Ivosidenib (IVO; AG-120) in mutant IDH1 relapsed/refractory acute myeloid leukemia (R/R AML): Results of a phase 1 study

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ORIGINAL ARTICLE

Durable Remissions with Ivosidenib in *IDH1*-Mutated Relapsed or Refractory AML

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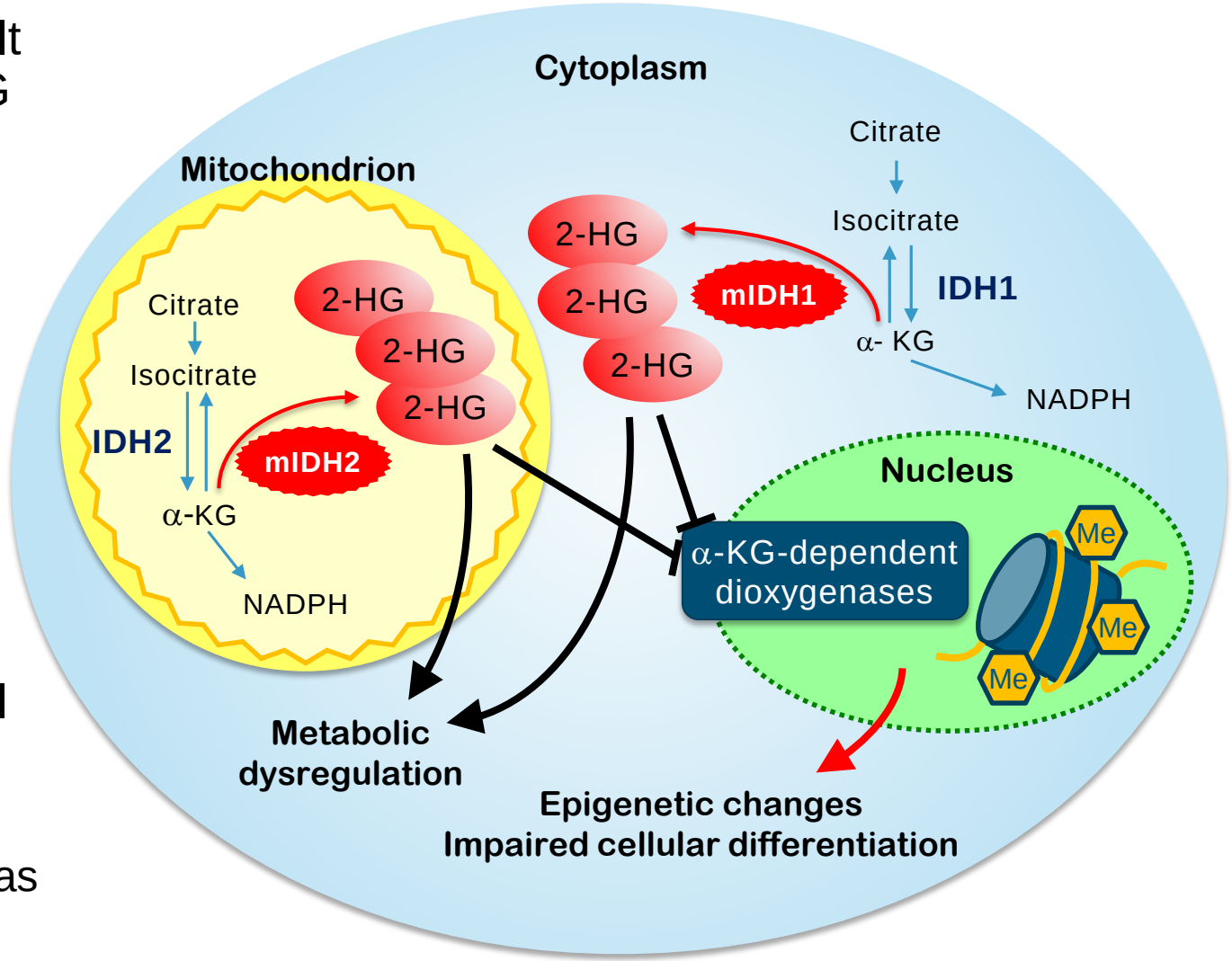
Isocitrate Dehydrogenase (IDH) Mutations as a Target in AML

- 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)

ClinicalTrials.gov NCT02074839. DLTs, dose limiting toxicities; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose

Primary Efficacy Endpoint and Analysis Set

Analysis set

- R/R AML 500 mg Set (n=179):
  - All patients with R/R AML whose ivosidenib starting dose was 500 mg QD

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 complete remission (CR), reported by Investigator. CR with partial hematologic recovery (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)	R/R AML 500 mg (n=179)
Ongoing treatment, n (%)	35 (13.6)	17 (9.5)
Discontinued treatment, n (%)	223 (86.4)	162 (90.5)
Progressive disease	124 (48.1)	92 (51.4)
Adverse event	35 (13.6)	27 (15.1)
Bone marrow transplant	25 (9.7)	17 (9.5)
Death	16 (6.2)	10 (5.6)
Withdrawal of consent	14 (5.4)	8 (4.5)
Investigator decision	7 (2.7)	6 (3.4)
Other	2 (0.8)	2 (1.1)
Discontinued study, n (%)	191 (74.0)	137 (76.5)
In post-transplant follow-up, n (%)	10 (3.9)	7 (3.9)
In survival follow-up, n (%)	22 (8.5)	18 (10.1)
Treatment duration in months, median (range)	3.9 (0.1–39.5)	3.9 (0.1–39.5)

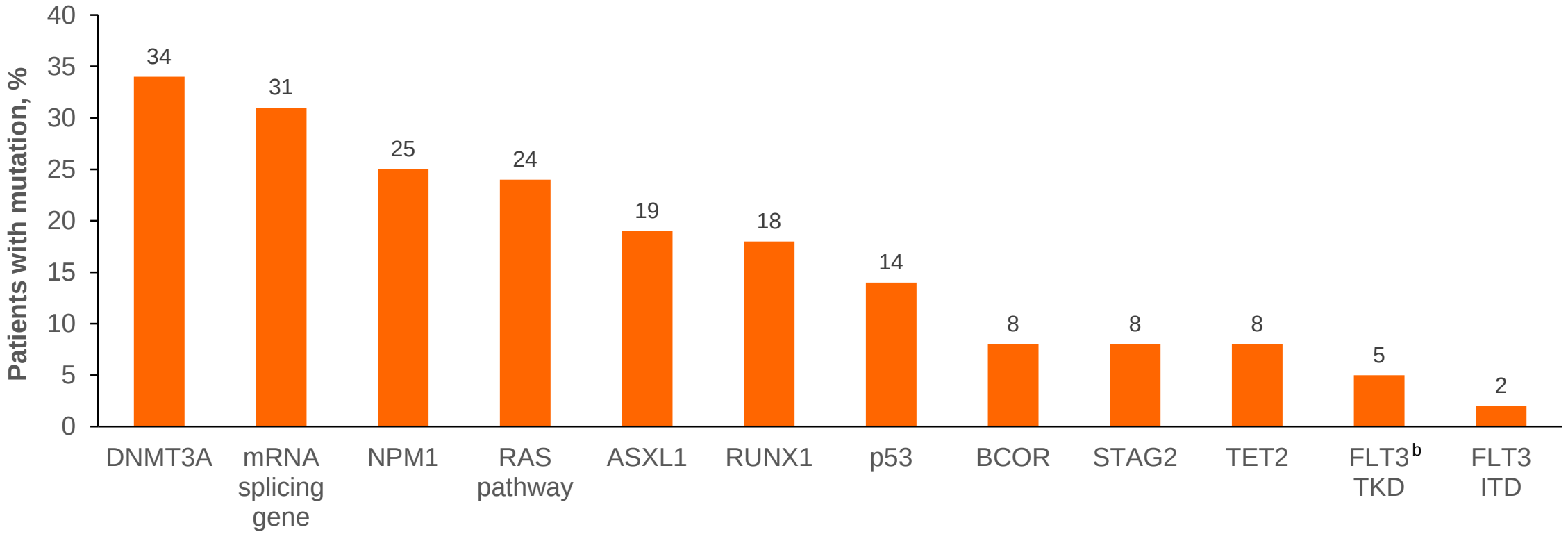
Baseline Characteristics: R/R AML 500 mg (n=179)

Characteristic	R/R AML 500 mg (n=179)
Women / men, n	89 / 90
Age in years, median (range)	67.0 (18–87)
Age category, n (%)	
< 60	47 (26.3)
60 to < 75	92 (51.4)
≥ 75	40 (22.3)
ECOG PS at baseline, n (%)	
0	36 (20.1)
1	99 (55.3)
2	42 (23.5)
3	2 (1.1)
De novo AML, n (%)	120 (67.0)
Secondary AML, n (%)	59 (33.0)

Characteristic	R/R AML 500 mg (n=179)
No. of prior therapies, median (range)	2.0 (1–6)
Prior AML therapy outcomes[a], n (%)	
Relapsed after transplant	43 (24.0)
In 2nd or later relapse	26 (14.5)
Refractory to initial induction/reinduction therapy	106 (59.2)
Relapsed ≤ 1 year of initial therapy	17 (9.5)
In first relapse	15 (8.4)
Other	5 (2.8)
Cytogenetic risk status by investigator, n (%)	
Intermediate	105 (58.7)
Poor	50 (27.9)
Unknown/missing	24 (13.4)

Data cutoff: 10Nov2017 [a]Not mutually exclusive, patients may be in more than one category

Baseline Comutation Rates: R/R AML 500 mg (n=179)[a]



mRNA splicing genes include *SF3B1*, *SRSF2*, *U2AF1*, *U2AF2*, and *ZRSR2*
RAS pathway includes *MAP2K4*, *NRAS*, *PTPN11*, *KRAS*, *NF1*, *BRAF*, and *KIT*

Data cutoff: 10Nov2017 [a]Assessed in 178 patients. [b]Includes 1 patient with a juxtamembrane domain point mutation

Most Common AEs Regardless of Causality (≥ 20%) R/R AML 500 mg (n=179)

R/R AML 500 mg Set (n=179)	Any grade, n (%)	Grade ≥ 3, n (%)
Any AE	179 (100)	148 (82.7)
Diarrhea	60 (33.5)	4 (2.2)
Leukocytosis	56 (31.3)	14 (7.8)
Nausea	56 (31.3)	1 (0.6)
Febrile neutropenia	52 (29.1)	52 (29.1)
Fatigue	51 (28.5)	3 (1.7)
Electrocardiogram QT prolonged	46 (25.7)	18 (10.1)
Dyspnea	44 (24.6)	7 (3.9)
Edema peripheral	43 (24.0)	0 (0.0)
Pyrexia	41 (22.9)	2 (1.1)
Anemia	40 (22.3)	36 (20.1)
Cough	38 (21.2)	1 (0.6)

AEs of Interest: R/R AML 500 mg (n=179)

- **Leukocytosis[a]**
  - Grade ≥ 3 leukocytosis reported in 14/179 patients (8%)
  - Managed with hydroxyurea
  - None were fatal
- **ECG QT prolongation**
  - Grade ≥ 3 QT prolongation reported in 18/179 patients (10%)
  - Study drug was reduced in 2 patients and held in 13 patients (all grades)
  - None were fatal
  - QT prolonging medications such as antifungals and fluoroquinolone anti-infectives were allowed on study with monitoring
- **IDH differentiation syndrome (IDH-DS)**
  - All grade reported in 19/179 patients (10.6%)
  - Resolved in 17 patients, ongoing in 2 patients at data cut
  - Grade ≥ 3 IDH-DS in 9 (5.0%)
  - 7/19 IDH-DS patients had co-occurring leukocytosis
  - Study drug held in 6 patients (3.4%)
  - No instances of IDH-DS led to dose reduction, permanent treatment discontinuation, or death
  - Managed with corticosteroids and diuretics, and hydroxyurea if accompanied by leukocytosis
  - Best response for the 19 patients with IDH-DS:

Best Response	CR	CRh	CRi/CRp	MLFS	SD	NE
n=19	5	0	3	2	8	1

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: 10Nov2017

CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; NE, not evaluable; SD, stable disease

Response in R/R AML 500 mg (n=179)

	R/R AML 500 mg (n=179)
CR+CRh rate, n (%) [95% CI]	**57 (31.8) [25.1, 39.2]**
Time to CR/CRh, median (range) months	2.0 (0.9, 5.6)
Duration of CR/CRh, median [95% CI] months	8.2 [5.6, 12.0]
CR rate, n (%) [95% CI]	43 (24.0) [18.0, 31.0]
Time to CR, median (range) months	2.8 (0.9, 8.3)
Duration of CR, median [95% CI] months	10.1 [6.5, 22.2]
CRh rate, n (%)	14 (7.8)
Duration of CRh, median [95% CI] months	3.6 [1.0, 5.5]

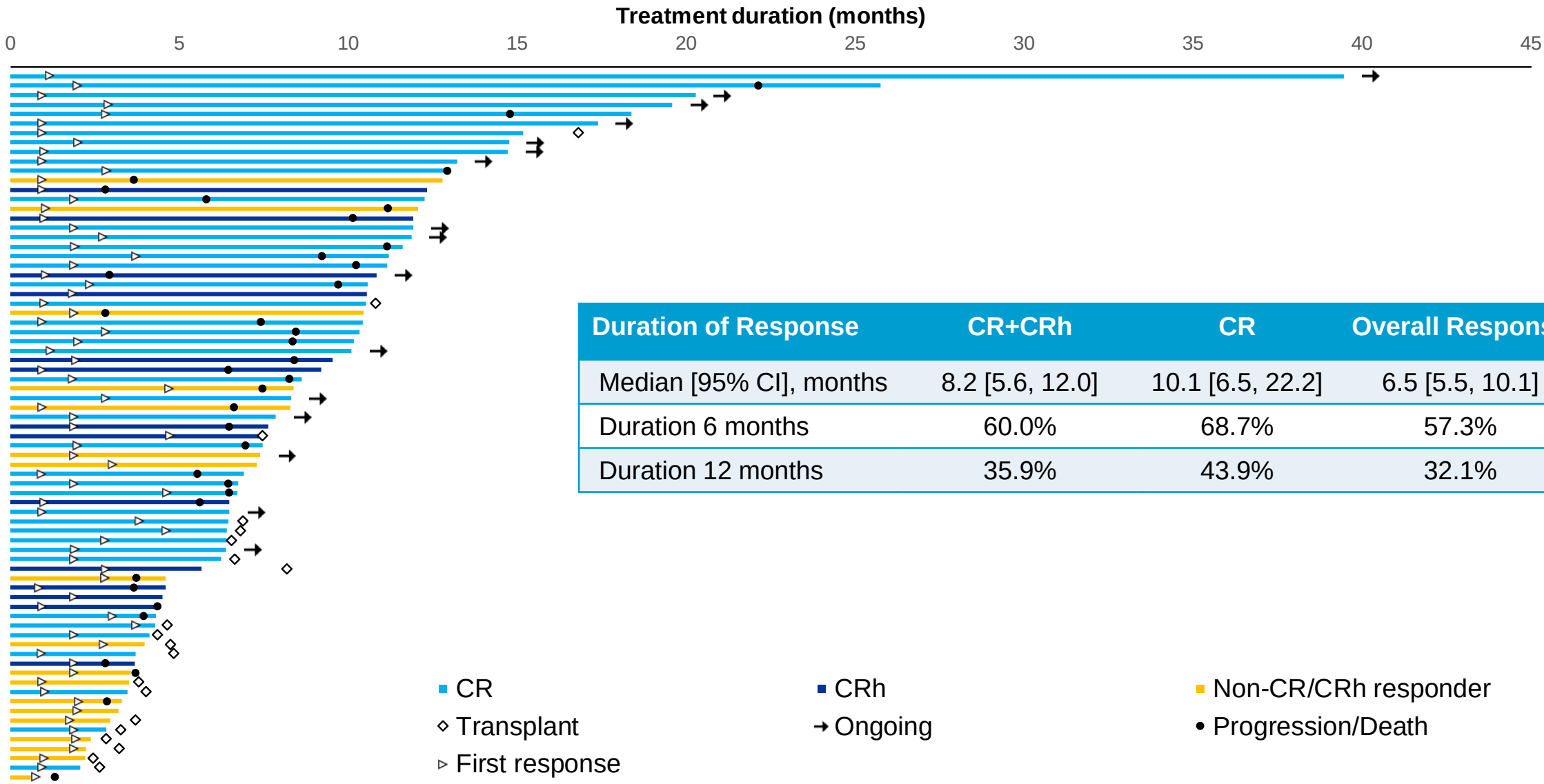
	R/R AML 500 mg (n=179)
Overall Response Rate, n (%) [95% CI]	**75 (41.9) [34.6, 49.5]**
Time to first response, median (range) months	1.9 (0.8, 4.7)
Duration of response, median [95% CI] months	6.5 [5.5, 10.1]
Best response, n (%)	
CR	43 (24.0)
CRi or CRp	21 (11.7)
MLFS	11 (6.1)
SD	68 (38.0)
PD	15 (8.4)
NA	21 (11.7)

CRh = 9 patients with investigator-assessed responses of CRi/CRp and 5 with MLFS

Among the 179 patients with R/R AML, 5 from dose escalation and 1 from dose expansion were not positive for mIDH1 by the companion diagnostic test and none of these 6 patients achieved a CR or CRh
CR+CRh was consistent across baseline age groups, including patients who were > 65 years of age
Overall response rate includes CR, CRi/CRp, MLFS and PR

Data cutoff: 10Nov2017. PD, progressive disease; PR, partial response

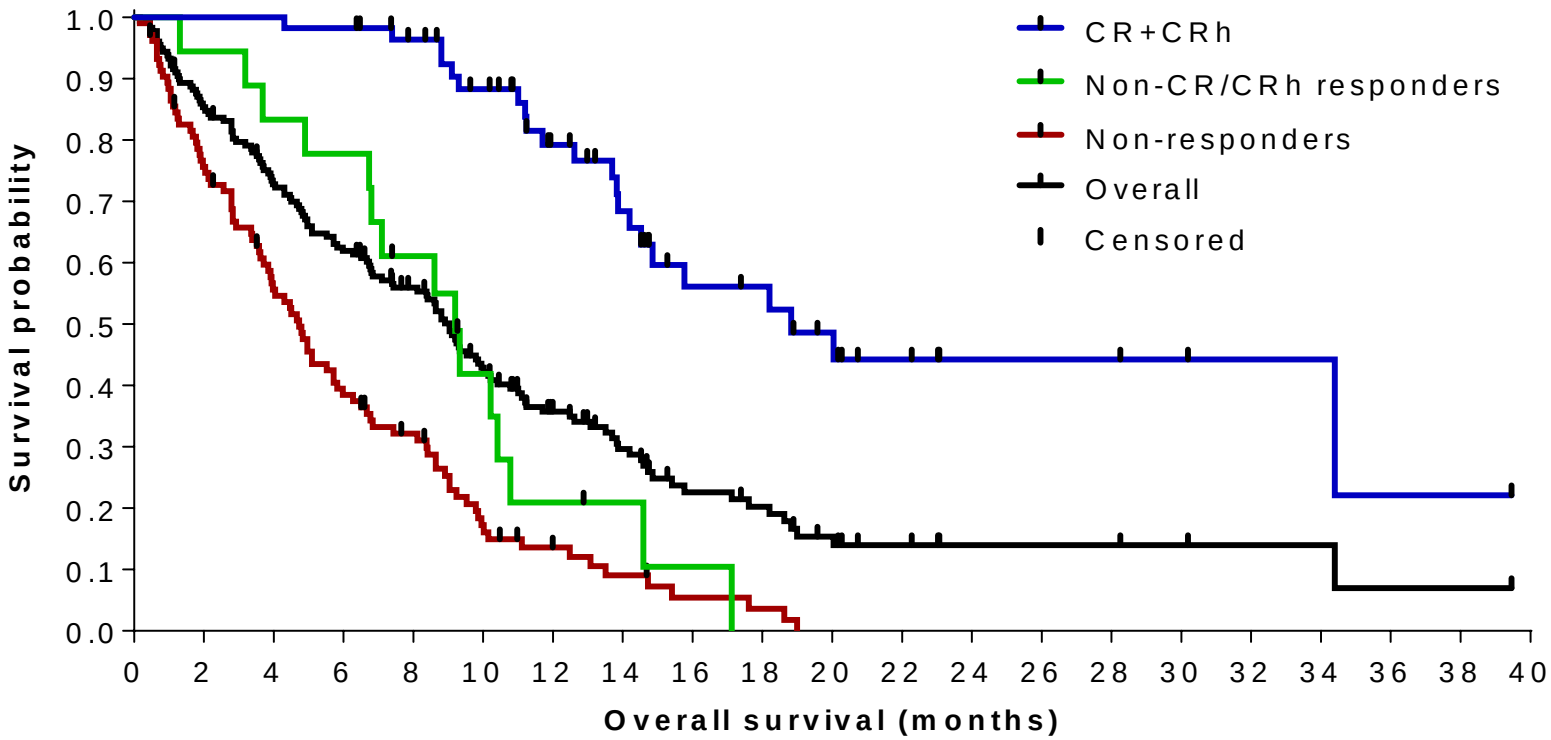
Duration of Treatment and Best Overall Response in Responders R/R AML 500 mg (n=75)



Duration of Response	CR+CRh	CR	Overall Response
Median [95% CI], months	8.2 [5.6, 12.0]	10.1 [6.5, 22.2]	6.5 [5.5, 10.1]
Duration 6 months	60.0%	68.7%	57.3%
Duration 12 months	35.9%	43.9%	32.1%

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 500 mg (n=179)



	Months
Overall survival, median [95% CI]	
CR+CRh	18.8 [14.2, NE]
Non-CR/CRh responders	9.2 [6.7, 10.8]
Non-responders	4.7 [3.7, 5.7]
All	9.0 [7.1, 10.0]
Overall follow-up, median (range)	15.3 (0.2–39.5)

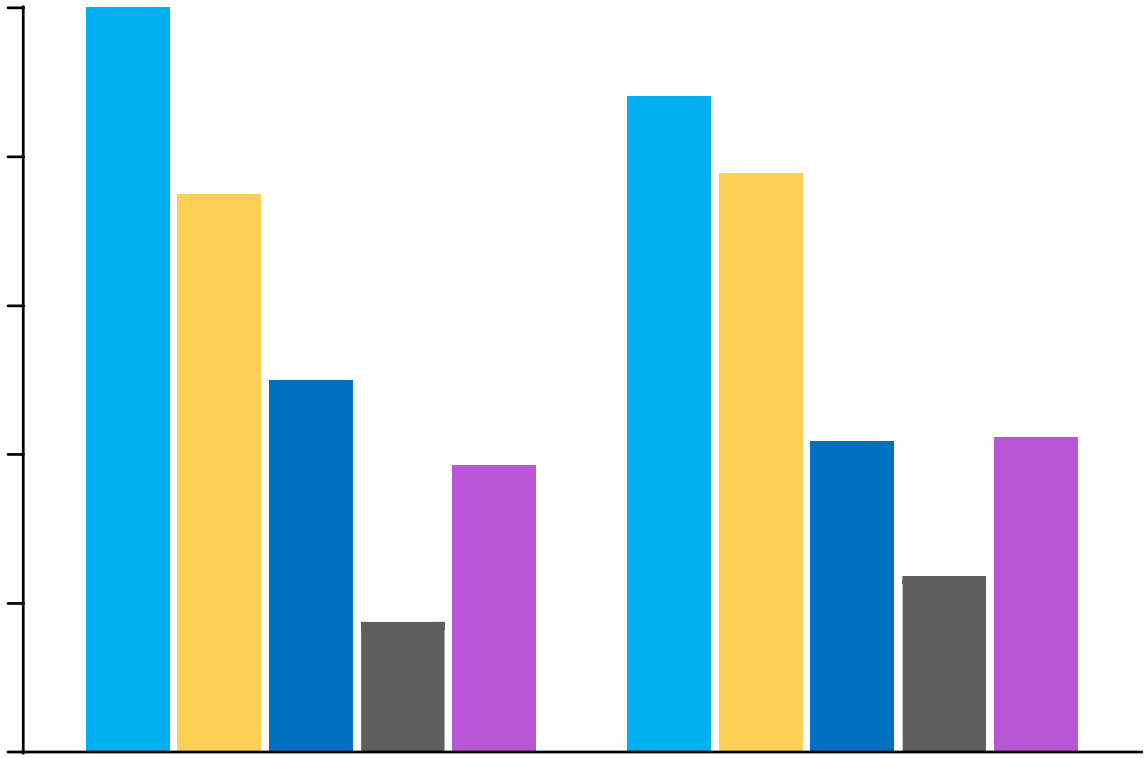
Number of patients at risk:

57	57	57	56	50	43	32	25	16	15	11	7	4	4	4	3	2	2	1	1
18	17	15	14	10	6	3	2	1	0										
104	77	55	38	29	15	9	6	3	2	0									

CR+CRh
Non-CR/CRh responders
Non-responders

Non-CR/CRh responders include CRi, CRp, and MLFS who are not CRh
Non-responders = all others including those with best responses of SD, PD, or not evaluable

Transfusion Independence was Observed Across all Response Categories in R/R AML 500 mg Patients Who Were Dependent at Baseline



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

Data cutoff: 10Nov2017

Non-CR/CRh responders include CRi, CRp, and MLFS who are not CRh
RBC, red blood cell

Exposure-adjusted Incidence of Febrile Neutropenia and Grade ≥ 3 Infections R/R AML 500 mg (n=179)

	Best response				
	CR (n=43)	CRh (n=14)	Non-CR/CRh responders (n=18)	Non-responders (n=104)	Overall (n=179)
All grade febrile neutropenia[a]	2.0 [1.0, 3.8]	3.7 [1.4, 9.8]	6.1 [2.7, 13.5]	12.1 [8.8, 16.5]	5.9 [4.5, 7.6]
Grade ≥ 3 infections[b]	2.6 [1.5, 4.6]	6.4 [3.1, 13.5]	13.1 [7.6, 22.6]	21.3 [16.8, 27.0]	10.2 [8.4, 12.4]

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

IDH1 Mutation Clearance in R/R AML 500 mg (n=179)

- Ivosidenib induced IDH1 mutation clearance[a] in bone marrow mononuclear cells from patients with best overall response of CR or CRh

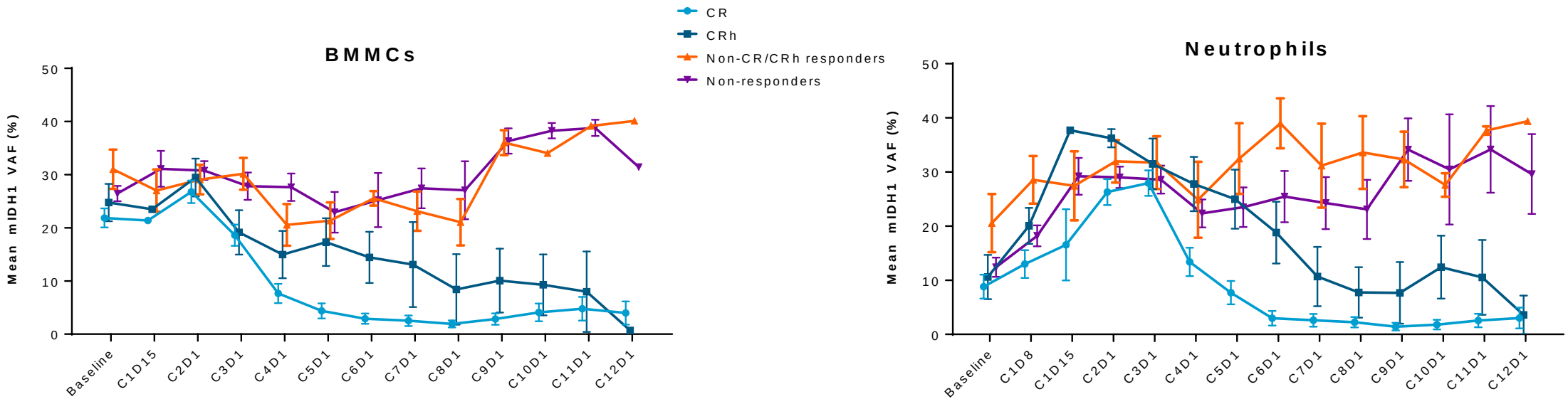
	n	IDH1 mutation clearance N (%)	Detectable IDH1 mutation N (%)
CR+CRh	47	11 (23)	36 (77)
CR	36	10 (28)	26 (72)
CRh	11	1 (9)	10 (91)
Others	64	0	64 (100)
Non-CR+CRh responders	9	0	9 (100)
Non-responders	55	0	55 (100)
p-value[b]		<0.001	

[a]Defined as a reduction in mIDH1 VAF 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 others (non-CR+CRh responders and non-responders)

Longitudinal Mean IDH1 VAF by Best Overall Response

- Ivosidenib reduced mIDH1 VAF in bone marrow mononuclear cells and neutrophils from patients with best overall response of CR or CRh
- 26% of patients with best response of CR/CRh for whom molecular data is available had mutation clearance in **both** bone marrow mononuclear cells and neutrophils



Number of patients:

	Baseline	C1D8	C1D15	C2D1	C3D1	C4D1	C5D1	C6D1	C7D1	C8D1	C9D1	C10D1	C11D1	C12D1
CR	36	1	33	34	25	29	27	27	21	20	17	14	14	
CRh	11	1	11	10	9	8	7	5	5	5	5	4	3	
Non-CR/CRh responders	9	4	8	6	6	6	2	3	3	2	1	1	1	
Non-responders	53	9	52	38	35	23	16	12	8	5	2	3	1	

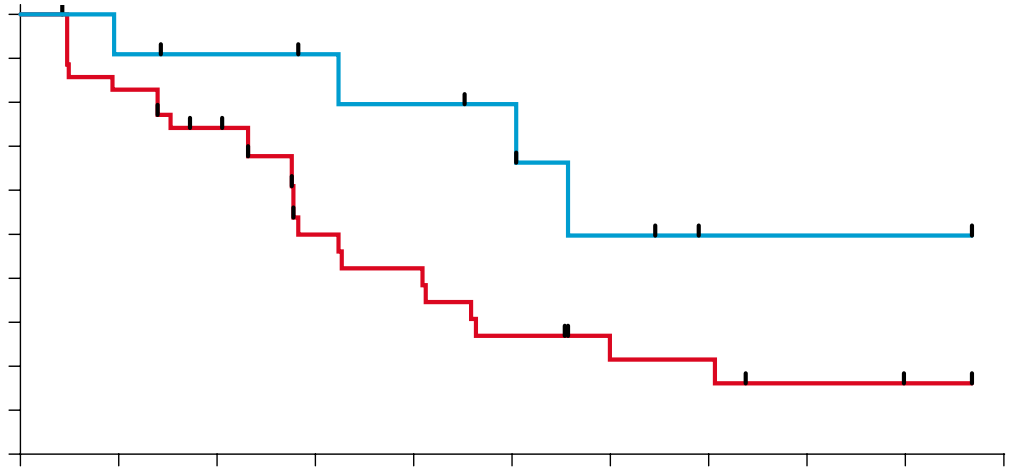
Number of patients:

	Baseline	C1D8	C1D15	C2D1	C3D1	C4D1	C5D1	C6D1	C7D1	C8D1	C9D1	C10D1	C11D1	C12D1
CR	35	33	5	32	33	30	32	29	28	24	20	19	20	17
CRh	9	10	1	10	10	11	10	9	7	5	4	5	5	4
Non-CR/CRh responders	10	10	5	9	8	7	5	3	4	4	4	2	2	2
Non-responders	63	61	11	50	40	31	23	14	12	10	5	3	4	3

Duration of Response and Overall Survival with IDH1 Mutation Clearance

- Patients with IDH1 mutation clearance had improved duration of CR+CRh and overall survival vs. patients with detectable mIDH1

Duration of CR+CRh



Overall survival

Conclusions

- In this high-risk, molecularly defined R/R AML patient population, ivosidenib induced durable responses:
  - CR+CRh rate 32%, duration 8.2 months, median overall survival 18.8 months
  - ORR 42%, duration 6.5 months
- Additional benefits:
  - Transfusion independence across response categories
  - Decreased frequency of febrile neutropenia and infections in responders
- Ivosidenib induced IDH1 mutation clearance in bone marrow mononuclear cells in 23% of patients with best overall response of CR or CRh
- Ivosidenib was well tolerated
  - AEs of interest were managed with standard of care treatments and ivosidenib dose modifications as required
- Ongoing AML studies:
  - Phase 1 ivosidenib or enasidenib+AZA (Poster 7042 Dinardo et al., June 4, 8–11:30 am)
  - AGILE: Global phase 3 first-line ivosidenib+AZA vs placebo+AZA (Poster TPS7074 Stein et al., June 4, 8–11:30 am)
  - Phase 1 ivosidenib or enasidenib in combination with standard AML induction and consolidation therapy

AZA, azacitidine

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BACK UP

Association of IDH1 Mutation Clearance: Bone Marrow Mononuclear Cells and Neutrophils

- Significant association of IDH1 mutation clearance between bone marrow mononuclear cells and neutrophils in R/R AML 500 mg patients with best response of CR or CRh

CR or CRh (n=42)		Neutrophils	
		IDH1 mutation clearance n (%)	Detectable IDH1 mutation n (%)
Bone marrow mononuclear cells	IDH1 mutation clearance	11 (26)	0
	Detectable IDH1 mutation	6 (14)	25 (60)

p<0.001 for the association between bone marrow mononuclear cells and neutrophils