# ENASIDENIB IN MUTANT-*IDH2* RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA (R/R AML): RESULTS OF A PHASE 1/2 STUDY

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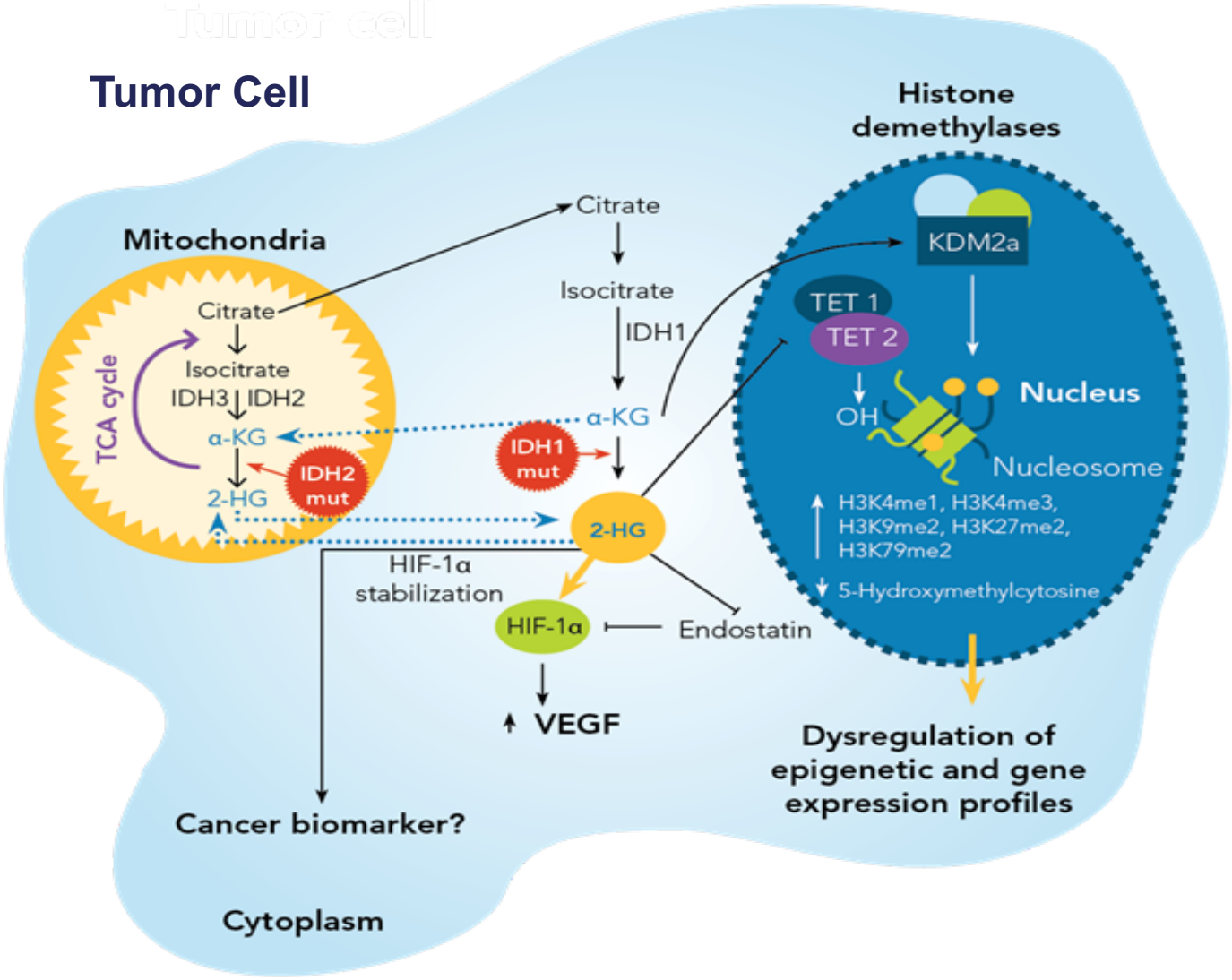
# ISOCITRATE DEHYDROGENASE (IDH) MUTATIONS AS A TARGET IN AML

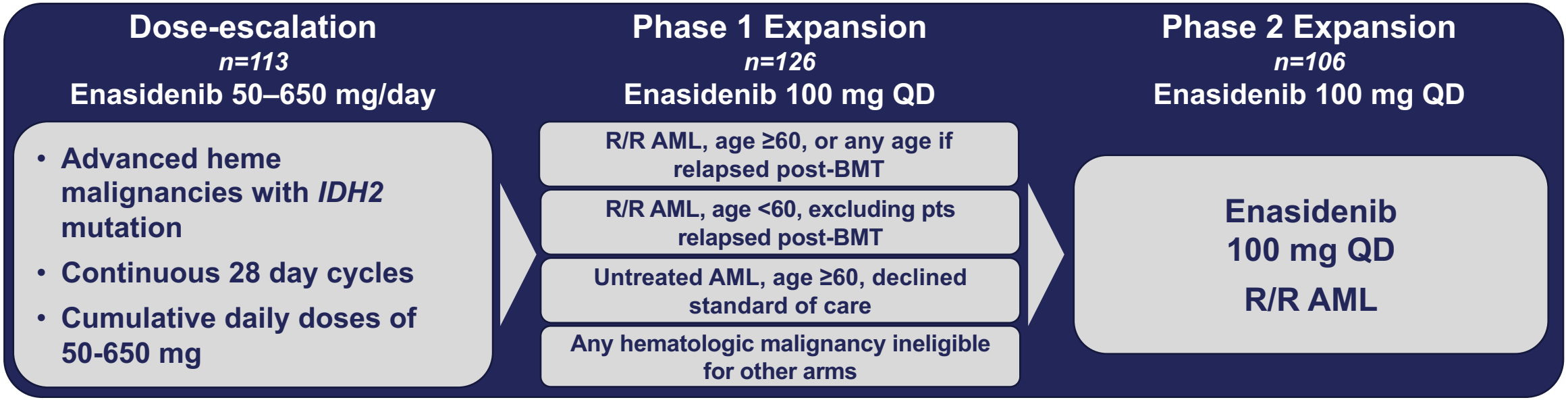
- IDH2 is an enzyme of the citric acid cycle
- Mutant *IDH2* (m*IDH2*) occurs in ~12% of patients with AML[1]
- m*IDH2* produces 2-HG, which alters DNA methylation and leads to a block in cellular differentiation
- Enasidenib (AG-221) is a selective, oral, potent inhibitor of mIDH2 enzyme
- Enasidenib 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
- Responses assessed by local investigator per IWG criteria[1]
- Assessment of clinical activity, with focus on 100-mg daily dose in patients with R/R AML

Data cutoff: 14 October 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 Patients N = 345 |
|---|---|---|---|
| | 100 mg/day dose n = 214 | All doses n = 281 | |
| **Age (years), median (range)** | 68 (19–100) | 68 (19–100) | 69 (19–100) |
| **Gender, %M / %F** | 51 / 49 | 54 / 46 | 58 / 42 |
| ***IDH2* mutation site, n (%)** | | | |
| R140 | 161 (75) | 208 (74) | 258 (75) |
| R172 | 50 (23) | 70 (25) | 82 (24) |
| **ECOG PS, n (%)** | | | |
| 0-1 | 181 (85) | 233 (83) | 283 (82) |
| 2 | 32 (15) | 47 (17) | 61 (18) |
| **Number of prior Tx, median (range)** | 2.0 (1–6) | 2.0 (1–14) | - |
| **Cytogenetic risk status, n (%)** | n=163 | n=211 | n=258 |
| Intermediate-risk | 108 (66) | 142 (67) | 174 (67) |
| Poor-risk | 55 (34) | 69 (33) | 84 (33) |
| **Prior AML therapy outcomes,* n (%)** | | | |
| Refractory to initial induction or re-induction treatment | 63 (32) | 85 (33) | -- |
| Relapsed/refractory to ≥2 cycles of 1st-line lower-intensity therapy† | 57 (29) | 75 (29) | -- |
| Relapsed within 1 year of initial treatment | 56 (29) | 70 (27) | -- |
| Relapsed >1 year after initial treatment | 13 (6.1) | 20 (7.1) | -- |
| Relapsed post-transplant | 29 (15) | 41 (16) | -- |
| In 2nd or later relapse | 26 (13) | 35 (14) | -- |

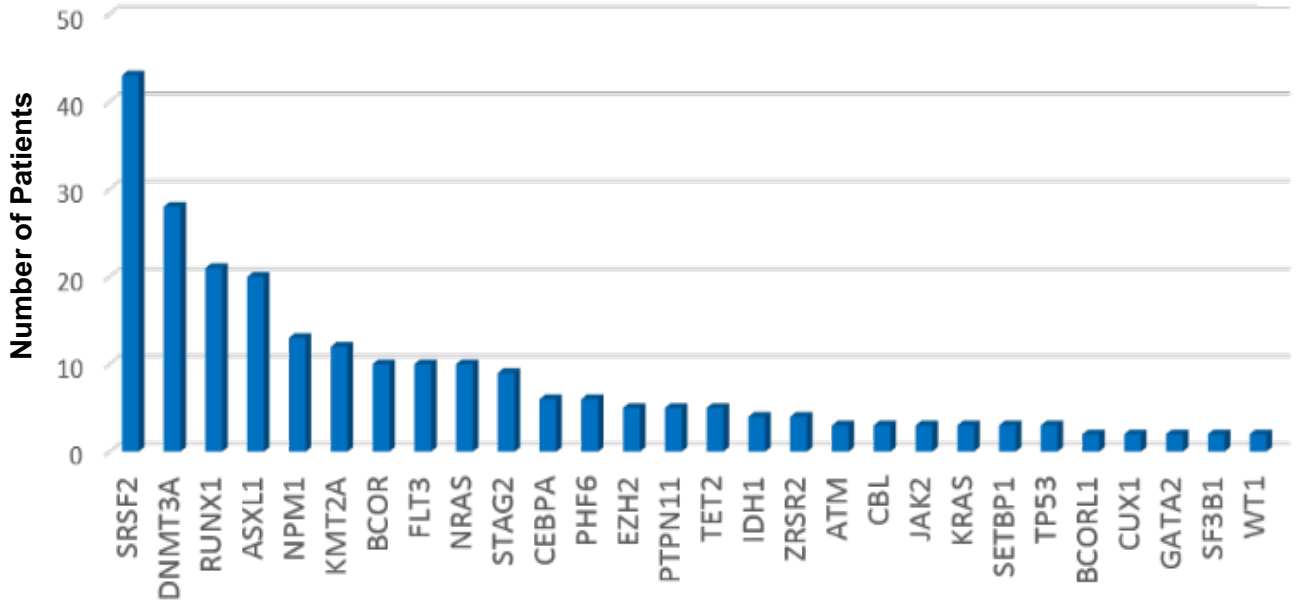
Data cutoff: 14 October 2016

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

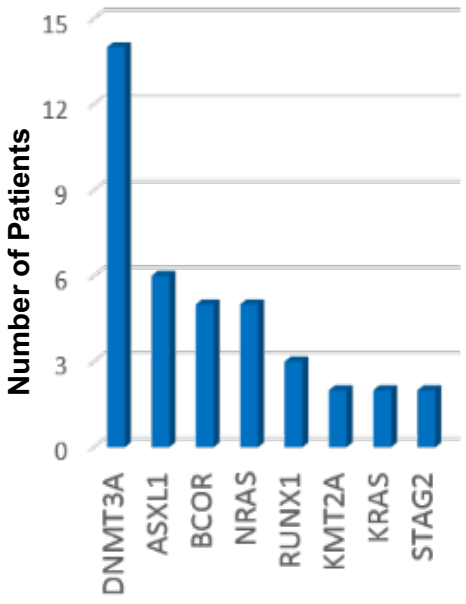
ECOG PS, Eastern Cooperative Oncology Group performance status score; Tx, treatment

# CO-OCCURRING MUTATIONS AT SCREENING

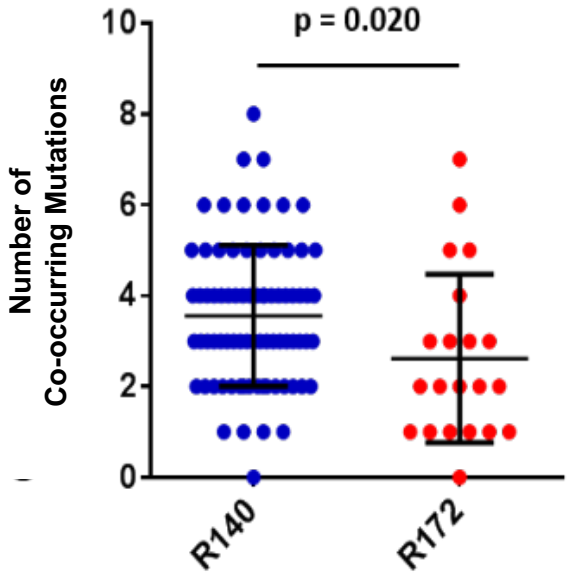
## R/R AML m*IDH2*-R140




## 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

Amatangelo et al. *Blood* 2017;doi.org/10.1182/blood-2017-04-779447 (Epub ahead of print)
Co-mutational data from 100 patient samples collected at study entry

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

| All Patients (N=345) | Any Grade | Grade 3-4 | |
|---|---|---|---|
| | | All | Treatment-related |
| Nausea | 48% | 5% | 2% |
| Diarrhea | 41% | 4% | < 1% |
| Fatigue | 41% | 8% | 2% |
| Decreased appetite | 34% | 4% | 2% |
| Blood bilirubin increased | 33% | 11% | 8% |
| Vomiting | 33% | 2% | < 1% |
| Dyspnea | 32% | 8% | 3% |
| Anemia | 32% | 24% | 6% |
| Cough | 30% | 8% | 0 |
| Febrile neutropenia | 30% | 29% | 2% |
| Peripheral edema | 29% | 1% | < 1% |
| Pyrexia | 28% | 3% | < 1% |
| Constipation | 27% | < 1% | 0 |
| Hypokalemia | 26% | 8% | < 1% |
| Thrombocytopenia | 21% | 18% | 3% |
| Headache | 20% | < 1% | < 1% |
| Pneumonia | 20% | 16% | 0 |

- **Serious treatment-related IDH-DS was reported for 7% of patients**

Data cutoff: 14 October 2016
IDH-DS, IDH-inhibitor-associated differentiation syndrome

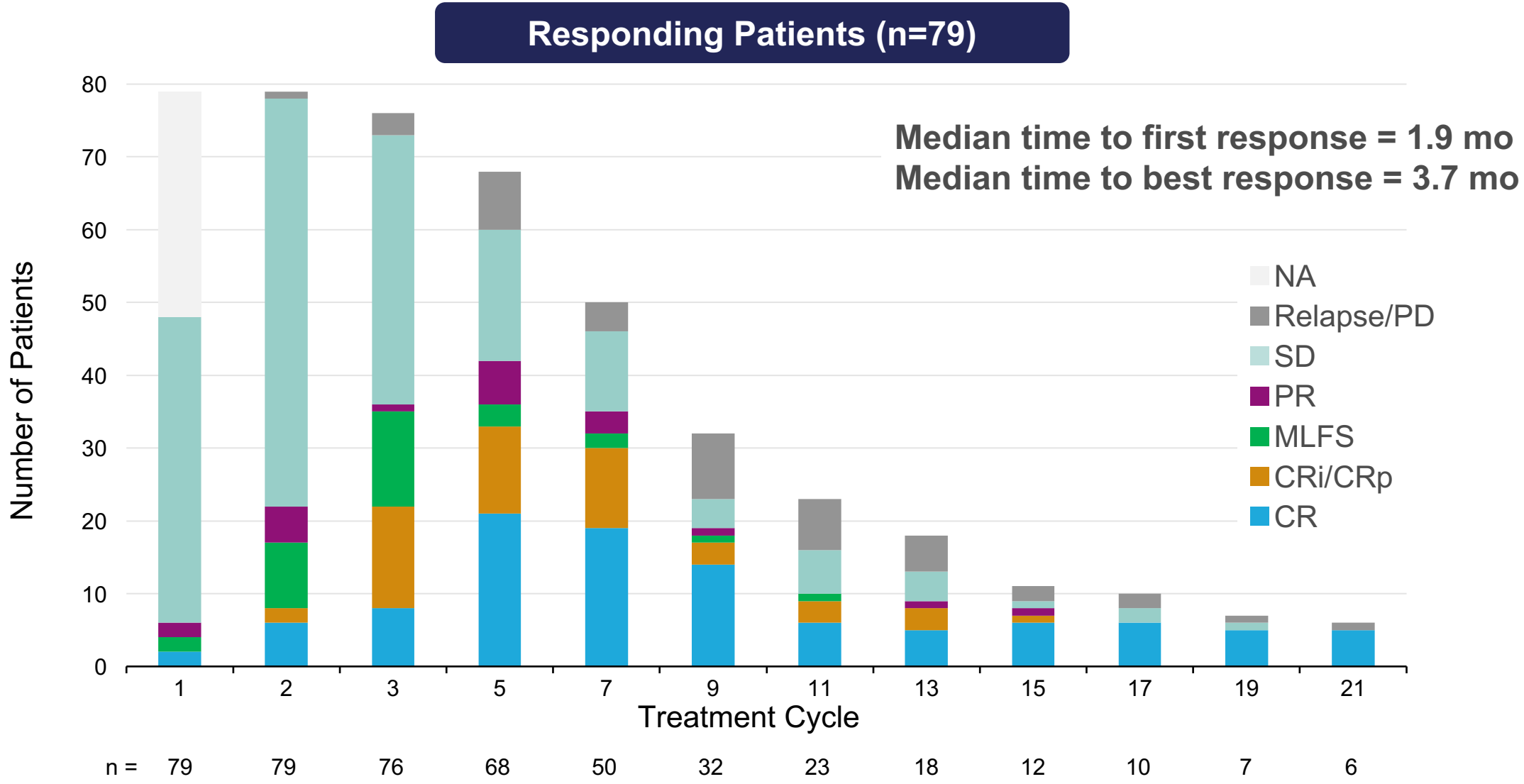
# RESPONSE IN R/R AML

| | Relapsed/Refractory AML | |
|---|---|---|
| | **Enasidenib 100 mg/day (n=214)** | **All doses (N=281)** |
| **Overall response rate**, % [n/N] | **37% (79/214)** | **38% (108/281)** |
| [95% CI] | [30.4, 43.8] | [32.7, 44.4] |
| **Best response** | | |
| CR, n (%) | **43 (20.1)** | **55 (19.6)** |
| [95% CI] | [14.9, 26.1] | [15.1, 24.7] |
| CRi or CRp, n (%) | 17 (7.9) | 22 (7.8) |
| PR, n (%) | 8 (3.7) | 16 (5.7) |
| MLFS, n (%) | 11 (5.1) | 15 (5.3) |
| SD, n (%) | 110 (51.4) | 137 (48.8) |
| PD, n (%) | 11 (5.1) | 15 (5.3) |
| NE, n (%) | 2 (0.9) | 3 (1.1) |
| **Time to first response (mos)**, median (range) | 1.9 (0.5–11.1) | 1.9 (0.5-11.1) |
| **Duration of response (mos)**, median [95%CI] | 5.6 [4.6, 7.4] | 5.6 [4.6, 6.5] |
| **Time to CR (mos)**, median (range) | 3.7 (0.7–11.2) | 3.8 (0.5-11.2) |
| **Duration of response in pts with CR (mos)**, median [95%CI] | 8.8 [5.6, NR] | 7.4 [6.4, 14.7] |

Data cutoff: 14 October 2016

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

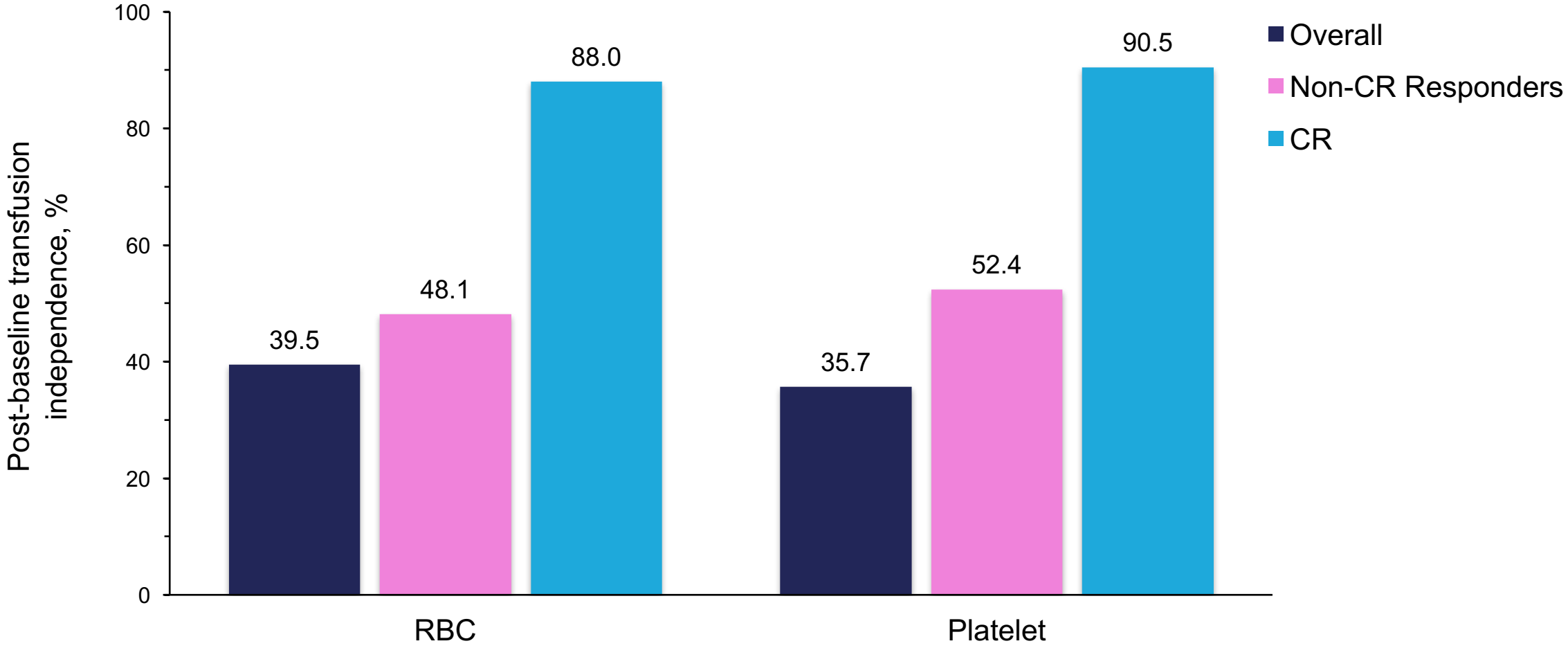
# ENASIDENIB 100 MG/DAY IN R/R AML: RESPONSE OVER TIME




Data cutoff: 14 October 2016

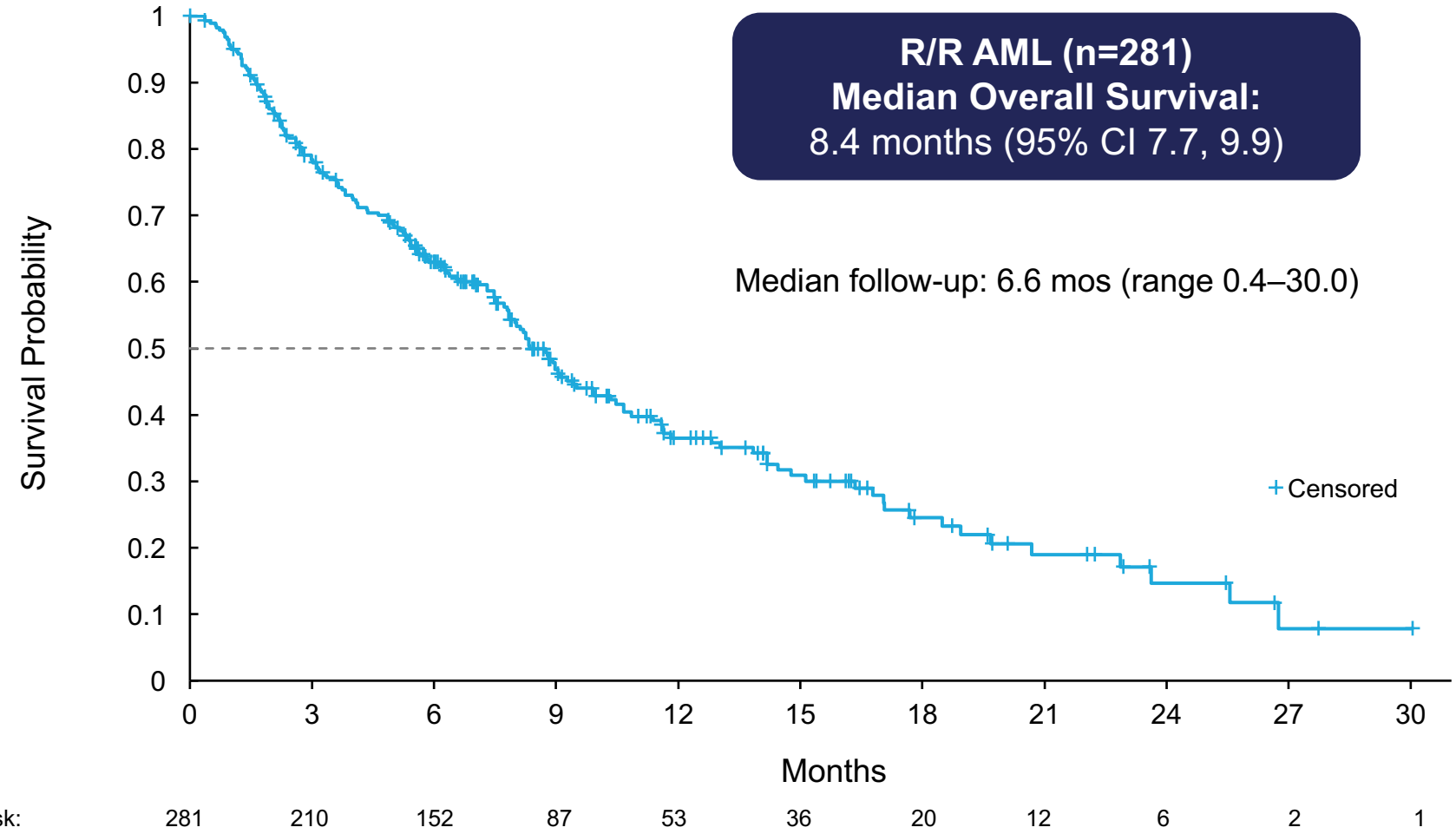
CR, complete remission; CRp, CR with incomplete platelet recovery; CRi, CR with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; PR, partial remission; SD, stable disease; PD, progressive disease

# ENASIDENIB 100 MG/DAY IN R/R AML: TRANSFUSION INDEPENDENCE




Data cutoff: 14 October 2016
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

# ENASIDENIB IN ALL R/R AML: OVERALL SURVIVAL

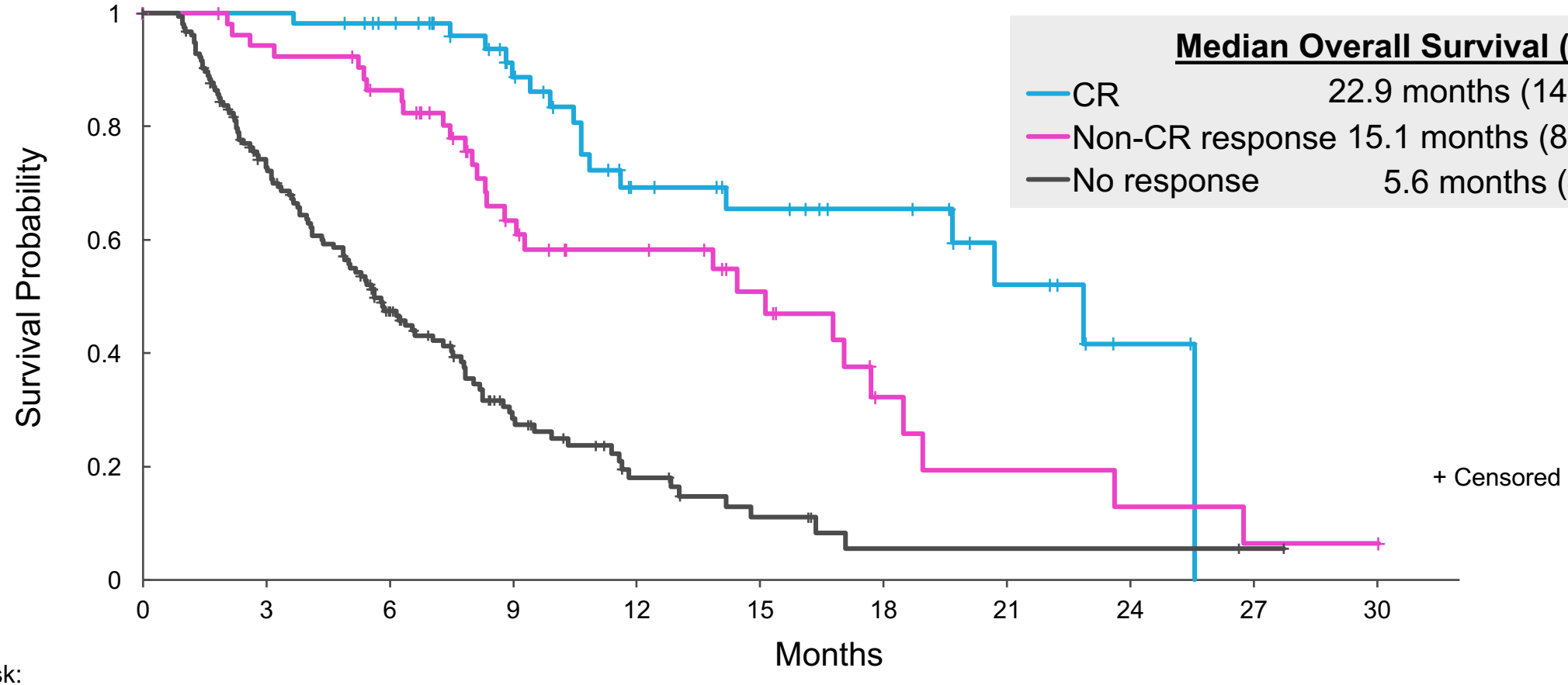



- **Median OS for patients treated with enasidenib 100 mg/day (n=214): 8.3 months (95%CI 7.5, 9.4)**

Data cutoff: 14 October 2016

# OVERALL SURVIVAL BY BEST RESPONSE

**R/R AML Patients (N=281)**




**Median Overall Survival (95% CI)**

| | |
|---|---|
| CR | 22.9 months (14.2, 25.6) |
| Non-CR response | 15.1 months (8.8, 18.5) |
| No response | 5.6 months (4.9, 7.3) |

Pts at risk:

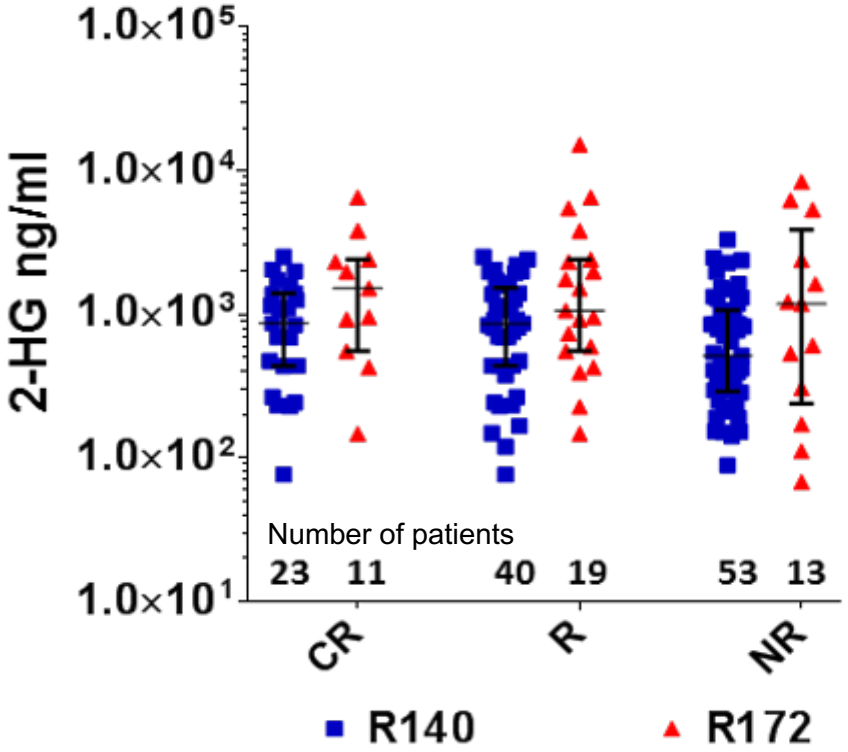
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CR | 55 | 55 | 50 | 35 | 21 | 17 | 13 | 7 | 2 | 0 | 0 |
| Non-CR response | 53 | 49 | 43 | 25 | 19 | 13 | 5 | 3 | 2 | 1 | 1 |
| No response | 155 | 104 | 58 | 26 | 12 | 6 | 2 | 2 | 2 | 1 | 0 |

Data cutoff: 14 October 2016
CR, complete remission

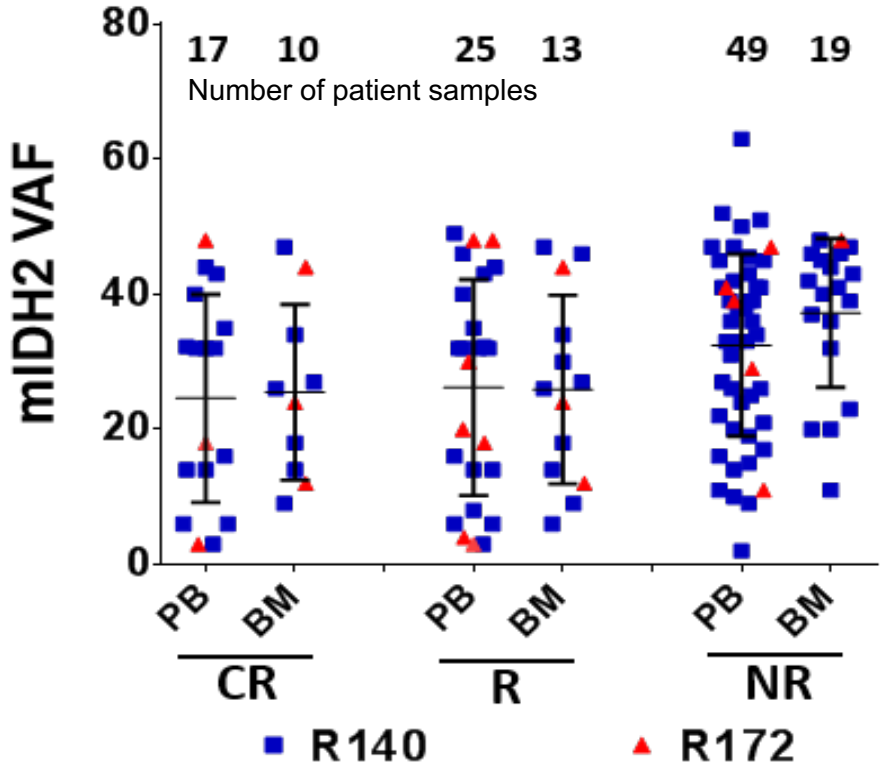
# 2-HG CONCENTRATIONS, VARIANT ALLELE FREQUENCY, AND RESPONSE

- **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

Amatangelo et al. *Blood* 2017;doi.org/10.1182/blood-2017-04-779447 (Epub ahead of print)
VAF, variant allele frequency

# CONCLUSIONS

- Enasidenib was well tolerated in this mainly older patient population; most adverse events were not treatment-related and were grade 1-2 in severity
- In patients with relapsed/refractory AML, most of whom had received multiple prior AML treatments, enasidenib induced durable CRs and was associated with OS of > 8 months
- 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

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