%	41.2%	24.6%

Non-CR/CRh responders include CRi, CRp, and MLFS who are not CRh
Where first response and first CR/CRh are the same time point, only the first CR/CRh symbol is shown

Overall Survival by Best Response in R/R AML (n=125)



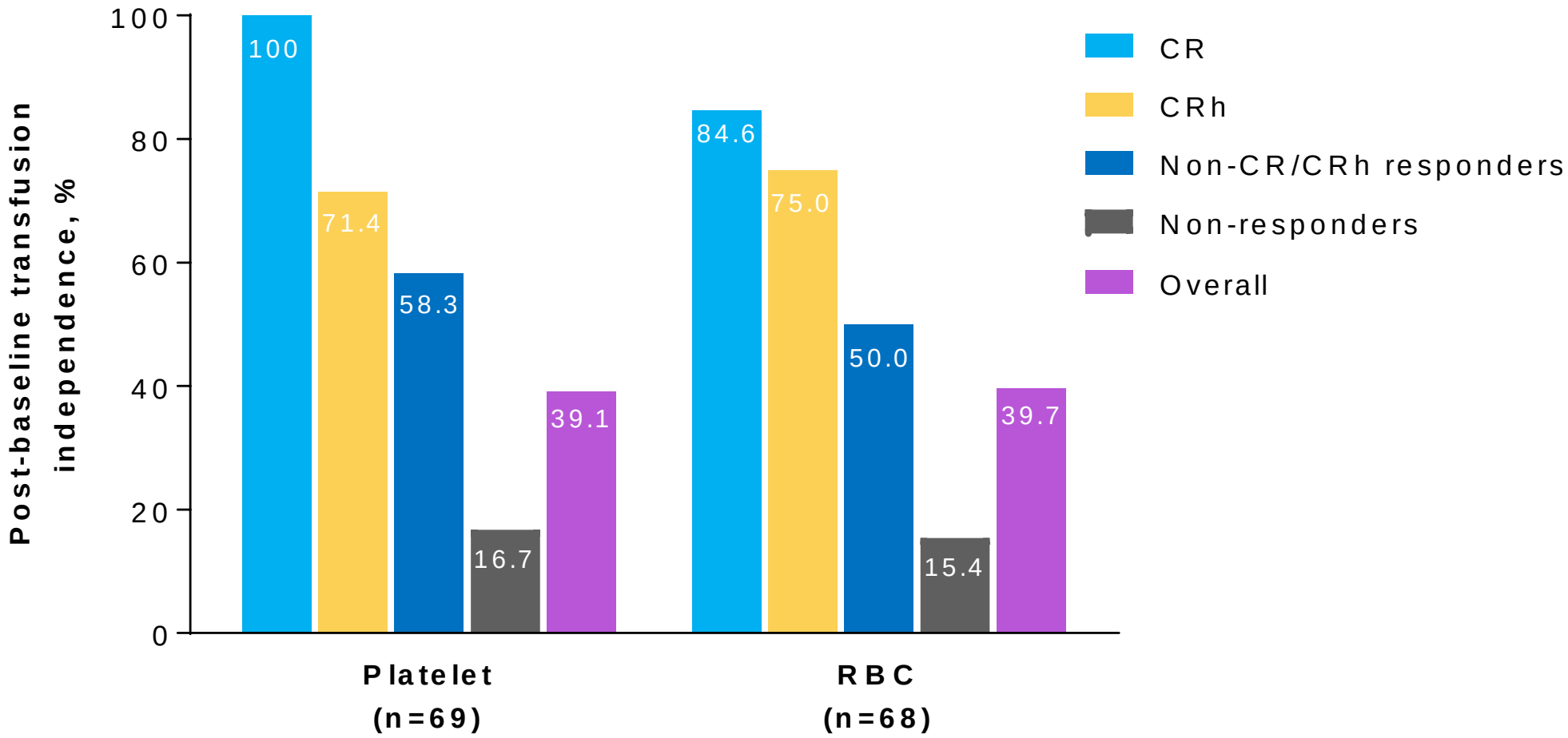
	Months
Overall Survival, median [95% CI]	
CR+CRh	**NE [13.8, NE]**
Non-CR/CRh responders	**9.3 [3.7, 10.8]**
Non-responders	**3.9 [2.8, 5.8]**
All	**8.8 [6.7, 10.2]**
Overall follow-up, median (range)	**14.8 (0.2–30.3)**

Number of patients at risk:

38	38	38	37	32	25	19	13	8	5	4	3	1	1	1	1	CR+CRh
14	13	11	11	8	5	2	2	1	0							Non-CR/CRh responders
73	51	32	24	19	8	7	4	2	1	0						Non-responders

Non-responders = all others including those with best responses of SD, PD or not evaluable

Transfusion Independence was Observed Across all Response Categories in Primary R/R AML Set Patients Who Were Dependent at Baseline



Post-baseline transfusion independence defined as no transfusion for at least one 56-day period.

Data cutoff: 12May2017.

Non-CR/CRh responders include CRi, CRp, and MLFS who are not CRh
CR, complete remission; CRh, CR with partial hematologic recovery; RBC, red blood cell

Exposure-adjusted Incidence of Febrile Neutropenia and Grade ≥ 3 Infections Primary R/R AML Set (n=125)

	Best Response				
	CR (n=27)	CRh (n=11)	Non-CR/CRh responders (n=14)	Non-responders (n=73)	Overall (n=125)
All Grade Febrile Neutropenia[a]	2.6 [1.2, 5.4]	3.8 [1.2, 11.8]	3.9 [1.3, 12.1]	14.2 [10.0, 20.0]	6.9 [5.1, 9.2]
Grade ≥ 3 Infections[b]	2.6 [1.2, 5.4]	6.4 [2.6, 15.3]	14.4 [8.0, 25.9]	23.0 [17.6, 30.2]	11.5 [9.2, 14.4]

Incidence rate reported as 100 patients / month [95% CI][c]

[a]Preferred term, including febrile bone marrow aplasia preferred term
[b]Based on MedDRA V20.0 System Organ Class of infection and infestations
[c]Calculated as total number of specific AEs / total person exposure time in months x 100 for all patients with the same best overall response

Data cutoff: 12May2017. CR, complete remission; CRh, CR with partial hematologic recovery

Response in Untreated AML and MDS

Characteristic	Untreated AML Arm 2[a] (n=34)	MDS Arm 3[b] (n=12)
Women / men, n	15 / 19	3 / 9
Age in years, median (range)	76.5 (64–87)	72.5 (52–78)
ECOG PS at screening, n (%) 0 1	 8 (23.5) 20 (58.8)	 4 (33.3) 6 (50.0)
Prior MDS, n (%)	18 (52.9)	NA
Response		
Overall Response Rate, n (%) [95% CI]	**19 (55.9) [37.9, 72.8]**	**11 (91.7) [61.5, 99.8]**
Duration of response, median [95% CI] months	9.2 [1.9, NE]	NE [2.3, NE]
Duration of CR, median [95% CI] months	NE [5.6, NE]	NE [2.8, NE]
Best response, n (%)		
CR	7 (20.6)	5 (41.7)
CRi/CRp	7 (20.6)	n/a
PR	1 (2.9)	n/a
MLFS/mCR	4 (11.8)	6 (50.0)
SD	10 (29.4)	0
PD	3 (8.8)	1 (8.3)
NA	2 (5.9)	0

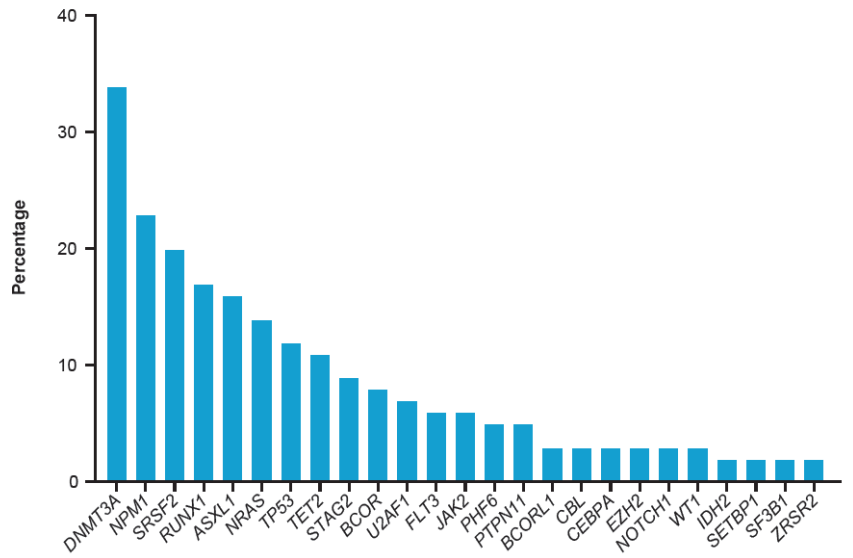
[a]Untreated AML patients not eligible for standard of care therapies in expansion Arm 2 and from dose escalation whose starting dose was 500 mg QD

[b]MDS patients in expansion Arm 3 and from dose escalation whose starting dose was 500 mg QD

Data cutoff: 12 May 2017. CR, complete remission; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; mCR, marrow CR; MLFS, morphologic leukemia-free state; NA, not assessed; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease

Baseline Mutation Analysis: Poster 2684, Stone RM et al.

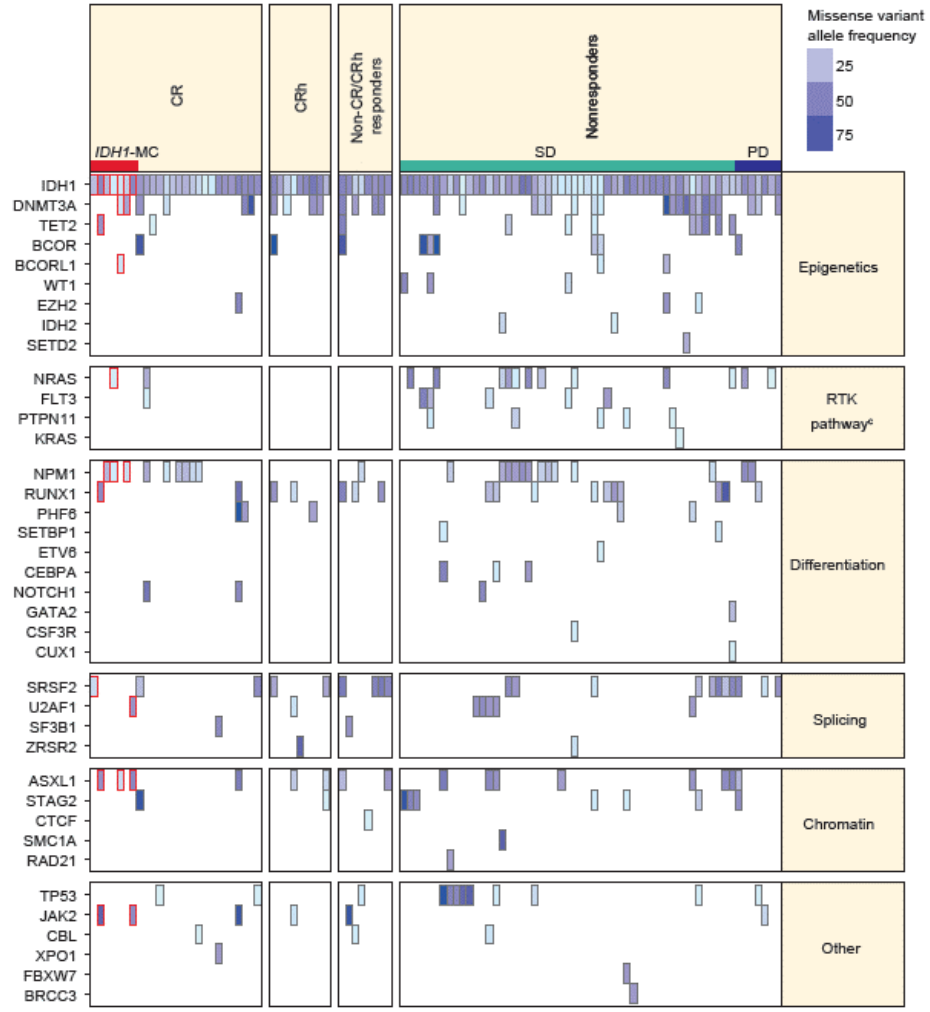
Figure 5. Most frequent (n≥2) co-occurring mutations at baseline in mIDH1 R/R AML patients (bone marrow)



Top five most frequently co-occurring mutations (*DNMT3A*, *NPM1*, *SRSF2*, *ASXL1*, *RUNX1*) in AG120-C-001 are consistent with published AML literature[6,11,12]

- No specific single gene mutation was significantly predictive of clinical response or resistance to treatment with ivosidenib in the R/R AML patients presented. However, RTK pathway mutations were associated with a lack of response

Figure 6. Co-occurring mutations at baseline (NGS, bone marrow, n=101)[a,b]



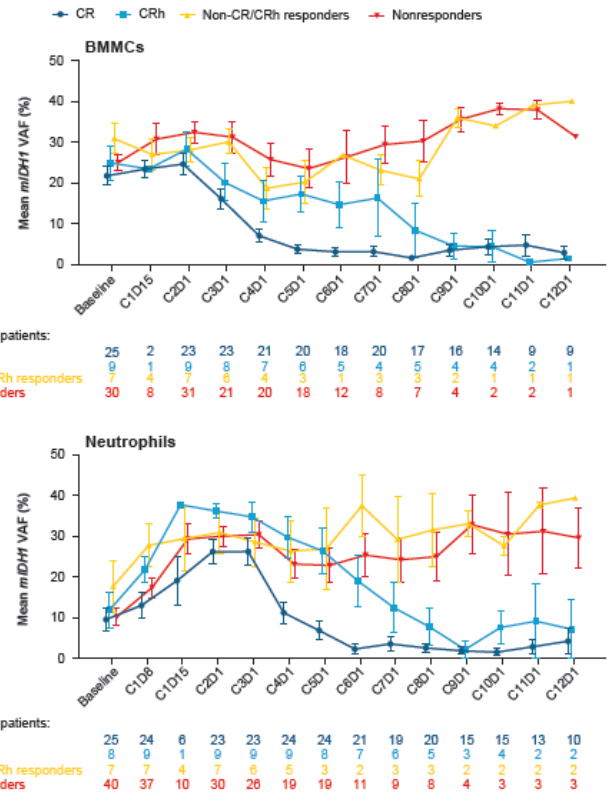
[a]In this heatmap, each column corresponds to a single R/R AML patient, arranged by best overall response to ivosidenib. Detected known or likely oncogenic mutations are denoted by boxes and shaded by VAF

[b]No specific single gene mutation was significantly predictive of clinical response or resistance to treatment with ivosidenib in the R/R AML patients presented

[c]RTK pathway genes assayed in this 95-gene NGS Rapid Heme Panel include: *FLT3* (TKD and ITD), *KRAS, NRAS, BRAF, KIT, MAP2K1, PTPN11*, and *RET*. In this dataset, RTK pathway mutations were detected in *NRAS, FLT3* (TKD only), *PTPN11*, and *KRAS*. Mutations in the RTK pathway occurred less frequently in patients who achieved CR or CRh as a best response relative to those who did not achieve CR or CRh (p=0.003 by Fisher's exact test)

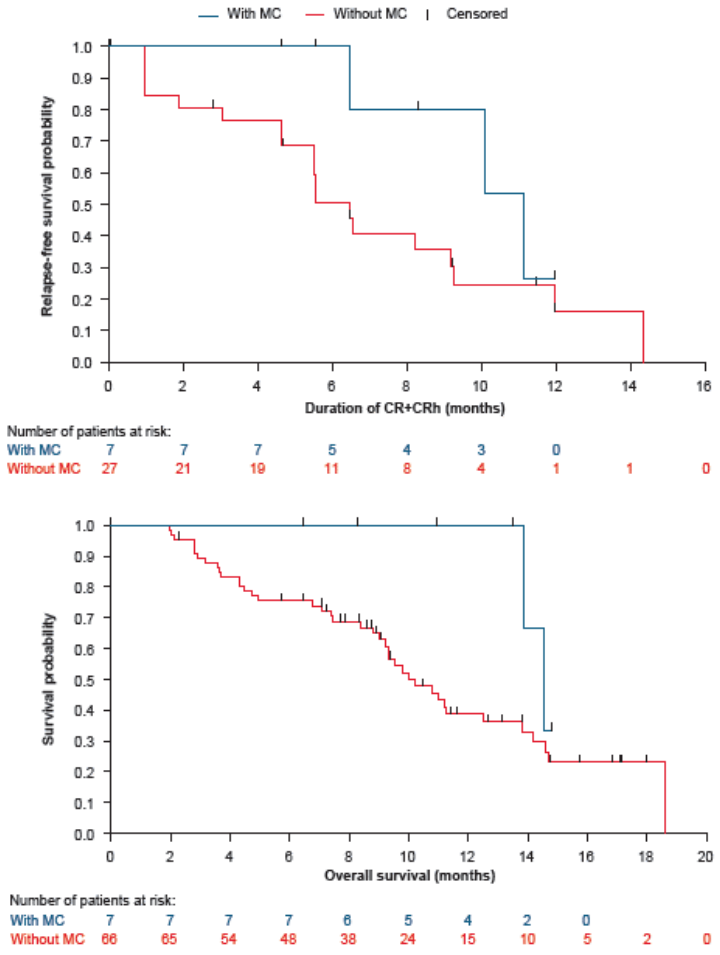
Longitudinal Mutant IDH1 Analysis: Poster 2684, Stone RM et al.

Figure 3. Ivosidenib treatment reduced *mIDH1* VAF in BMMCs and neutrophils from patients with best overall response of CR or CRh (R/R AML)



Mean ± SE is presented
Clinical response was assessed by the investigator according to the modified 2003 International Working Group criteria
CRh was derived by the sponsor and defined as CR except absolute neutrophil count >0.5×10⁹/L (500/μL) *and* platelet count >50×10⁹/L (50,000/μL)
Non-CR/CRh responders include CRi/CRp and MLFS not meeting criteria for CRh, and PR; nonresponders include SD and PD
Numbers below the graph represent number of patients with *mIDH1* VAF data at each visit
CRh = CR with partial hematologic recovery; CRi = CR with incomplete hematologic recovery; CRp = CR with incomplete platelet recovery; MLFS = morphologic leukemia-free state; PD = progressive disease; PR = partial response; SD = stable disease

Figure 4. Patients with *IDH1*-MC had improved duration of CR+CRh and overall survival (R/R AML, BMMCs)



Duration of CR+CRh = date of first documented CR/CRh to date of first documented confirmed relapse or death
Overall survival = time from first dose to the date of death due to any cause
Statistical testing not provided owing to small sample size and low event rate

- Ivosidenib reduced *mIDH1* allele burden in both BMMCs and neutrophils in R/R AML patients in the expansion phase who achieved CR or CRh
- MRD-negative CR was observed in 7 of 25 (28%) R/R AML patients who achieved CR
  - Patients with MRD-negative CR had improved duration of CR compared to patients with CR with persistent MRD in this limited dataset
  - Patients with MRD-negative CR had improved overall survival compared to all other R/R AML patients with persistent MRD

Data cutoff: 12May2017. BMMCs, bone marrow mononuclear cells; MC, mutation clearance

Conclusions

- Ivosidenib was well tolerated; most AEs were grade 1–2 in severity
- In patients with R/R AML, most of whom had received multiple prior AML treatments, ivosidenib induced durable responses, with CR+CRh and ORR rates of 30.4% and 41.6% respectively, and corresponding durations of 8.2 and 6.5 months, with additional benefits:
  - Transfusion independence across best response categories
  - Decreased frequency of febrile neutropenia and infections in responders
- Durable responses were observed in patients with untreated AML, with CR and ORR rates of 20.6% and 55.9% and corresponding durations of NE and 9.2 months
- Ongoing AML studies:
  - Phase 1 of ivosidenib or enasidenib with AZA: presented this morning
  - AGILE: Global Phase 3, ivosidenib+AZA vs placebo+AZA in 1st-line AML
  - Phase 1 of ivosidenib or enasidenib in combination with standard AML induction and consolidation therapy, to be presented next

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