Enasidenib Monotherapy is Effective and Well-Tolerated in Patients with Previously Untreated Mutant-*IDH2* Acute Myeloid Leukemia

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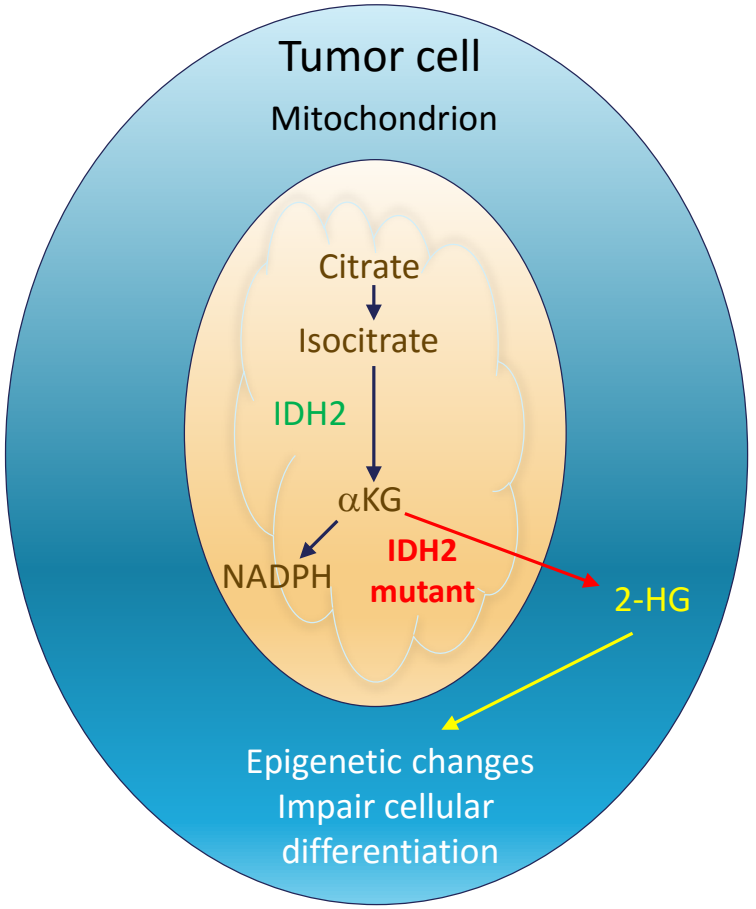
ISOCITRATE DEHYDROGENASE (*IDH*) MUTATIONS ARE A TARGET IN AML

- IDH2 is an enzyme of the citric acid (TCA) cycle
- *IDH2* mutations (m*IDH2*) occur in ~12% of patients with AML[1]
- m*IDH2* produces 2-hydroxyglutarate (2-HG), an oncometabolite that alters DNA methylation and leads to a block in cellular differentiation[2]
- Enasidenib (IDHIFA®; CC-90007/AG-221) is a selective, oral, potent inhibitor of cells with mIDH2, approved in the US for use in adult patients with R/R AML with an *IDH2* mutation
- The mechanism of action of enasidenib is through induction of differentiation[3,4]



1. DiNardo et al. *Am J Hematol* 2015;90:732-6. 2. Prensner & Chinnaiyan. *Nature Med* 2011;17:291. 3. Amatangelo et al. *Blood* 2017;130(6):732-41. 4. Yen et al. *Cancer Discov* 2017;7(5):478-93.
IDH, isocitrate dehydrogenase; 2-HG, 2-hydroxyglutarate

BACKGROUND

- Clinical outcomes of a phase 1 study of enasidenib monotherapy in patients with relapsed and refractory AML with m*IDH2* showed[1]:
  - Complete remission (CR) rate of 19.3%
  - Overall response rate (ORR) of 40.3%
  - Median overall survival (OS) of 9.3 months
  - Median OS for patients who achieved CR: 19.7 months
- Older patients are frequently poor candidates for intensive chemotherapy due to:
  - Patient-related factors that increase treatment-related mortality[2]
  - Adverse biological features that decrease response rates[2]
- As a result, the majority of older patients with AML are not offered any treatment[3]

Better-tolerated, more effective therapies are needed for older patients with newly diagnosed AML

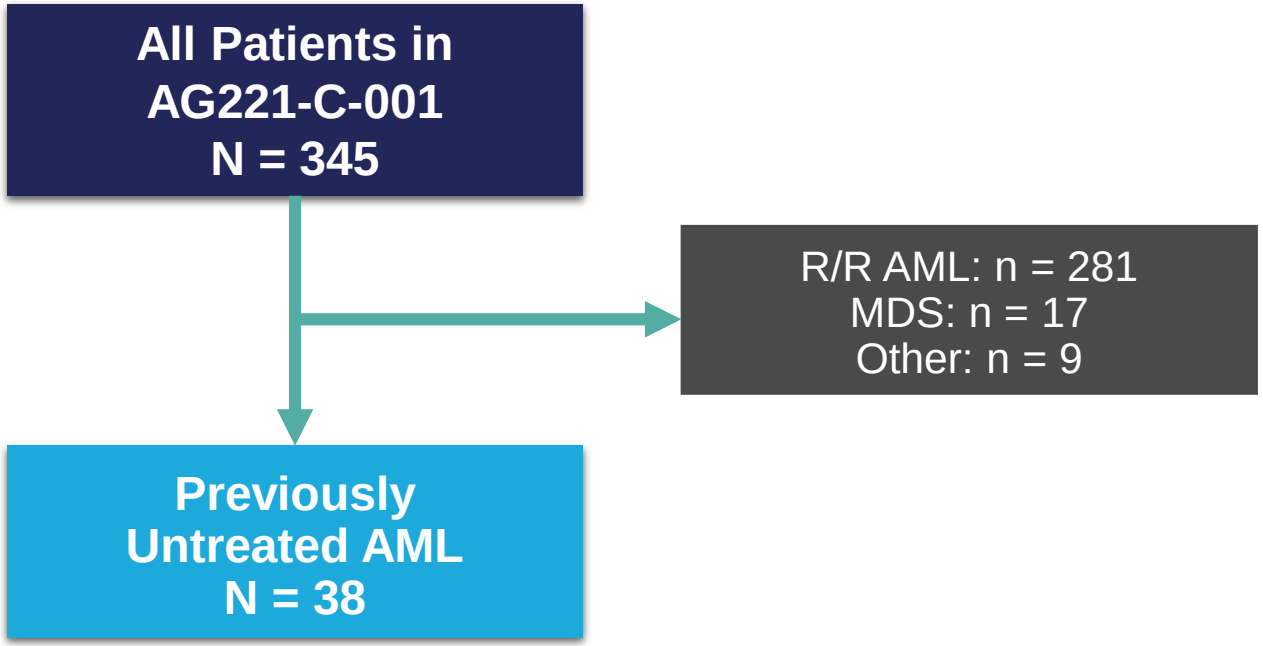
1. Stein et al. *Blood* 2017;130(6):722-31. 2. Walter & Estey. *Leukemia*, 2015;29:770-5. 3. Medeiros et al. *Ann Hematol* 2015;94:1127-38.
CR, complete remission; CRi/CRp, CR with incomplete neutrophil or platelet recovery; PR, partial remission; MLFS, morphologic leukemia-free state; NR, not reached; ORR, overall response rate; R/R, relapsed or refractory; OS, overall survival

OLDER PATIENTS WITH PREVIOUSLY UNTREATED *IDH2*-POSITIVE AML WERE ELIGIBLE TO ENROLL IN PHASE 1 OF THE PIVOTAL STUDY

- A subgroup of older patients (≥60 years) with previously untreated m*IDH2* AML received enasidenib monotherapy in the phase 1 portions of the AG221-C-001 study*

- Patients:
  - Untreated m*IDH2* AML
  - ECOG PS 0-2
  - Not candidates for standard treatment

- Enasidenib dosing:
  - Dose-escalation: 50-650 mg/day
  - Expansion phase: 100 mg QD
  - Continuous 28-day treatment cycles



*NCT01915498
Data cutoff: 1 Sept 2017
ECOG PS, Eastern Cooperative Oncology Group performance status

BASELINE DEMOGRAPHIC AND DISEASE CHARACTERISTICS

	Previously Untreated m*IDH2* AML N=38
Age (years), median (range)	77.0 (58-87)
Age ≥75 years, n (%)	23 (61)
Gender, % M/F	71/29
Prior non-AML systemic anti-cancer therapy, n (%)	9 (24)
***IDH2* mutation location**, n (%)	
R140	25 (66)
R172	12 (32)
Co-mutations in >25% of pts, n (%)	n=15
ASXL1	8 (53)
SRSF2	8 (53)
STAG2	5 (33)
DNMT3A	4 (27)
RUNX1	4 (27)
Number of mutations, n (%)	n=15
1	2 (13)
2-3	6 (40)
≥4	7 (47)

	Previously Untreated m*IDH2* AML N=38
ECOG PS, n (%)	
0	12 (32)
1	17 (45)
2	9 (24)
WHO AML classification, n (%)	
Myelodysplasia-related changes	13 (34)
Recurrent genetic abnormalities	2 (5)
Therapy-related	2 (5)
Not otherwise specified	20 (53)
Missing	1 (3)
NCCN cytogenetic risk, n (%)	n=29
Intermediate	19 (50)
Poor	10 (26)
Missing	9 (24)
BM blasts (%)*, median (range)	38.0 (14-92)

*Local assessment

BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group performance status; NCCN, National Comprehensive Cancer Network; pts, patients; WHO, World Health Organization

TREATMENT-RELATED TREATMENT-EMERGENT ADVERSE EVENTS (TEAEs)

- 2 patients discontinued because of a treatment-related TEAE (cardiac tamponade, thrombocytopenia)
- Serious treatment-related TEAEs in >1 patient were IDH differentiation syndrome (n=4) and tumor lysis syndrome (n=2)

Treatment-related TEAEs	Previously Untreated m*IDH2* AML N=38		All study patients N=239[1]
	Any grade (≥10% of pts)	Grade 3-4	Grade 3-4
	n (%)		n (%)
Hyperbilirubinemia	12 (32)	5 (13)	29 (12)
Nausea	9 (24)	0	5 (2)
Thrombocytopenia	7 (18)	6 (16)	15 (6)
Fatigue	7 (18)	1 (3)	6 (3)
Decreased appetite	7 (18)	1 (3)	NR
Rash	7 (18)	0	NR
Anemia	6 (16)	5 (13)	12 (5)
IDH differentiation syndrome	4 (11)	4 (11)	15 (6)
Tumor lysis syndrome	4 (11)	3 (8)	8 (3)
ECG QT prolonged	4 (11)	1 (3)	NR
Dysgeusia	4 (11)	0	NR
Peripheral neuropathy	4 (11)	0	NR
Vomiting	4 (11)	0	NR

Data cutoff: 1 Sept 2017

ECG, electrocardiogram; IDH-DS, IDH-inhibitor-associated differentiation syndrome; NR, not reported; pts, patients; R/R AML, relapsed/refractory AML; TEAE, treatment-emergent adverse event

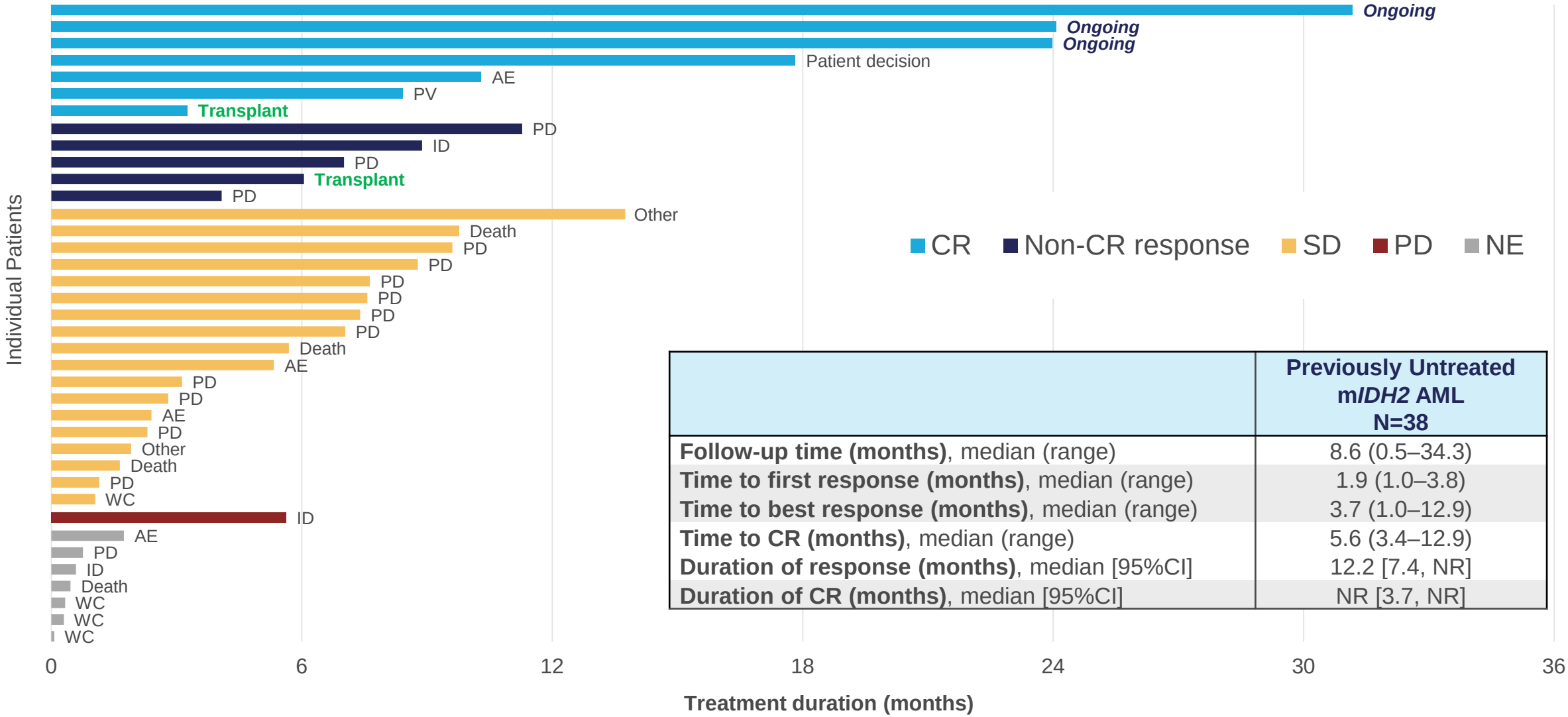
RESPONSE

- Median number of enasidenib treatment cycles: 6.5 (range 1-35)

	Previously Untreated m*IDH2* AML N=38
Overall response (CR, CRi/CRp, PR, MLFS), n (%)	**12 (32)**
ORR 95%CI	17.5%, 48.7%
Best response, n (%)	
CR	7 (18)
CRi/CRp	1 (3)
PR	2 (5)
MLFS	2 (5)
Stable Disease*, n (%)	18 (47)
Disease Progression, n (%)	1 (3)
Not evaluable, n (%)	7 (18)

*Failure to achieve a response but not meeting criteria for progressive disease for a period of ≥8 weeks
Data cutoff: 1 Sept 2017
CR, complete remission; CRi/CRp, CR with incomplete neutrophil or platelet recovery; MLFS, morphologic leukemia-free state; ORR, Overall response rate; PR, partial remission;

TREATMENT DURATION, RESPONSE AND DISPOSITION

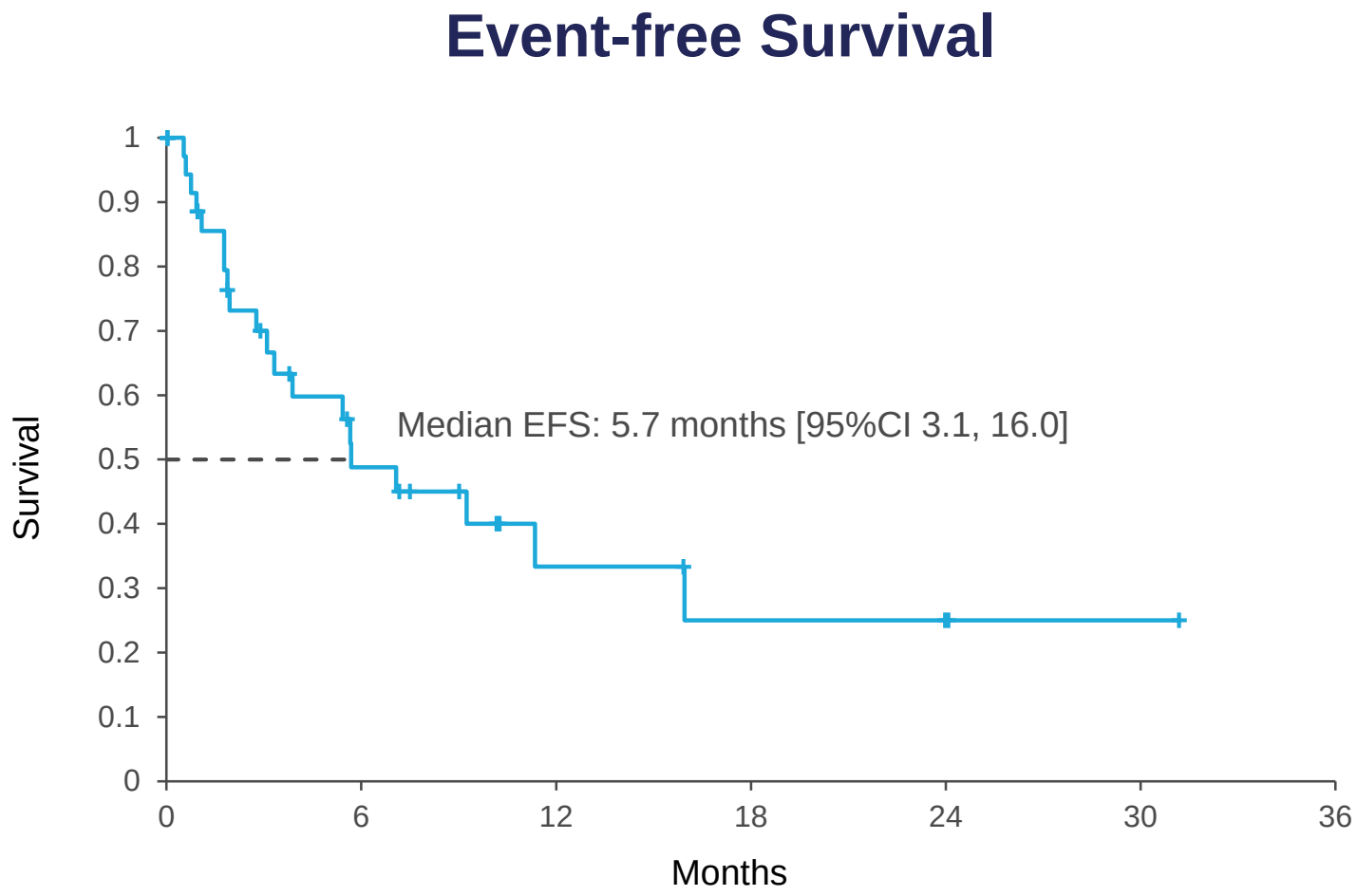


	Previously Untreated m*IDH2* AML N=38
Follow-up time (months), median (range)	8.6 (0.5–34.3)
Time to first response (months), median (range)	1.9 (1.0–3.8)
Time to best response (months), median (range)	3.7 (1.0–12.9)
Time to CR (months), median (range)	5.6 (3.4–12.9)
Duration of response (months), median [95%CI]	12.2 [7.4, NR]
Duration of CR (months), median [95%CI]	NR [3.7, NR]

Data cutoff: 1 Sept 2017

AE, adverse event; CR, complete remission; ID, investigator decision; NE, not evaluable; NR, not reached; PD, progressive disease; PV, protocol violation; SD, stable disease; WC, withdrew consent

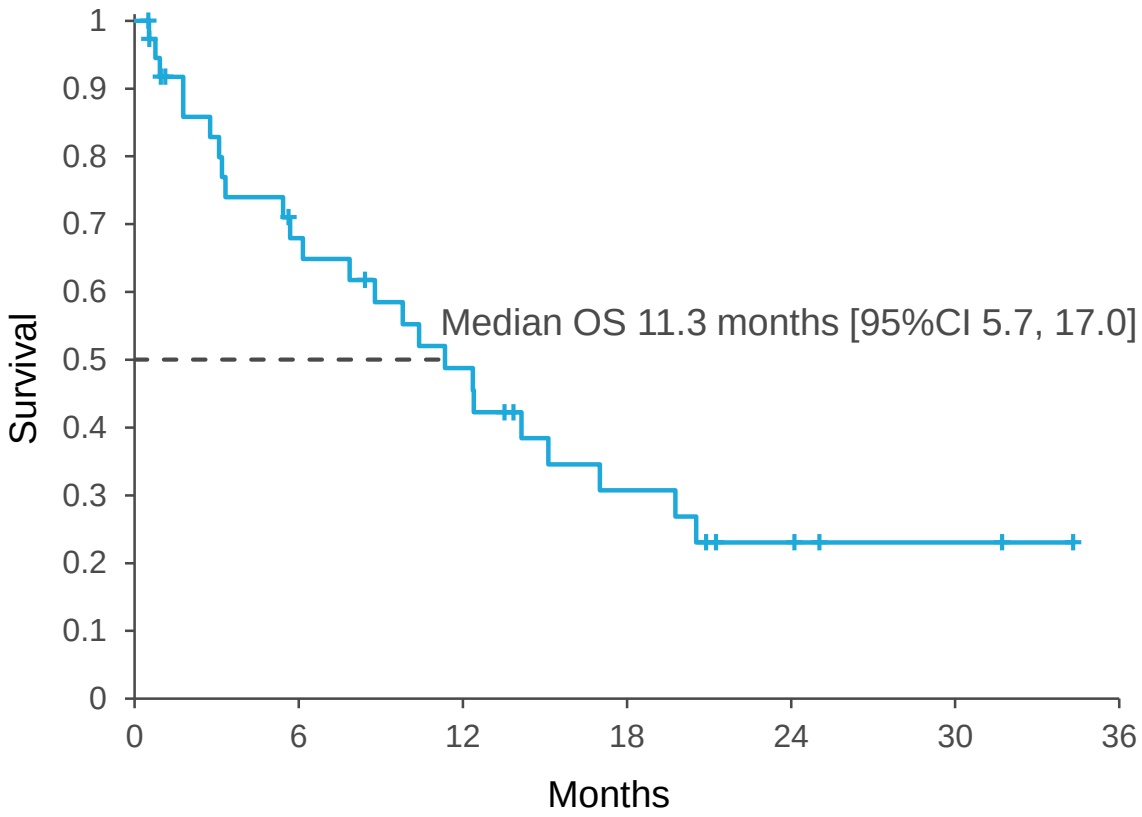
EVENT-FREE SURVIVAL



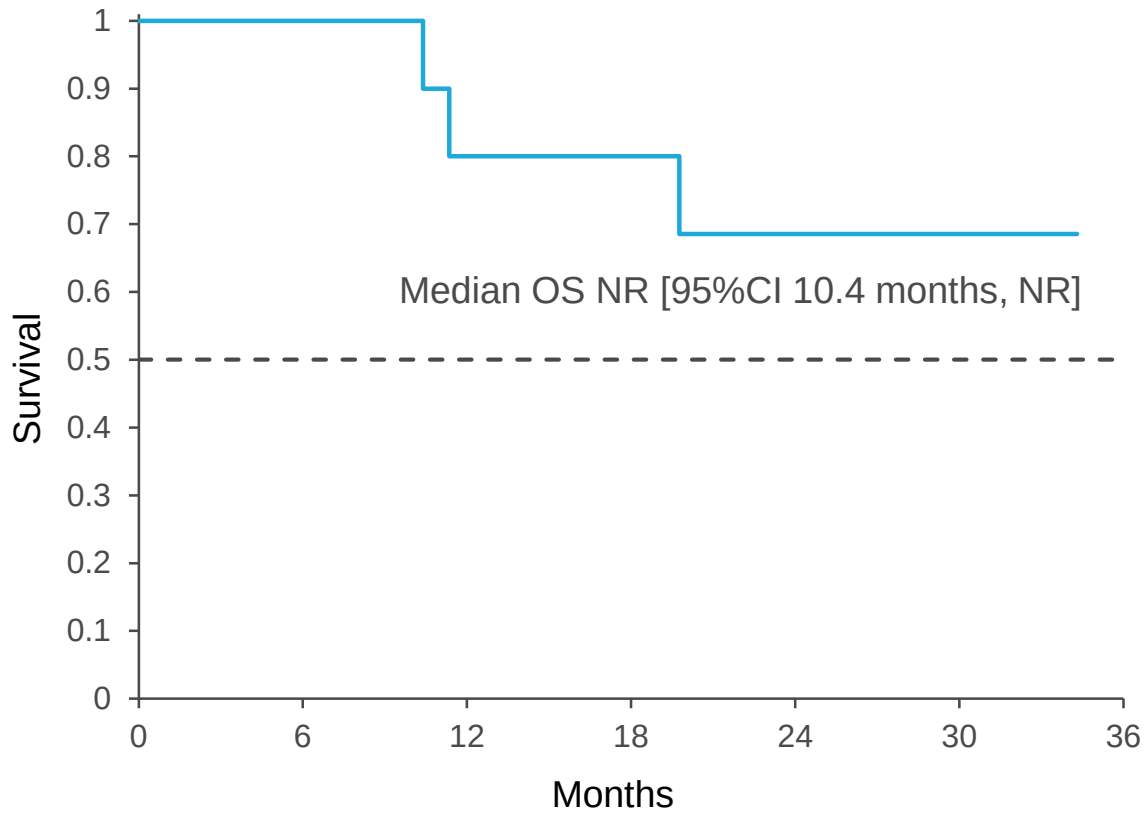
Data cutoff: 1 Sept 2017

OVERALL SURVIVAL

Overall Survival



Overall Survival: Responders



Data cutoff: 1 Sept 2017
NR, not reached; OS, overall survival

CONCLUSIONS

- Enasidenib monotherapy was generally well tolerated by older patients with previously untreated m*IDH2* AML
  - Treatment-related TEAEs were infrequent; only 2 patients discontinued due to a treatment-related TEAEs
  - Grade 3-4 cytopenias were relatively uncommon (≤16% of patients)
  - Safety profile similar to that reported for all patients in the phase 1 portions of the study
- Enasidenib was associated with a promising response rate
  - Approximately one-third of patients responded, including 8 who attained CR, CRi, or CRp
  - Responses were durable: at median follow-up of 8.6 months, median duration of any response was >1 year and median duration of CR was not reached
- Median OS was 11.3 months and median EFS was 5.7 months; median OS for those who achieved a response was not reached
- The use of enasidenib in patients with newly diagnosed AML is a promising strategy with several ongoing follow up studies
  - The AG221-AML-005 study of enasidenib or ivosidenib (an IDH1 inhibitor) in combination with azacitidine in patients not eligible for induction (NCT02677922)
  - The AG120-221-C-001 study of enasidenib or ivosidenib in combination with standard 7+3 induction chemotherapy and consolidation (NCT02632708) (Oral presentation of interim results, Monday Dec 11, Abstract 726, Stein et al)
  - The Beat AML Master Trial including enasidenib in patients aged ≥60 years (NCT03013998)

BACKUP SLIDES