ENASIDENIB IN MUTANT-*IDH2* RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA (R/R AML): RESULTS OF A PHASE 1 DOSE-ESCALATION AND EXPANSION STUDY

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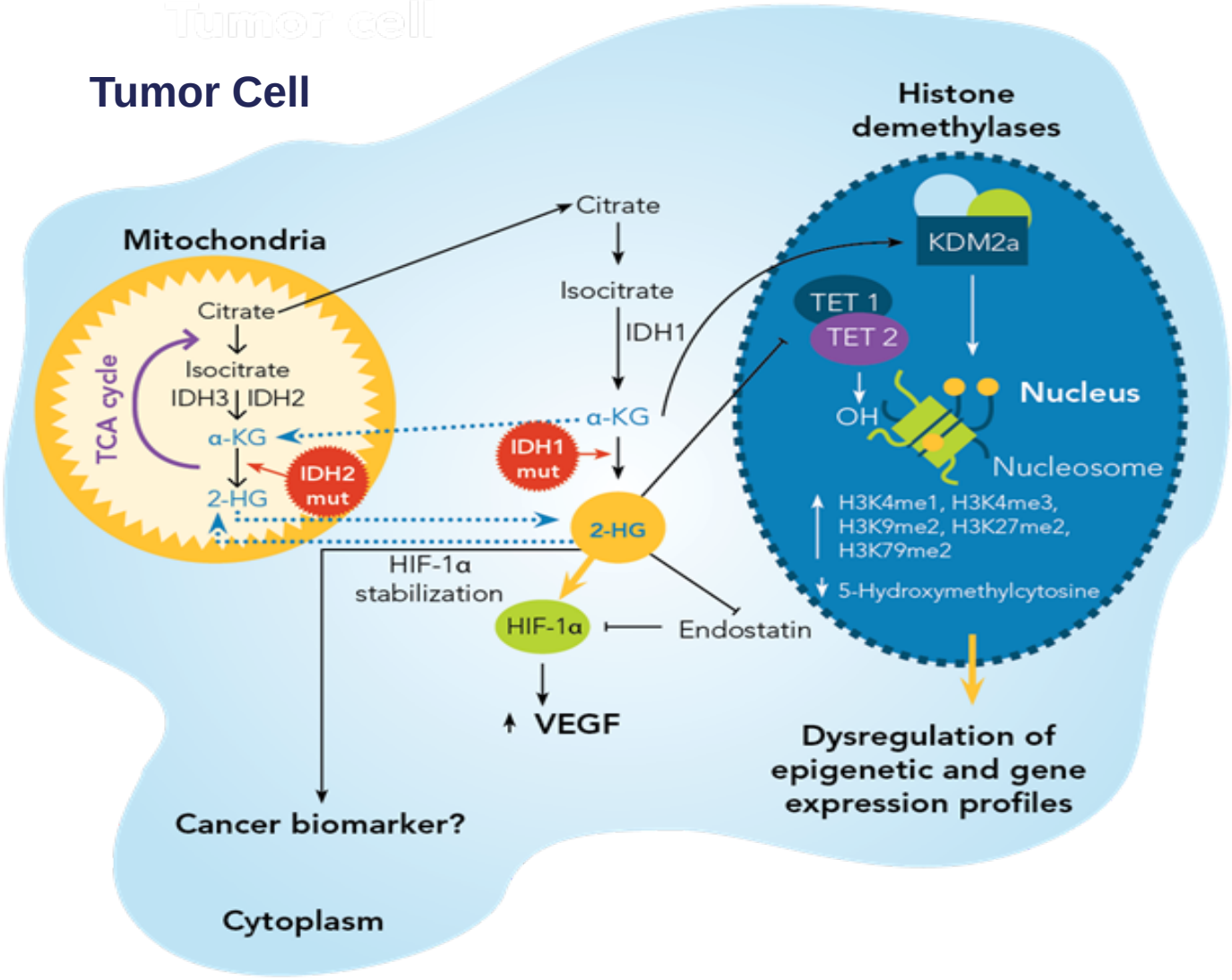
ISOCITRATE DEHYDROGENASE (IDH) MUTATIONS AS A TARGET IN AML

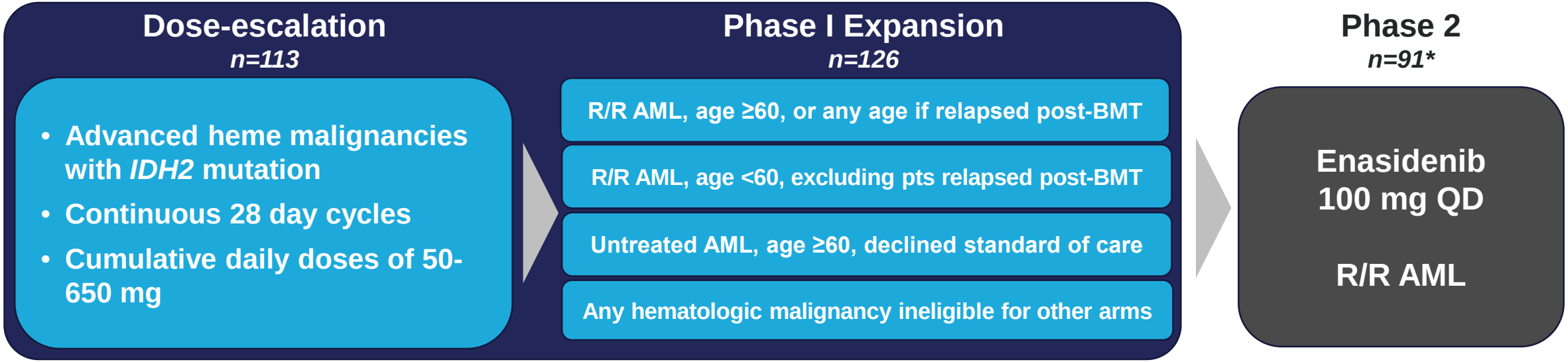
- **IDH2 is an enzyme of the citric acid cycle**
- **Mutant *IDH2* (m*IDH2*) occurs in ~12% of patients with AML[1]**
- **m*IDH2* produces 2-HG, which alters DNA methylation and leads to a block in cellular differentiation**
- **Enasidenib (AG-221) is a selective, oral, potent inhibitor of mIDH2 enzyme**
- **Enasidenib induces differentiation of leukemic cells**



1. DiNardo et al. *Am J Hematol* 2015;90:732-6

IDH, isocitrate dehydrogenase; 2-HG, 2-hydroxyglutarate

PHASE 1/2 STUDY DESIGN



Key Endpoints:

- **Safety, tolerability, MTD, DLTs**
  - **MTD not reached at doses up to 650 mg/day**
- **Response rates in R/R AML patients, assessed by local investigator per IWG criteria[1]**
- **Assessment of clinical activity**

*As of April 15, 2016

BMT, bone marrow transplant; DLTs, dose-limiting toxicities; IWG, International Working Group; MTD, maximum tolerated dose; R/R AML, relapsed/refractory AML

1. Cheson et al. *J Clin Oncol* 2003;21(24):4642-9

BASELINE CHARACTERISTICS

Characteristic	Relapsed / Refractory AML		All Phase 1 Patients N=239
	100 mg/day dose n=109	All doses n=176	
Age (years), median (range)	67 (19–100)	67 (19–100)	70 (19–100)
Gender, %M / %F	42 / 58	51 / 49	57 / 43
***IDH2* mutation site, n (%)**			
R140	83 (76)	130 (74)	179 (75)
R172	25 (23)	45 (26)	57 (24)
ECOG PS, n (%)			
0-1	93 (85)	145 (82)	194 (81)
2	16 (15)	31 (18)	45 (19)
Number of prior Tx, median (range)	1 (1–14)	2 (1–14)	-
Cytogenetic risk status, n (%)	n=80	n=128	n=175
Intermediate-risk	51 (64)	85 (66)	117 (67)
Poor-risk	29 (36)	43 (34)	58 (33)
Prior AML therapy outcomes,* n (%)			
Refractory to initial induction or re-induction treatment	35 (32)	57 (32)	-
Relapsed/refractory to ≥2 cycles of 1st-line lower-intensity therapy†	25 (23)	43 (24)	-
Relapsed within 1 year of initial treatment	27 (25)	41 (23)	-
Relapsed >1 year after initial treatment	8 (7)	15 (9)	-
Relapsed post-transplant	12 (11)	24 (14)	-
In 2nd or later relapse	13 (12)	22 (13)	-

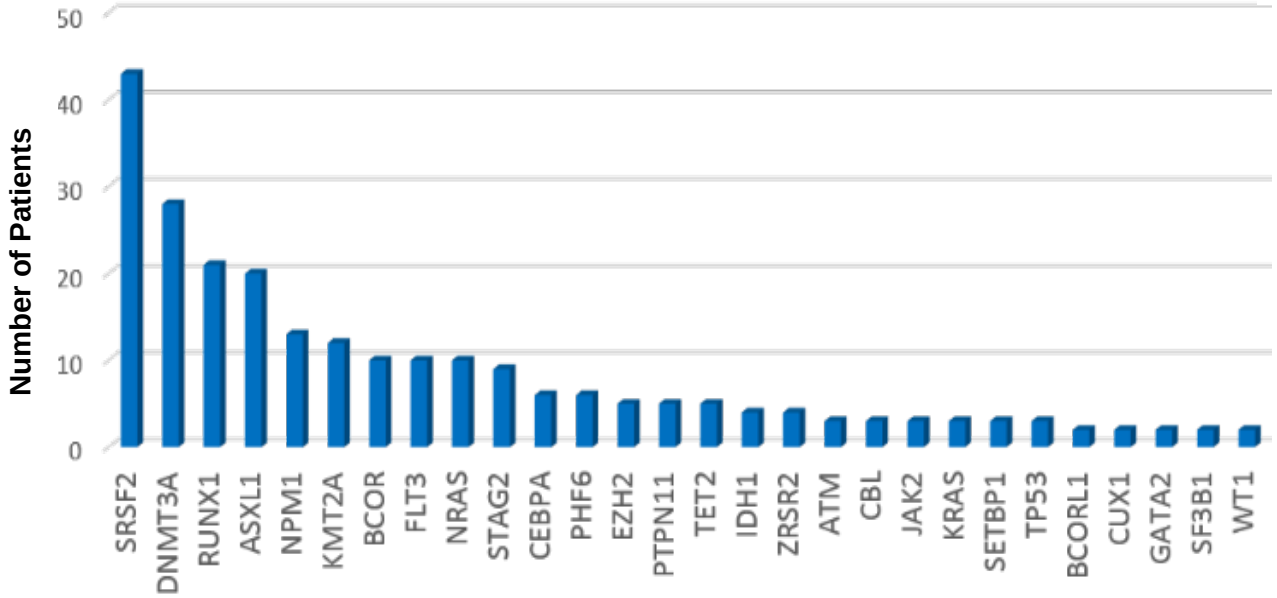
Data cutoff: April 15, 2016

*Individual patients may be counted in more than one category; †Includes hypomethylating agents, low-dose cytarabine

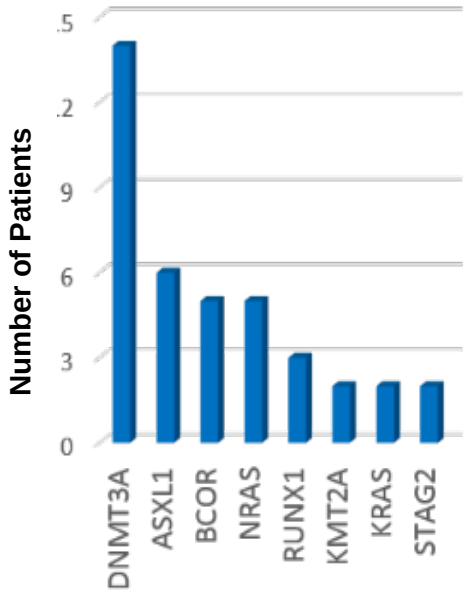
ECOG PS, Eastern Cooperative Oncology Group performance status score; Tx, treatment

CO-OCCURRING MUTATIONS AT SCREENING

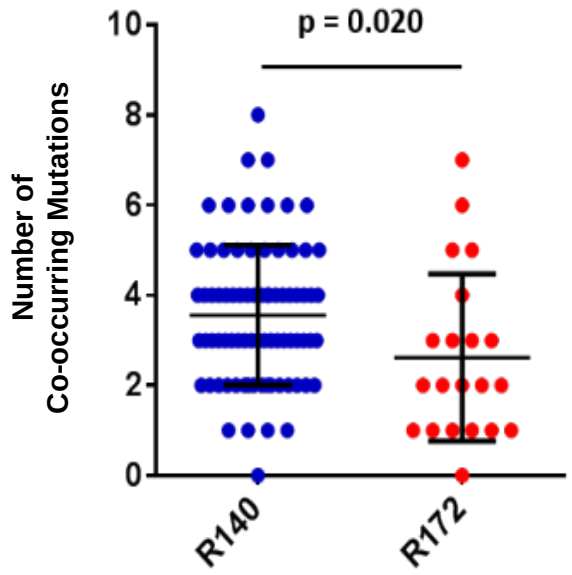
R/R AML m*IDH2*-R140



R/R AML m*IDH2*-R172



Co-mutational Burden: m*IDH2*-R140 vs m*IDH2*-R172



- **m*IDH2*-R140 associated with significantly higher co-mutational burden vs m*IDH2*-R172**

Co-mutational data from 100 patient samples collected at study entry

MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS (≥20% OF ALL PATIENTS)

All Patients (N=239)	Any Grade	Grade 3-4	
		All	Treatment-related
Nausea	46%	5%	2%
Hyperbilirubinemia	45%	18%	12%
Diarrhea	40%	4%	< 1%
Fatigue	40%	8%	3%
Decreased appetite	38%	5%	3%
Vomiting	32%	2%	< 1%
Dyspnea	31%	8%	1%
Cough	29%	< 1%	0%
Pyrexia	28%	3%	< 1%
Febrile neutropenia	28%	27%	1%
Thrombocytopenia	27%	23%	6%
Anemia	27%	19%	5%
Constipation	27%	< 1%	0%
Hypokalemia	27%	8%	< 1%
Peripheral edema	27%	2%	< 1%
Pneumonia	21%	18%	0%
Hyperuricemia	20%	3%	< 1%

- **Serious treatment-related IDH-DS was reported for 8% of patients (see Abstract and Poster 7015)**

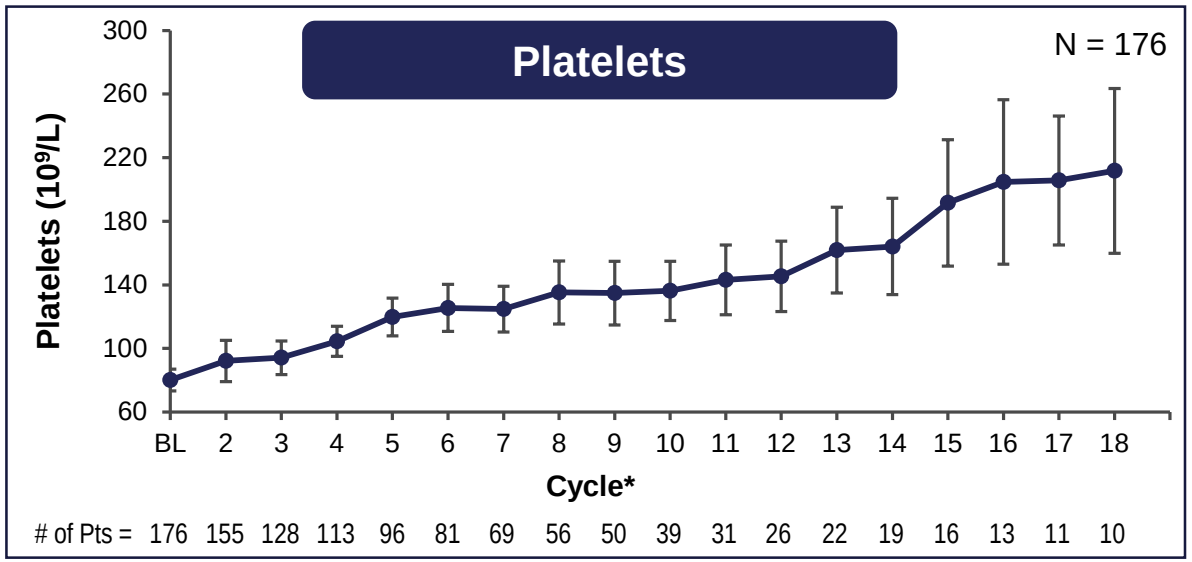
Data cutoff: April 15, 2016

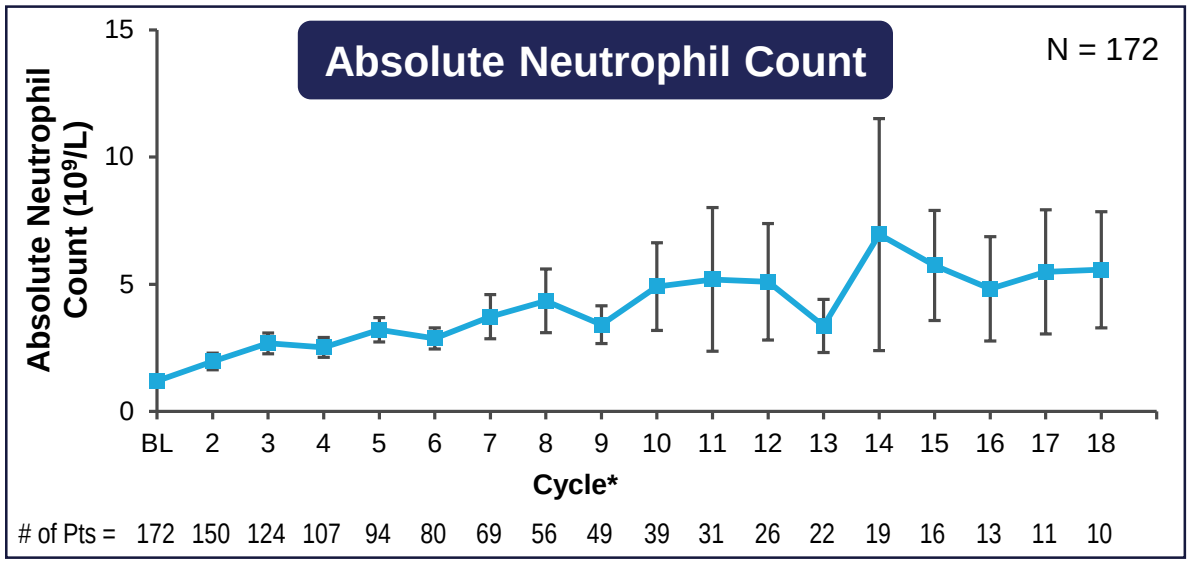
RESPONSE

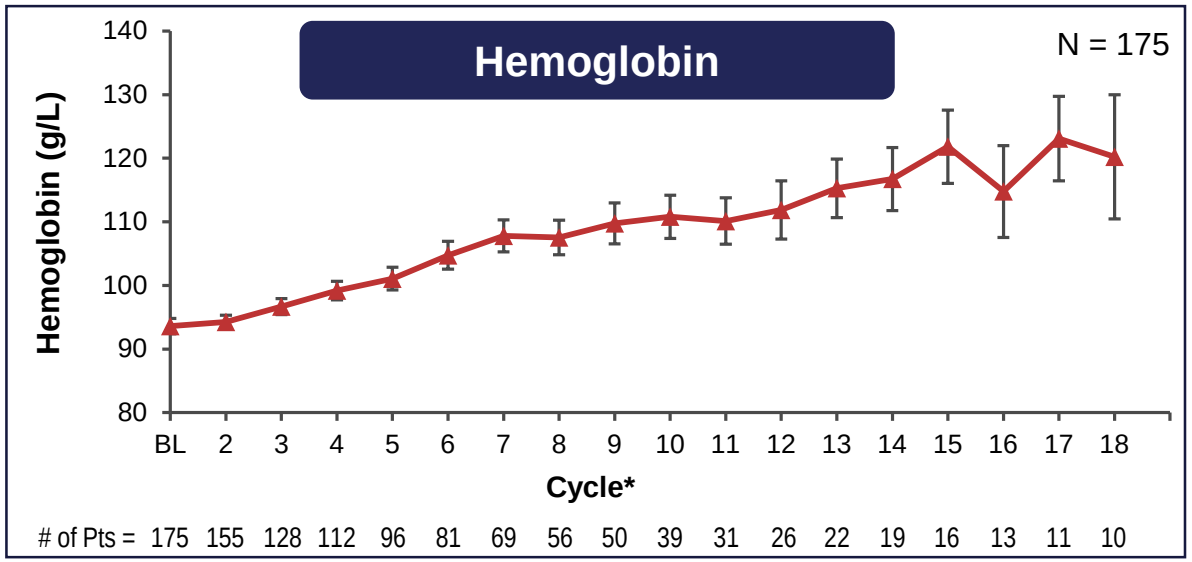
	Relapsed or refractory AML	
	Enasidenib 100 mg/day (n=109)	**All doses (N=176)**
Overall response rate, % [n/N]	**38.5% (42/109)**	**40.3% (71/176)**
95% CI	[29.4, 48.3]	[33.0, 48.0]
Best response		
CR, n (%)	**22 (20.2)**	**34 (19.3)**
[95% CI]	[13.1, 28.9]	[13.8, 25.9]
CRi or CRp, n (%)	7 (6.4)	12 (6.8)
PR, n (%)	3 (2.8)	11 (6.3)
MLFS, n (%)	10 (9.2)	14 (8.0)
SD, n (%)	58 (53.2)	85 (48.3)
PD, n (%)	5 (4.6)	9 (5.1)
NE, n (%)	2 (1.8)	3 (1. 7)
Time to first response (mos), median (range)	1.9 (0.5-9.4)	1.9 (0.5-9.4)
Duration of response (mos), median [95%CI]	5.6 [3.8, 9.7]	5.8 [3.9, 7.4]
Time to CR (mos), median (range)	3.7 (0.7-11.2)	3.8 (0.5-11.2)
Duration of response in patients with CR (mos), median [95%CI]	8.8 [5.3, NR]	8.8 [6.4, NR]

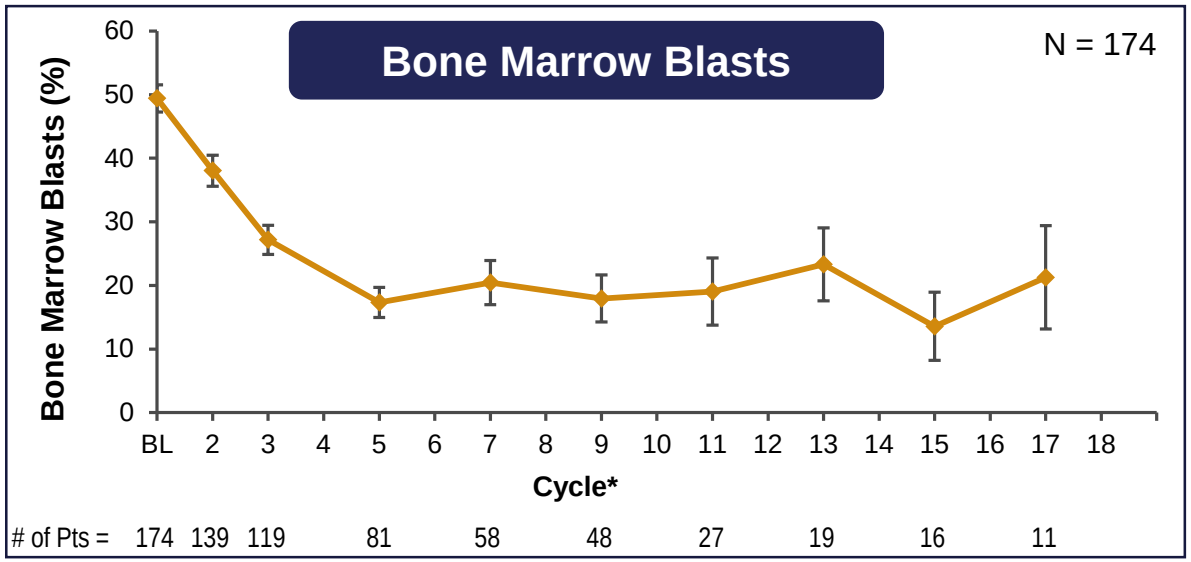
CR, complete remission; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; mos, months; NE, not evaluable; PD, progressive disease; PR, partial remission; SD, stable disease

HEMATOLOGICAL PARAMETERS OVER TIME IN R/R AML PATIENTS



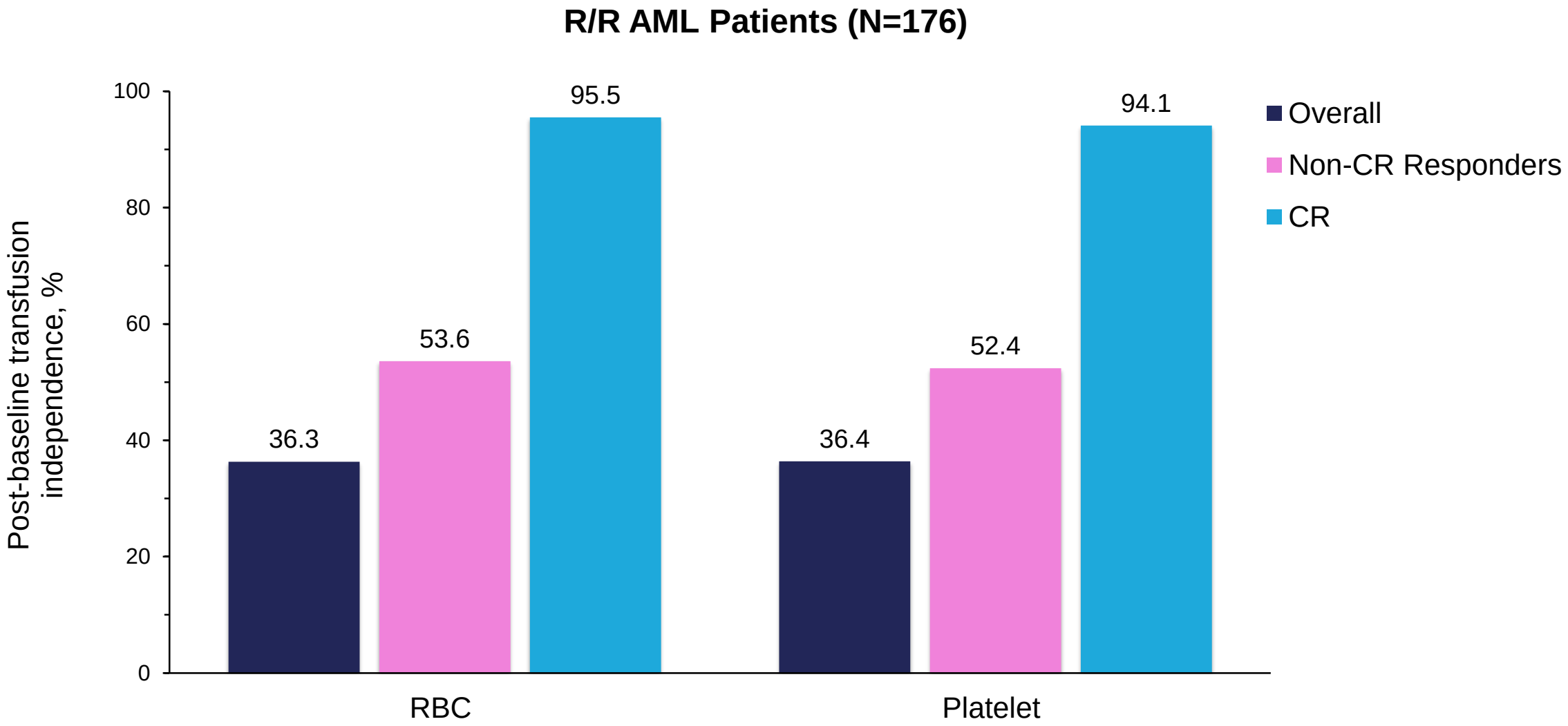






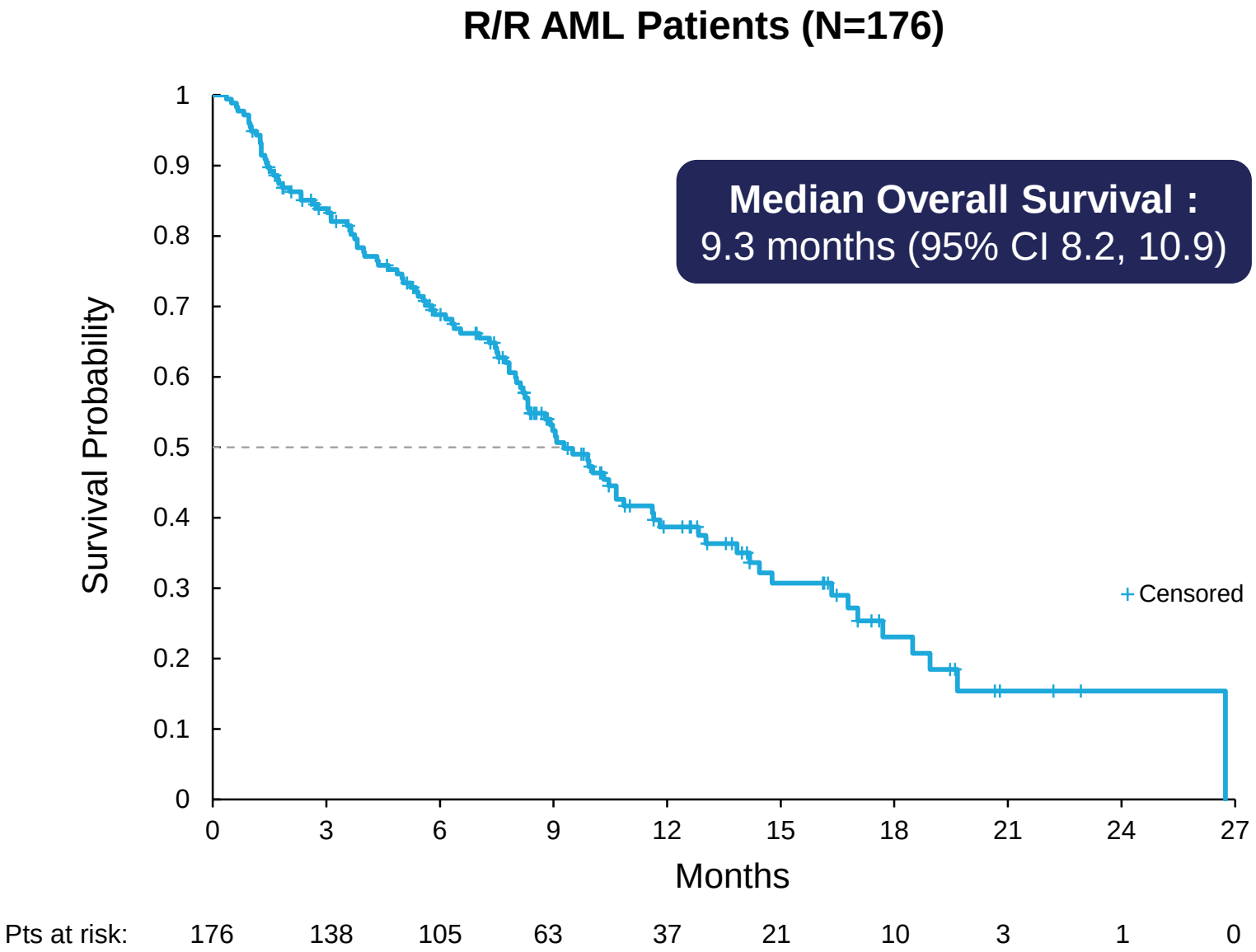
*Day 1 of each cycle

TRANSFUSION INDEPENDENCE

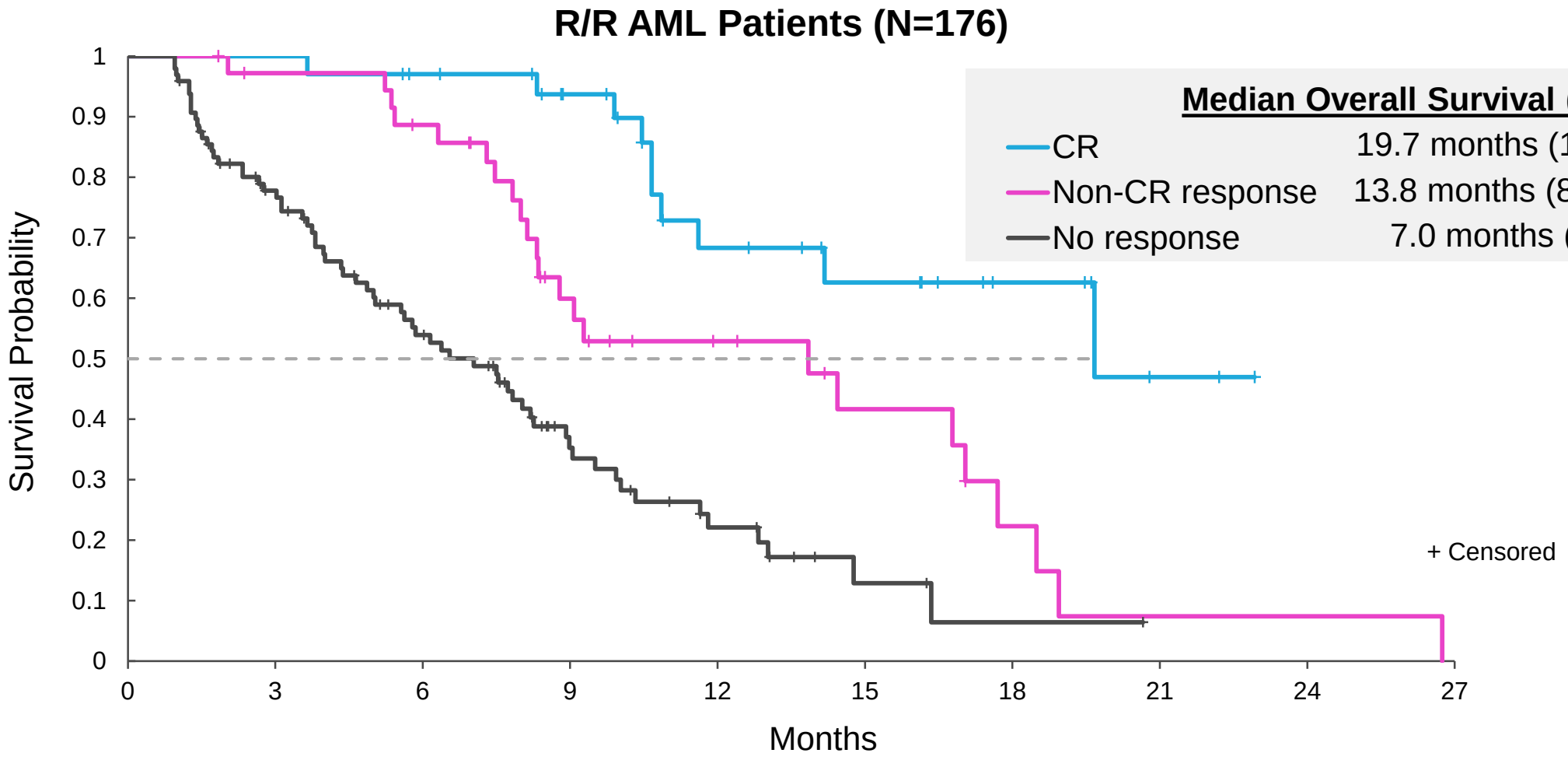


Transfusion independence assessed in baseline transfusion-dependent patients (defined as ≥1 RBC/platelet transfusion during the 4 weeks prior to and 4 weeks after first dose of enasidenib).
Post-baseline transfusion independence defined as no transfusion during any consecutive 56-day period on-study.
CR, complete remission
Data cutoff: April 15, 2016

OVERALL SURVIVAL



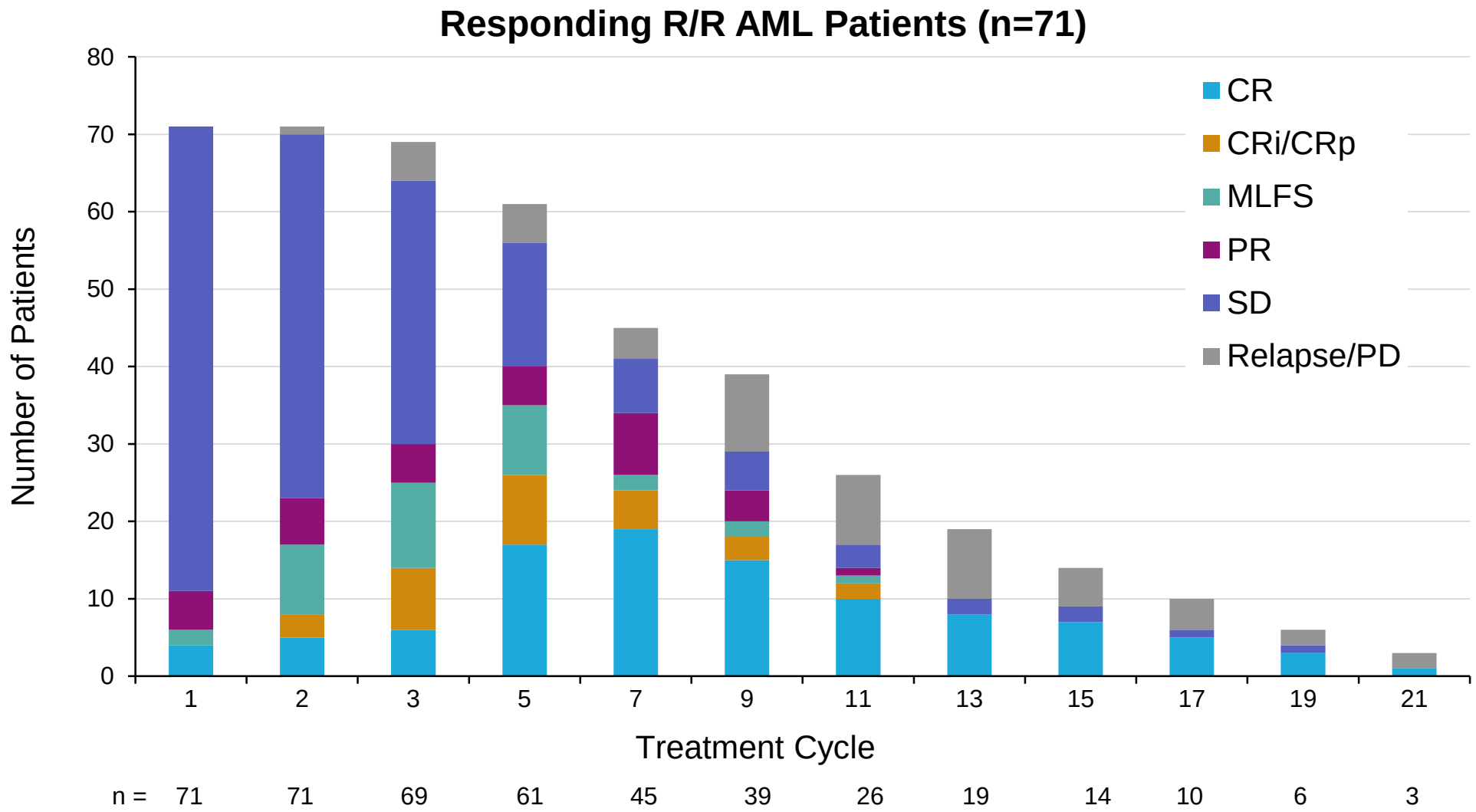
OVERALL SURVIVAL BY BEST RESPONSE



Pts at risk:										
CR	34	34	31	25	15	11	6	2	0	
Non-CR response	37	34	30	17	11	7	3	1	1	0
No response	97	68	43	20	10	3	1	0		

CR, complete remission

QUALITATIVE IMPROVEMENT IN RESPONSE OVER TIME

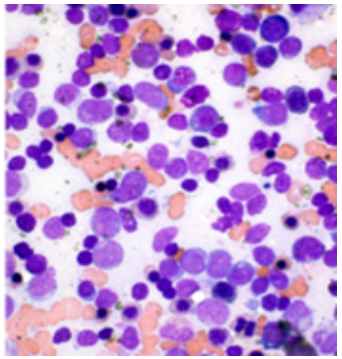


CR, complete remission; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; PR, partial remission; SD, stable disease; PD, progressive disease

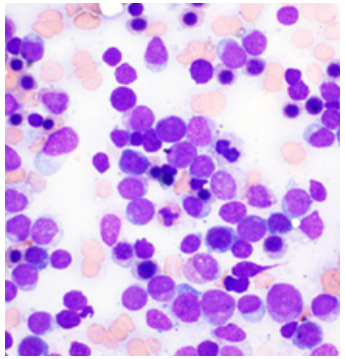
DIFFERENTIATION OF MYELOBLASTS WITH ENASIDENIB

Patient 1: Morphological evidence of myeloid differentiation

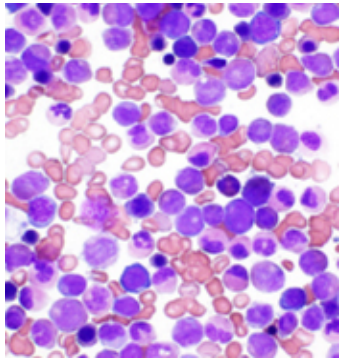
Screening
37% blasts



Cycle 1 Day 15
Evidence of cellular differentiation

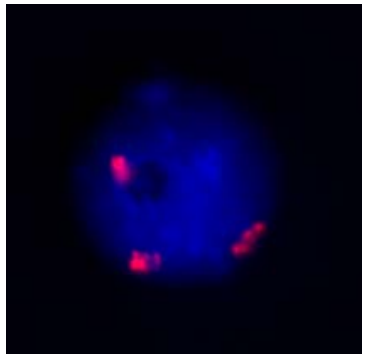


Cycle 3 Day 1
4% blasts

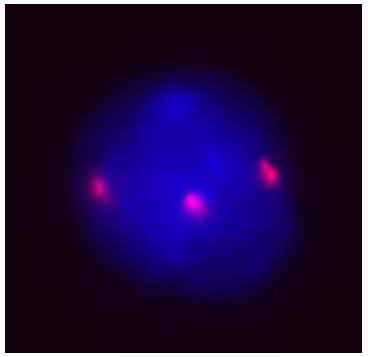


Patient 2: FISH evidence of myeloid differentiation (CEP8)

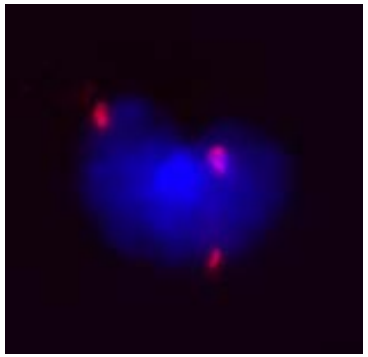
Blasts



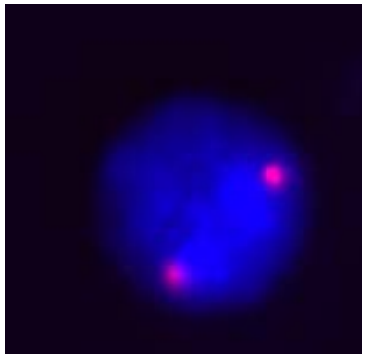
Promyelocytes



Mature Granulocytes



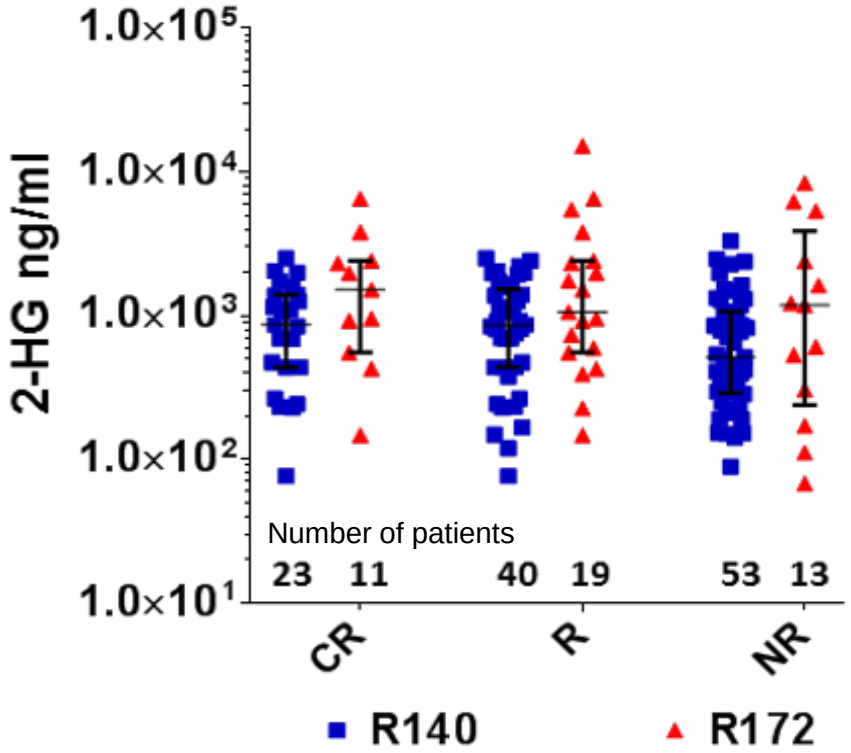
Lymphocytes



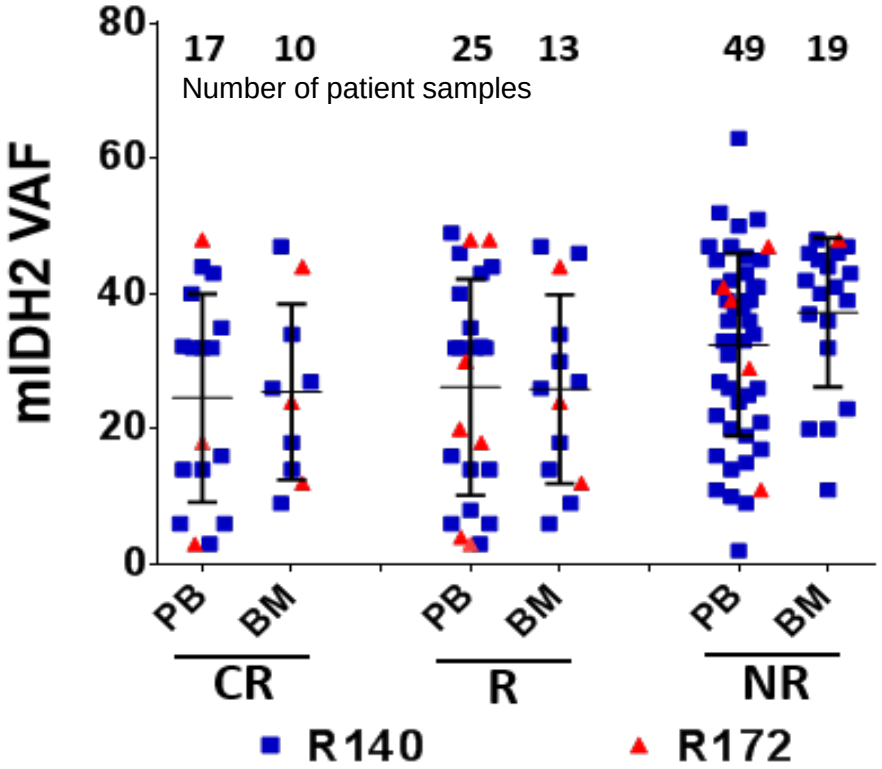
2-HG CONCENTRATIONS, VARIANT ALLELE FREQUENCY AND RESPONSE

- **Baseline 2-HG levels and baseline m*IDH2* VAF were similar for responding and non-responding patients**

CR: Complete remission
R: Any response
NR: No response



Plasma 2-HG (ng/mL) at baseline in 125 efficacy-evaluable R/R AML patients with baseline 2-HG data



Baseline m*IDH2* VAF from peripheral blood (PB) or bone marrow (BM) in R/R AML patient samples

VAF, variant allele frequency

CONCLUSIONS

- **Enasidenib was well tolerated; most adverse events were not treatment-related, and grade 1-2 in severity**
- **Enasidenib induced durable CRs and was associated with OS of > 9 months in this relapsed/refractory patient population, the majority of whom were age ≥ 65 years and had received multiple prior AML treatments**
- **Unlike cytotoxic chemotherapy, responses to enasidenib may require several treatment cycles and responses can improve over time with continued treatment**
- **Differentiation of myeloblasts, not cytotoxicity, appears to drive the clinical efficacy of enasidenib**
- **Ongoing studies:**
  - **Phase 3 IDHentify: enasidenib monotherapy vs conventional care regimens in older patients with late-stage AML**
  - **Phase 1/2 studies of enasidenib combination therapy regimens in newly diagnosed AML**

AVAILABLE ONLINE TODAY

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Enasidenib Induces Acute Myeloid Leukemia Cell Differentiation to Promote Clinical Response

Michael D. Amatangelo*, Lynn Quek*, Alan Shih*, Eytan M. Stein, Mikhail Roshal, Muriel D. David, Benoit Marteyn, Noushin Rahnamay Farnoud, Stephane de Botton, Olivier A. Bernard, Bin Wu, Katharine E. Yen, Martin S. Tallman, Elli Papaemmanuil, Virginie Penard-Lacronique, Anjan Thakurta†, Paresh Vyas†, Ross L. Levine†

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