Ivosidenib (AG-120) induces durable remissions and transfusion independence in patients with IDH1-mutant untreated AML: Results from a phase 1 dose escalation and expansion study

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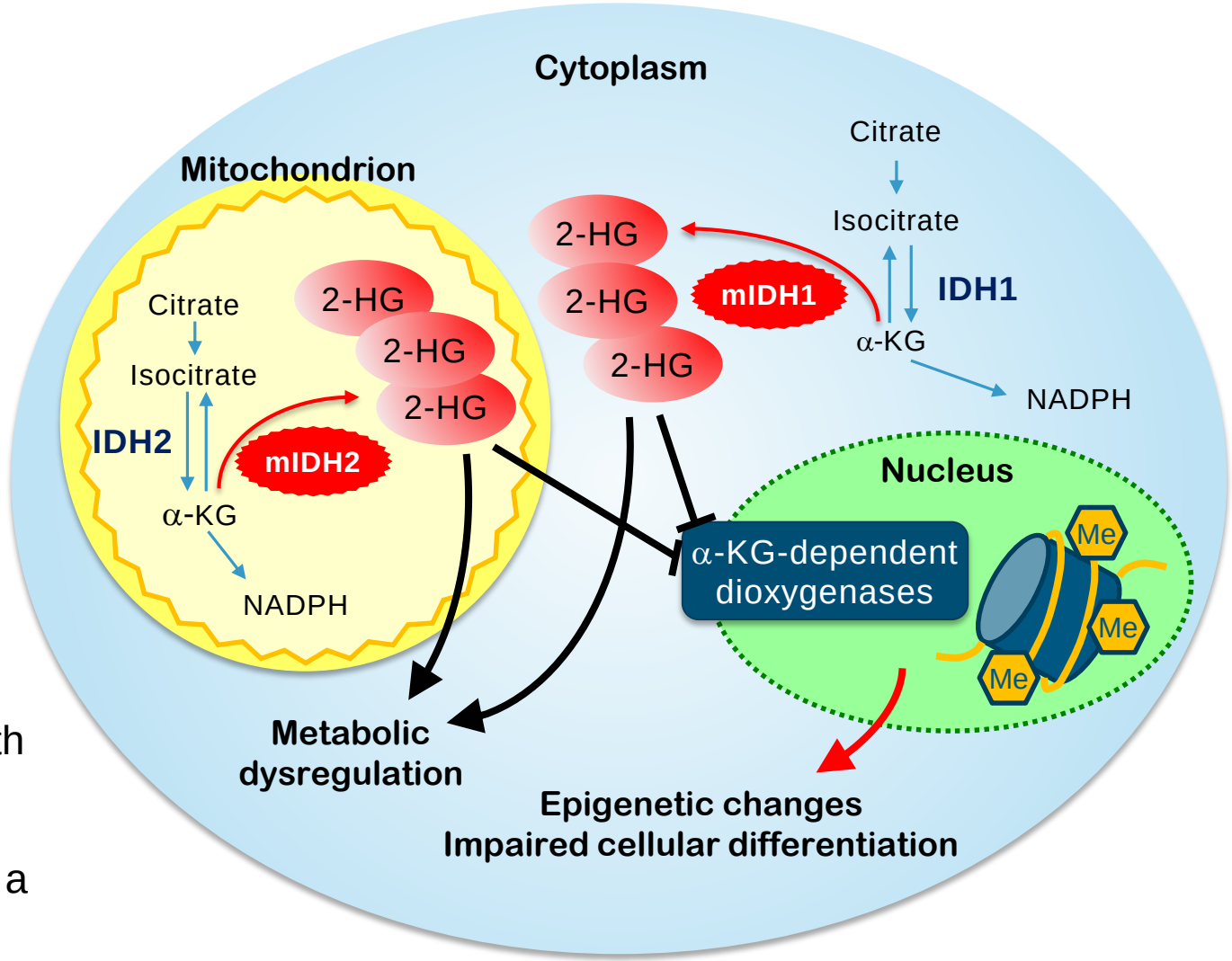
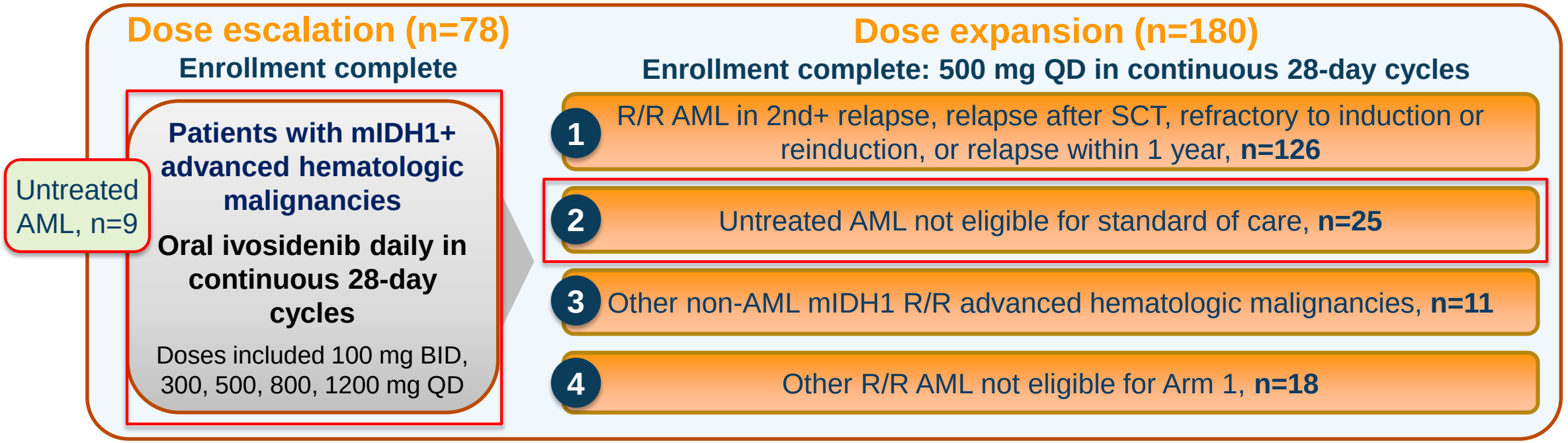
Isocitrate dehydrogenase (IDH) mutations as a target in AML

- 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 in ~6–10% of patients with AML
- **Ivosidenib (AG-120):** a first-in-class, oral, potent, reversible, targeted inhibitor of the mIDH1 enzyme
  - FDA approved on July 20, 2018 for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation as detected by an FDA-approved test
  - 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



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 co-mutations and m*IDH1* variant allele frequency (VAF)

Analysis set and efficacy endpoints

Analysis set

- Untreated AML 500 mg (n=34):
  - All patients with untreated AML whose ivosidenib starting dose was 500 mg QD

Efficacy endpoints (untreated AML)

- n=33, based on patients confirmed positive for mIDH1 by the companion diagnostic test
- Primary efficacy endpoint: CR+CRh. Additional endpoints: ORR, CR, duration of response, time to response
  - ORR = CR + CRi + CRp + PR + MLFS

Response definitions[1]

Response	Bone marrow blasts (%)	ANC (/µL)	Platelets (/µL)
CR	<5	>1000	>100,000
CRh	<5	>500	>50,000
CRi	<5	<1000	>100,000
CRp	<5	>1000	<100,000
MLFS	<5	-	-
PR	5–25 (>50% reduction)	>1000	>100, 000

IWG responses, including CR, reported by Investigator. CRh derived by Sponsor
CR, complete response; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; PR, partial response; ORR, objective response rate

1. Modified IWG 2003 criteria. Cheson B et al. *J Clin Oncol* 2013;21:4642-9

Disposition and treatment duration

	Untreated AML 500 mg (n=34)
Ongoing treatment, n (%)	8 (23.5)
Discontinued treatment, n (%)	26 (76.5)
Progressive disease	12 (35.3)
Adverse event	5 (14.7)
Hematopoietic stem cell transplant	3 (8.8)
Withdrawal of consent	4 (11.8)
Death	1 (2.9)
Investigator decision	1 (2.9)
In post-transplant follow-up, n (%)	2 (5.9)
Discontinued study, n (%)	24 (70.6)
Treatment duration in months, median (range)	4.3 (0.3–35.1)

Baseline characteristics: Untreated AML 500 mg (n=34)

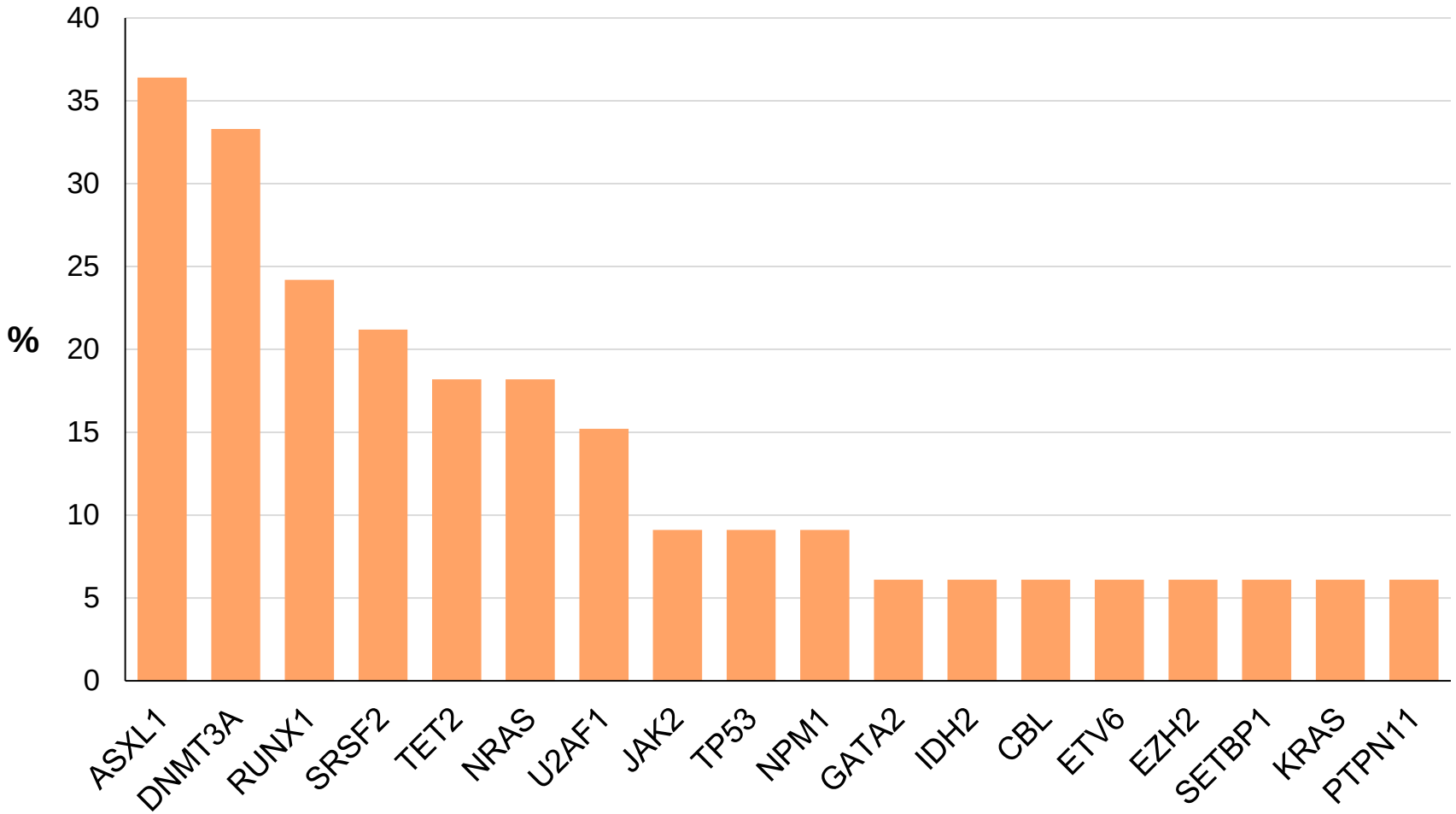
Characteristic	Untreated AML 500 mg (n=34)[a]
Women / men, n	15 / 19
Age in years, median (range)	76.5 (64–87)
Age category, n (%)	
60 to <75	15 (44.1)
≥75	19 (55.9)
ECOG PS at baseline, n (%)	
0	8 (23.5)
1	20 (58.8)
2	5 (14.7)
3	1 (2.9)

Characteristic	Untreated AML 500 mg (n=34)[a]
Nature of AML, n (%)	
De novo	7 (20.6)
Secondary	27 (79.4)
History of MDS	18 (52.9)
History of MPD	4 (11.8)
Treatment-related	4 (11.8)
Other	1 (2.9)
Prior hypomethylating agent, n (%)	14 (41.2)
Cytogenetic risk status by investigator, n (%)	
Intermediate	24 (70.6)
Poor	9 (26.5)
Unknown	1 (2.9)

[a]One patient enrolled in dose escalation was positive for the IDH1-D54N mutation by local testing and was not positive for the IDH1-R132 mutation by the companion diagnostic test

ECOG PS = Eastern Cooperative Oncology Group Performance Status; MDS = myelodysplastic syndrome; MPD = myeloproliferative disease

Baseline co-mutation rates: Untreated AML 500 mg (n=33)[a]



Assessed using next-generation sequencing panel for hematologic malignancies. Mutations occurring in ≥2 patients shown

[a]One patient enrolled in dose escalation was positive for the IDH1-D54N mutation by local testing and was not positive for the IDH1-R132 mutation by the companion diagnostic test

AEs regardless of causality: Untreated AML 500 mg (n=34)

Most common AEs (≥20% of patients)

	Any grade, n (%)	Grade ≥3, n (%)
Diarrhea	18 (52.9)	2 (5.9)
Fatigue	15 (44.1)	3 (8.8)
Nausea	13 (38.2)	2 (5.9)
Decreased appetite	11 (32.4)	1 (2.9)
Leukocytosis	9 (26.5)	1 (2.9)
Anemia	9 (26.5)	4 (11.8)
Edema peripheral	9 (26.5)	0
Thrombocytopenia	8 (23.5)	5 (14.7)
Dyspnea	8 (23.5)	1 (2.9)
Hypomagnesemia	8 (23.5)	0
Dizziness	8 (23.5)	0
Arthralgia	7 (20.6)	1 (2.9)
Hypokalemia	7 (20.6)	1 (2.9)
Constipation	7 (20.6)	1 (2.9)
Abdominal pain	7 (20.6)	1 (2.9)
Insomnia	7 (20.6)	0

Most common SAEs (≥5% patients)

	SAE, n (%)
IDH differentiation syndrome	5 (14.7)
Febrile neutropenia	3 (8.8)
Pneumonia	3 (8.8)
ECG QT prolonged	2 (5.9)

AEs of interest: Untreated AML 500 mg (n=34)

- **Leukocytosis[a]**
  - Grade ≥3 leukocytosis reported in 1/34 patients (3%)
  - Not fatal
- **ECG QT prolongation**
  - All grade reported in 6/34 patients (17.6%)
  - Grade ≥3 reported in 3/34 patients (8.8%)
  - Study drug was reduced in 2 patients and held in 4 patients
  - None were fatal
  - QT-prolonging medications such as antifungals and fluoroquinolone anti-infectives were allowed on study with monitoring
- **Differentiation syndrome (DS)**
  - All grade reported in 6/34 patients (17.6%)
  - Resolved in all 6 patients
  - Grade ≥3 DS in 3 (8.8%)
  - 2/6 patients had co-occurring leukocytosis
  - Study drug held in 3 patients (8.8%)
  - No instances of DS led to dose reduction, permanent treatment discontinuation, or death
  - Best response in patients with DS: 3 CR, 2 CRh, 1 NA

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

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

Data cutoff: 11May2018 NA = not assessed

Response: Untreated AML 500 mg (n=33)

	Untreated AML 500 mg (n=33)
CR+CRh rate, n (%) [95% CI]	**14 (42.4) [25.5, 60.8]**
Time to CR/CRh, median (range), months	2.8 (1.9–12.9)
Duration of CR/CRh, median [95% CI], months	NE [6.5, NE]
CR rate, n (%) [95% CI]	10 (30.3) [15.6, 48.7]
Time to CR, median (range), months	2.8 (1.9–4.6)
Duration of CR, median [95% CI], months	NE [4.2, NE]
CRh rate, n (%) [95% CI]	4 (12.1) [3.4, 28.2]
Time to CRh, median (range), months	3.7 (1.9–12.9)
Duration of CRh, median [95% CI], months	8.3 [6.5, NE]

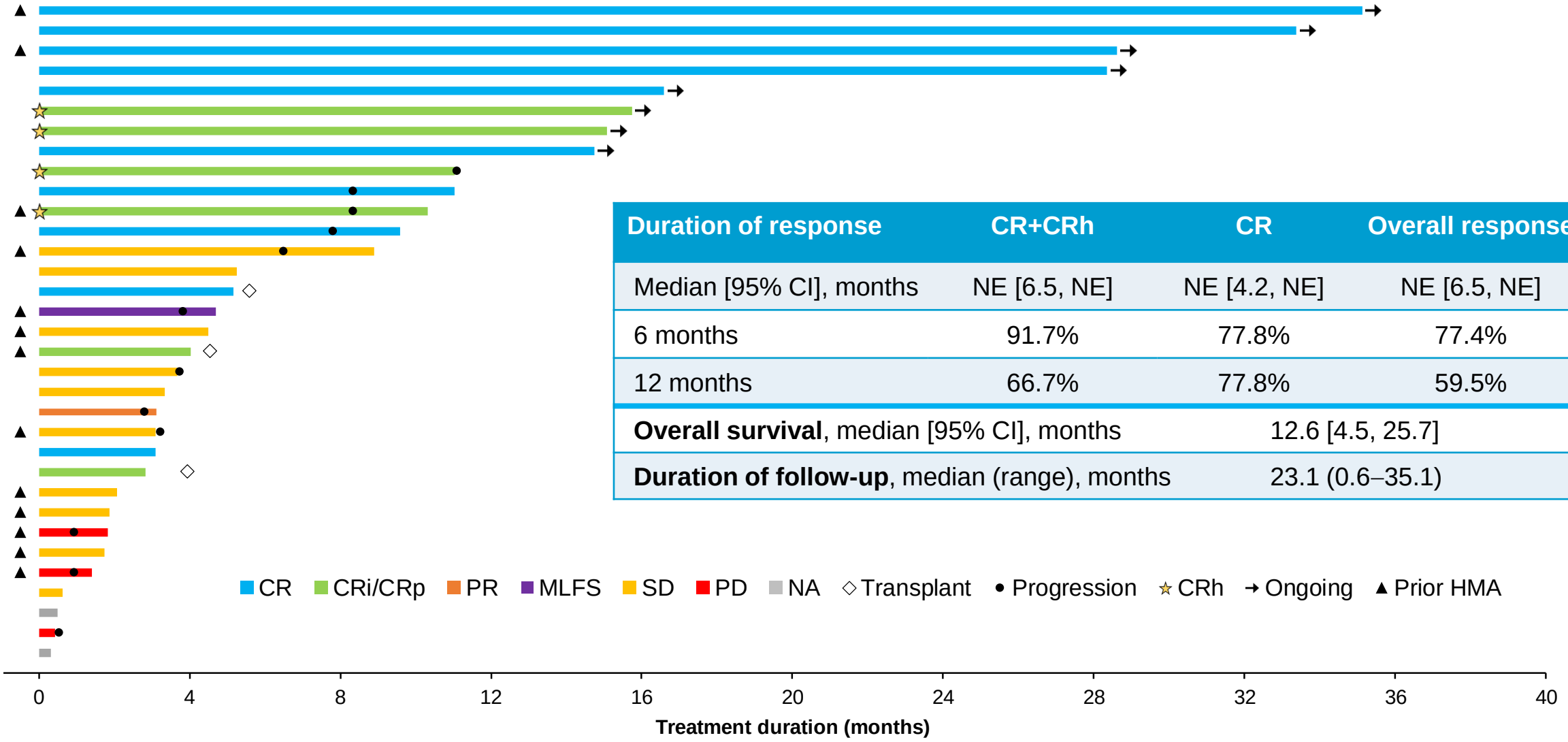
	Untreated AML 500 mg (n=33)
ORR[a] by IWG, n (%) [95% CI]	**19 (57.6) [39.2, 74.5]**
Time to first response, median (range), months	1.9 (0.9–3.6)
Duration of response, median [95% CI], months	NE [6.5, NE]
Best response by IWG, n (%)	
CR	10 (30.3)
CRi or CRp	6 (18.2)
PR	1 (3.0)
MLFS	1 (3.0)
SD	10 (30.3)
PD	3 (9.1)
NA	2 (6.1)

CRh = 4 patients with investigator-assessed responses of CRi/CRp

[a]ORR includes CR, CRi/CRp, MLFS, and PR

Data cutoff: 11May2018 NE = not estimable; PD = progressive disease; PR = partial response; SD = stable disease

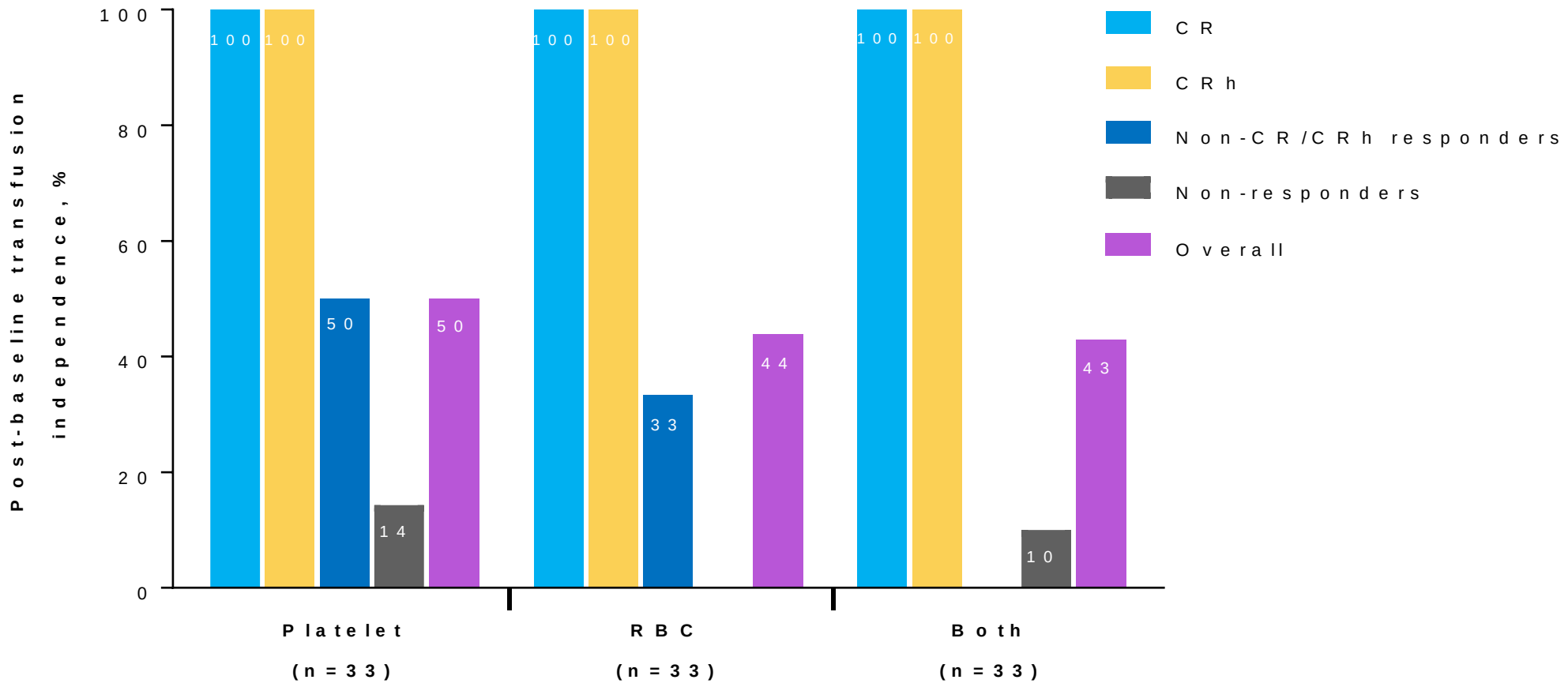
Duration of treatment and best overall response: Untreated AML 500 mg (n=33)



Duration of response	CR+CRh	CR	Overall response
Median [95% CI], months	NE [6.5, NE]	NE [4.2, NE]	NE [6.5, NE]
6 months	91.7%	77.8%	77.4%
12 months	66.7%	77.8%	59.5%
Overall survival, median [95% CI], months		12.6 [4.5, 25.7]	
Duration of follow-up, median (range), months		23.1 (0.6–35.1)	

Data cutoff: 11May2018 HMA = hypomethylating agent

Transfusion independence across response categories in patients who were dependent at baseline: Untreated AML 500 mg (n=33)



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

IDH1 mutation clearance: Untreated AML 500 mg (n=30)

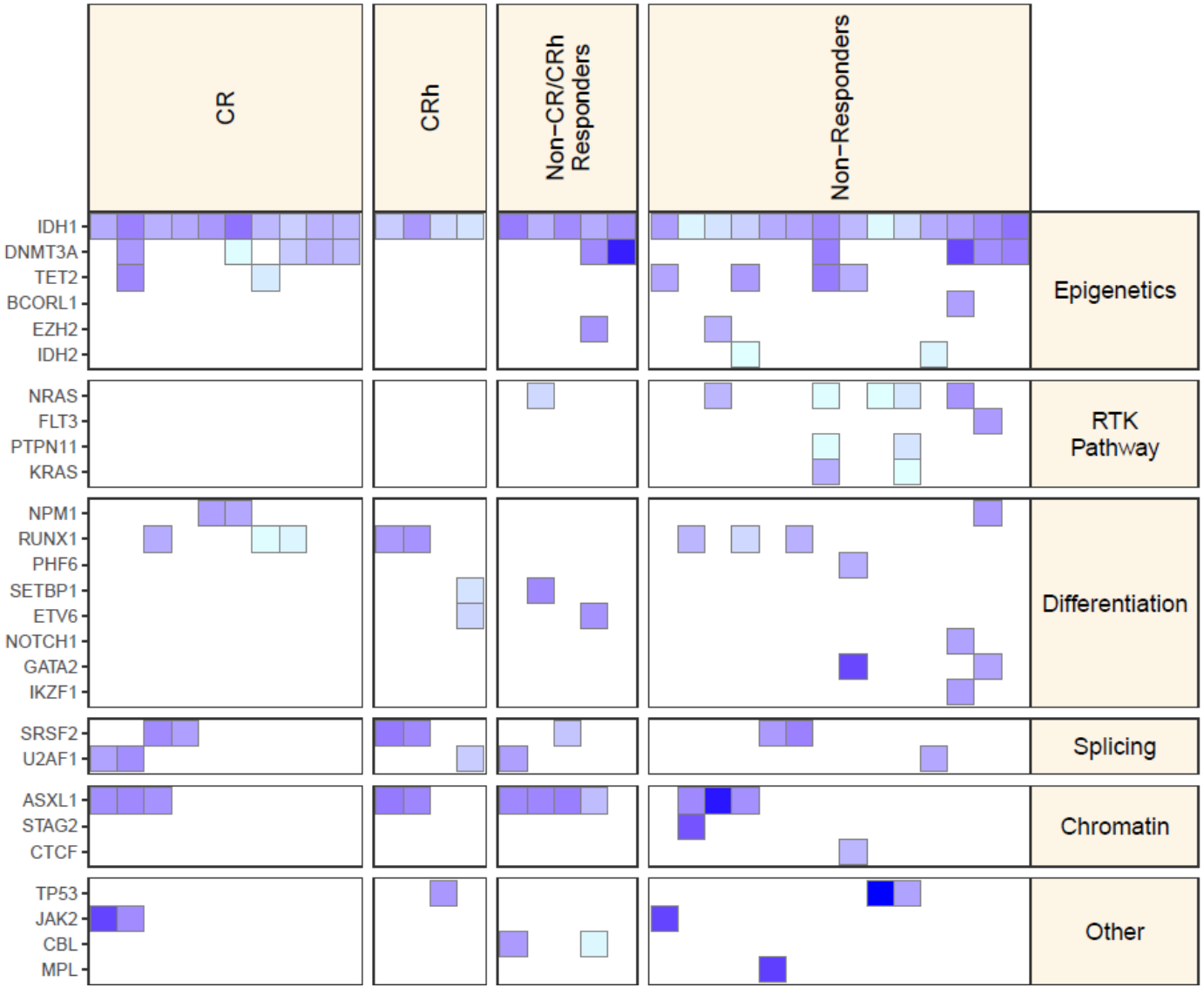
Ivosidenib induced *IDH1* mutation clearance[a] in BMMCs

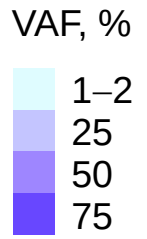
	n	*IDH1* mutation clearance n (%)
CR+CRh	14	9 (64)
CR	10	5 (50)
CRh	4	4 (100)
Others	16	0
Non-CR+CRh responders	5	0
Non-responders	11	0
p-value[b]		<0.001

[a]Defined as a reduction in m*IDH1* variant allele frequency to below the limit of detection of 0.02–0.04% ($2–4\times10^{-4}$) by digital PCR for at least one on-study time point

[b]p-value based on Fisher's exact test comparing *IDH1* mutation clearance in patients with best overall response of CR+CRh to patients with other responses (non-CR+CRh responders and non-responders)

Most frequent baseline co-occurring mutations and mutational burden by clinical response (n=33)





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

RTK = receptor tyrosine kinase

Conclusions

- These patients with mIDH1 untreated AML represent a molecularly defined elderly population with poor prognosis
  - Secondary AML 79%
  - Prior HMA exposure 41%
  - ≥75 years of age 56%
- Ivosidenib induced durable responses
  - CR+CRh rate 42%, median duration not estimable, lower bound of 95% CI 6.5 months
  - ORR 58%, median duration not estimable
- Ivosidenib was well tolerated
  - AEs of interest were managed with standard-of-care treatments and brief ivosidenib dose interruptions as required
  - Low rate of grade ≥3 AEs, including febrile neutropenia
- Transfusion independence across response categories
- Ivosidenib induced *IDH1* mutation clearance in 5/10 patients with CR and all 4 with CRh

Ongoing AML studies

- Ongoing and future AML studies:
  - Phase 1, first-line ivosidenib+AZA or enasidenib+AZA in patients not eligible for intensive chemotherapy[1]
  - AGILE: global, phase 3, first-line ivosidenib+AZA vs placebo+AZA in patients not eligible for intensive chemotherapy[2]
  - Phase 1 ivosidenib or enasidenib in combination with standard AML induction and consolidation therapy (previous presentation 560 in this session; Stein E et al.)[3]
  - HOVON 150/AMLSG: international, randomized, first-line ivosidenib or enasidenib in combination with induction and consolidation therapy followed by maintenance therapy

Acknowledgment

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1. DiNardo CD et al. *ASCO 2018*: Poster 7042; **2.** Stein EM et al. *ASCO 2018*: Poster TPS7074; **3.** Stein EM et al. *ASH 2018*: Oral presentation 560.

AZA = azacitidine

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