# Management of Newly Diagnosed and Previously Treated AML with IDH Mutations

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# The Promise of Differentiation Therapy - APL

## Use of All-*Trans* Retinoic Acid in the Treatment of Acute Promyelocytic Leukemia

By Huang Meng-er, Ye Yu-chen, Chen Shu-rong, Chai Jin-ren, Lu Jia-Xiang, Zhoa Lin, Gu Long-jun, and Wang Zhen-yi

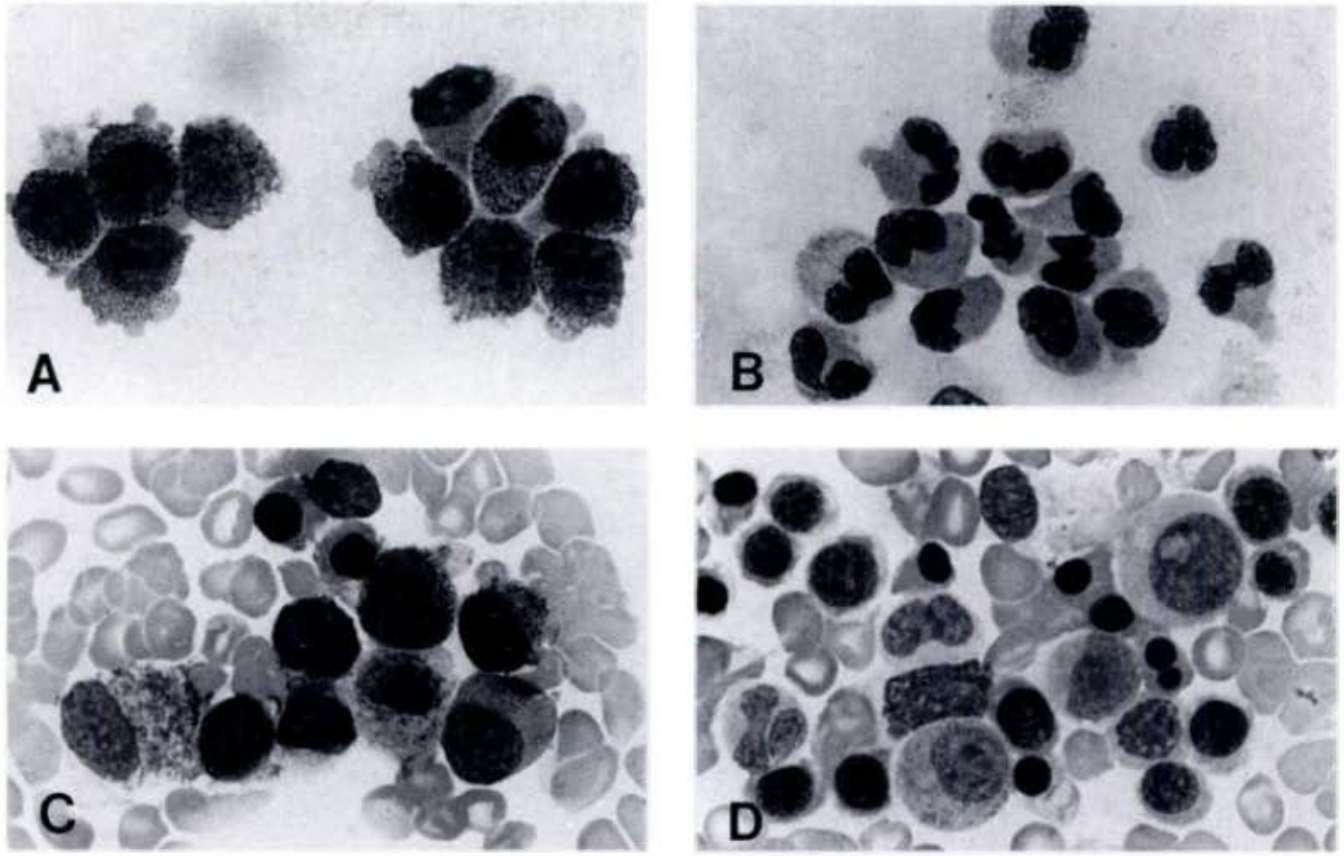


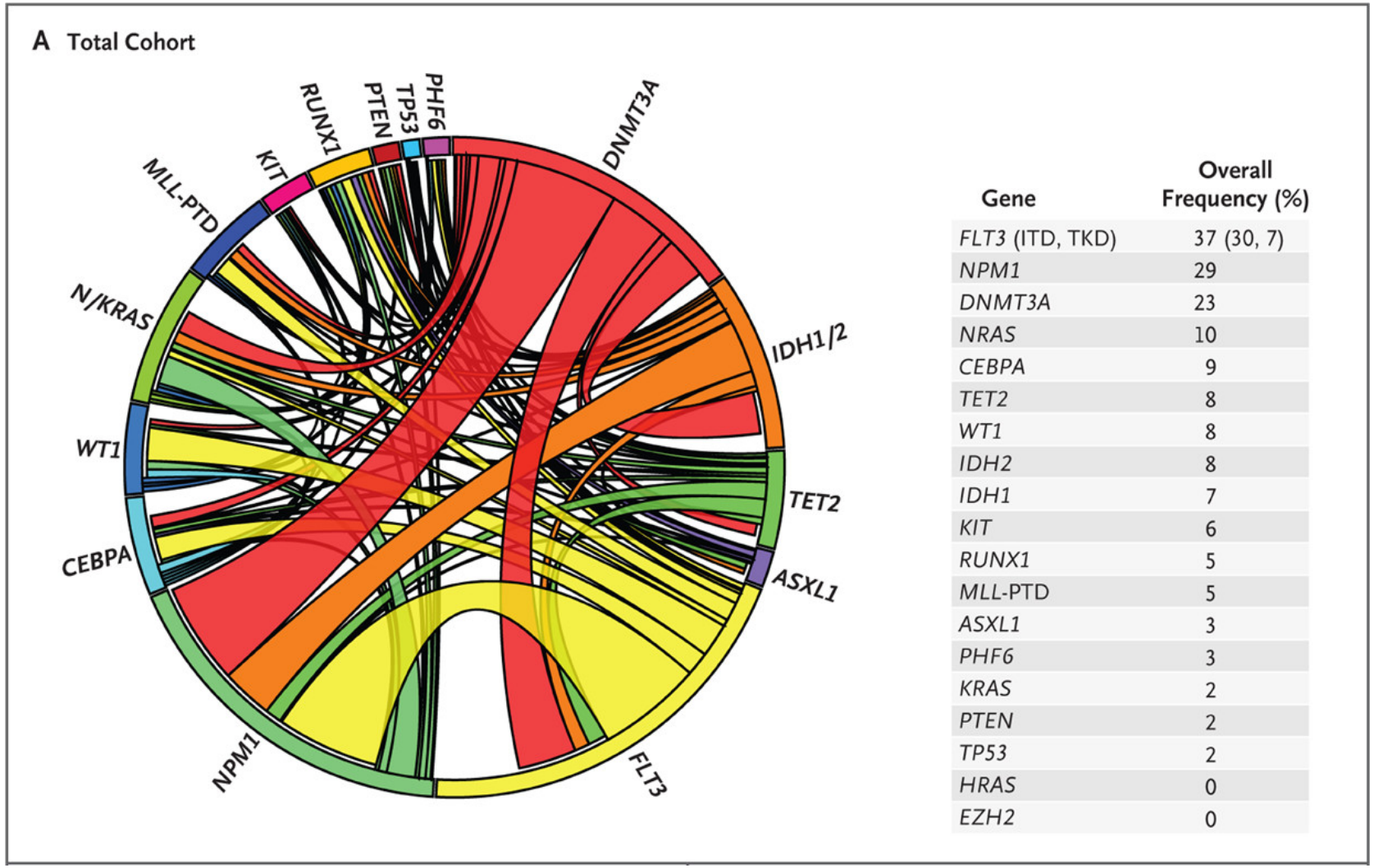

Fig 1. Morphological maturation of leukemic cells of case 10 in vitro and in vivo. (A) Cells cultured without RA, consisting of promyelocytes with characteristic cytoplasmic granules (×1,000). (B) Cells cultured with RA, showing maturation to granulocytes (×1,000). (C) Bone marrow before RA treatment. The predominance of promyelocytes (76%) indicates typical APL. (D) Bone marrow after 5 weeks of RA treatment. Promyelocyte level <2% and restoration of normal hematopoiesis without a phase of aplasia are consistent with differentiation induction.



Courtesy of Eytan M Stein, MD

Meng-er H, Blood, 1988

# Recurring Mutations in Patients with AML



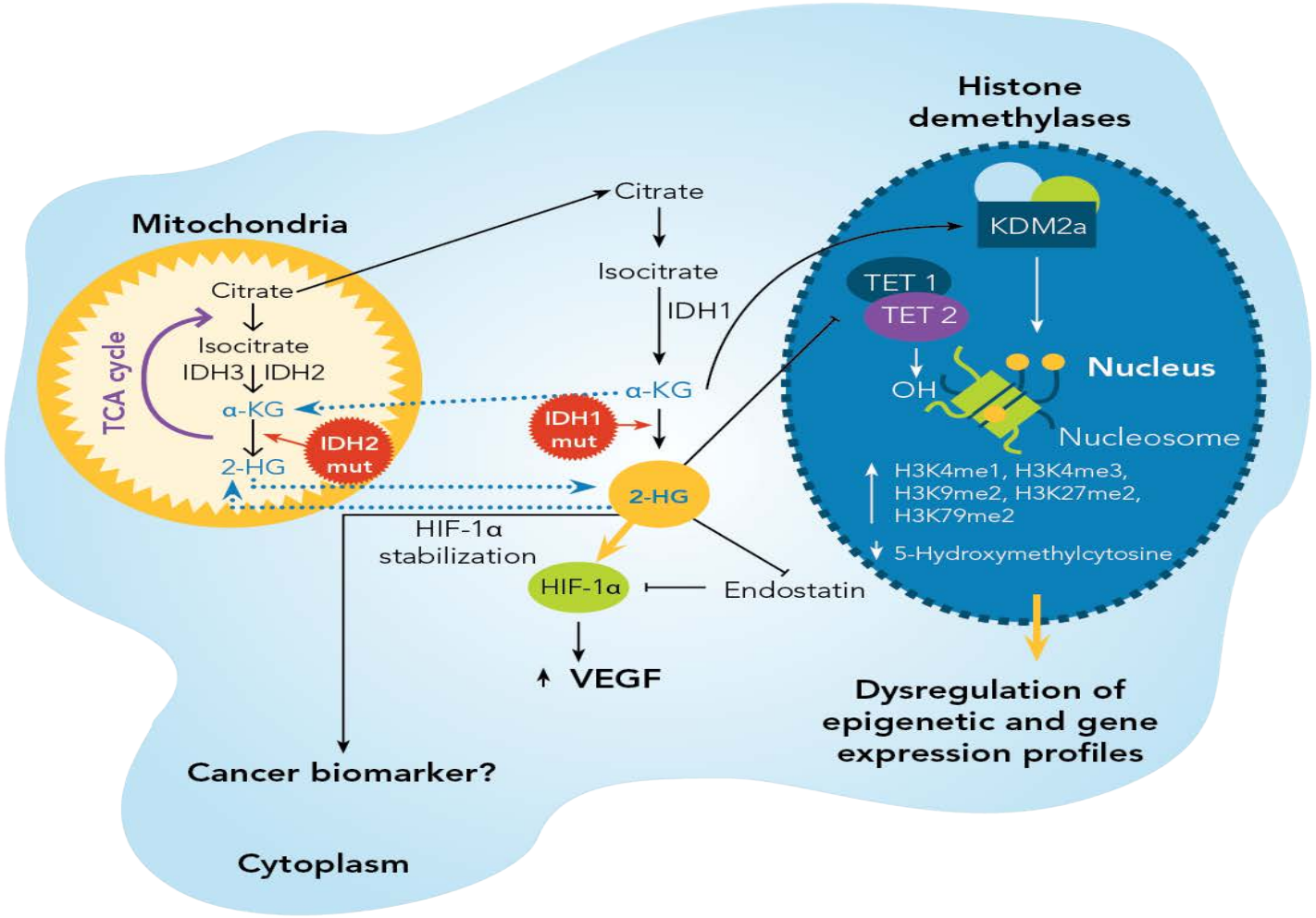

| Gene | Overall Frequency (%) |
|---|---|
| *FLT3* (ITD, TKD) | 37 (30, 7) |
| *NPM1* | 29 |
| *DNMT3A* | 23 |
| *NRAS* | 10 |
| *CEBPA* | 9 |
| *TET2* | 8 |
| *WT1* | 8 |
| *IDH2* | 8 |
| *IDH1* | 7 |
| *KIT* | 6 |
| *RUNX1* | 5 |
| *MLL-PTD* | 5 |
| *ASXL1* | 3 |
| *PHF6* | 3 |
| *KRAS* | 2 |
| *PTEN* | 2 |
| *TP53* | 2 |
| *HRAS* | 0 |
| *EZH2* | 0 |



Courtesy of Eytan M Stein, MD

Patel JP et al. N Engl J Med 2012;366:1079-1089.

# Pathogenesis of IDH Mutant AML




- IDH1 in cytoplasm and IDH2 in mitochondria
- Cancer-associated IDHm produces 2-hydroxyglutarate (R-2-HG)



Courtesy of Eytan M Stein, MD

Prensner and Chinnaiyan Nature, 2011

# IDH2m and IDH1m: Distinct Genetically Defined Populations

| IDH Mutations Seen in Multiple Cancer Types | | |
|---|---|---|
| Target | Indication | IDHm (%) |
| IDH2m | AML | 15% |
| | MDS/MPN | 5% |
| | Angio-immunoblastic NHL | 25% |
| | Others (melanoma, glioma, chondro) | 3-5% |
| | Type II D-2HG Aciduria (inborn error of metabolism) | 100% |
| | | |
| IDH1m | Low-grade glioma & 2$^{ary}$ GBM | 70% |
| | Chondrosarcoma | >50% |
| | AML | 7.5% |
| | MDS/MPN | 5% |
| | Intrahepatic cholangiocarcinoma | 20% |
| | Others (colon, melanoma, lung) | 1-2% |



Courtesy of Eytan M Stein, MD

# ENAsidenib (IDH2) – Relapsed and Refractory AML.

# Efficacy of Enasidenib in R/R AML

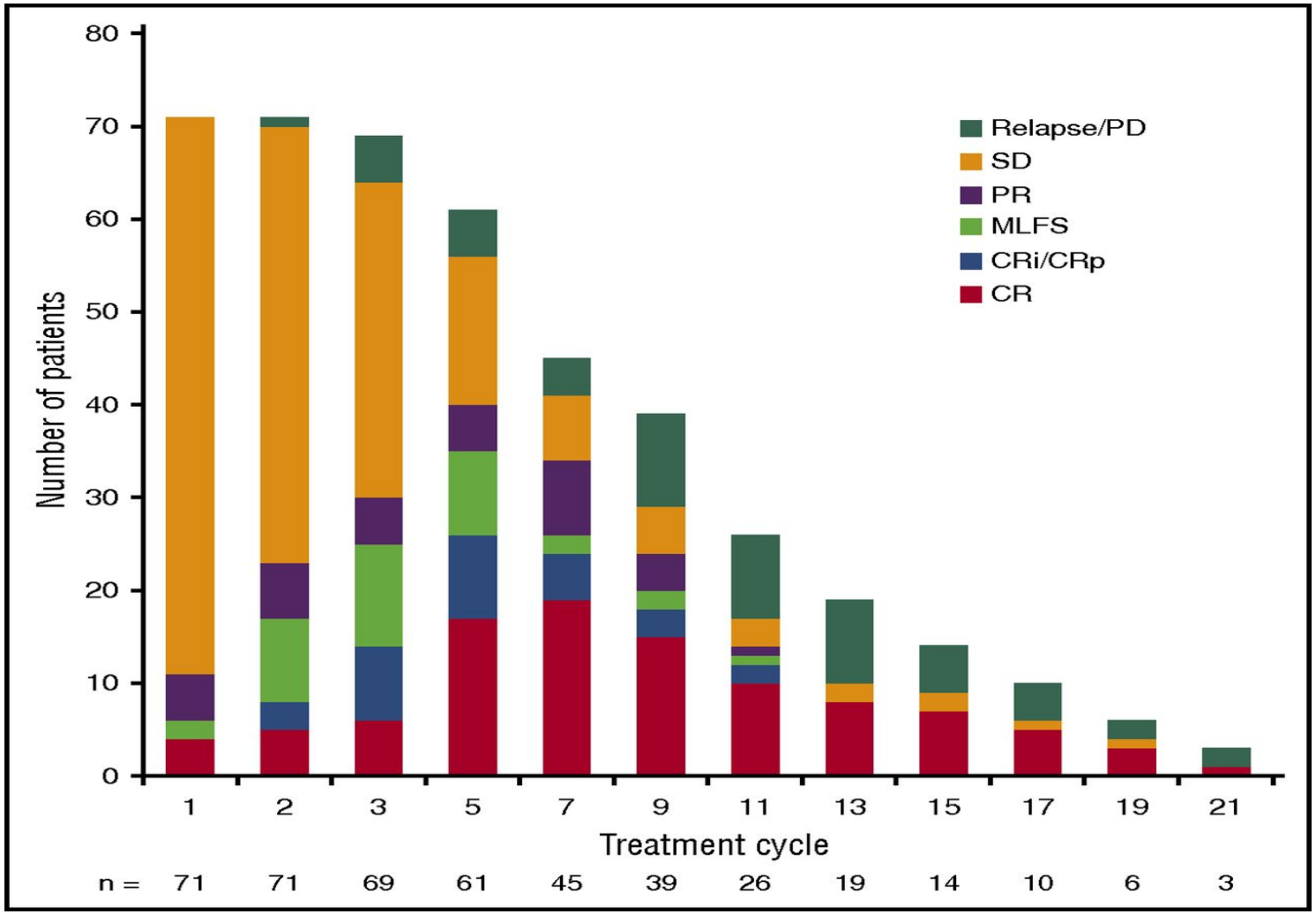
| | Relapsed/Refractory AML | |
|---|---|---|
| | Enasidenib 100 mg/day (n=214) | All patients (N=280) |
| Overall response rate, n (%) | 38·8% (83/214) | 39·6% (111/280) |
| CR + CRi/CRp | 62 (29·0) | 78 (27·9) |
| Best response, n (%) | | |
| Complete remission | 42 (19·6) | 53 (18·9) |
| CR with incomplete count recovery (CRi/CRp) | 20 (9·3) | 25 (8·9) |
| Partial remission, n (%) | 9 (4·2) | 17 (6·1) |
| Morphologic leukemia-free state, n (%) | 12 (5·6) | 16 (5·7) |
| Stable disease, n (%) | 98 (45·8) | 122 (43·6) |
| Progressive disease, n (%) | 19 (8·9) | 26 (9·3) |
| Not evaluable, n (%) | 3 (1·4) | 4 (1·4) |



Courtesy of Eytan M Stein, MD

Stein EM, Dinardo CD, Blood 2017

# Response Kinetics with Enasidenib

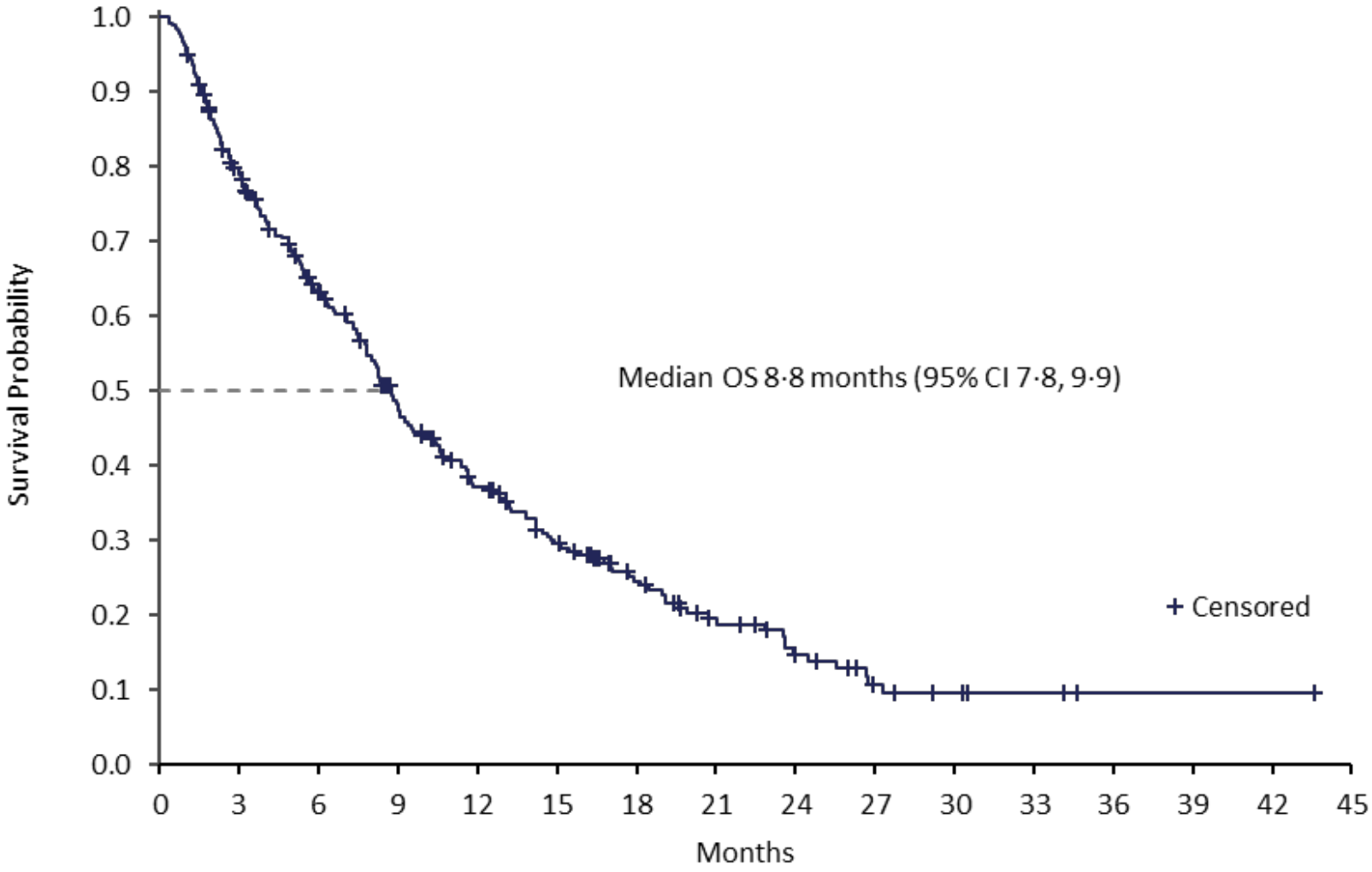





Courtesy of Eytan M Stein, MD

Stein EM, Dinardo CD, Blood 2017

# Overall Survival – All R/R Patients

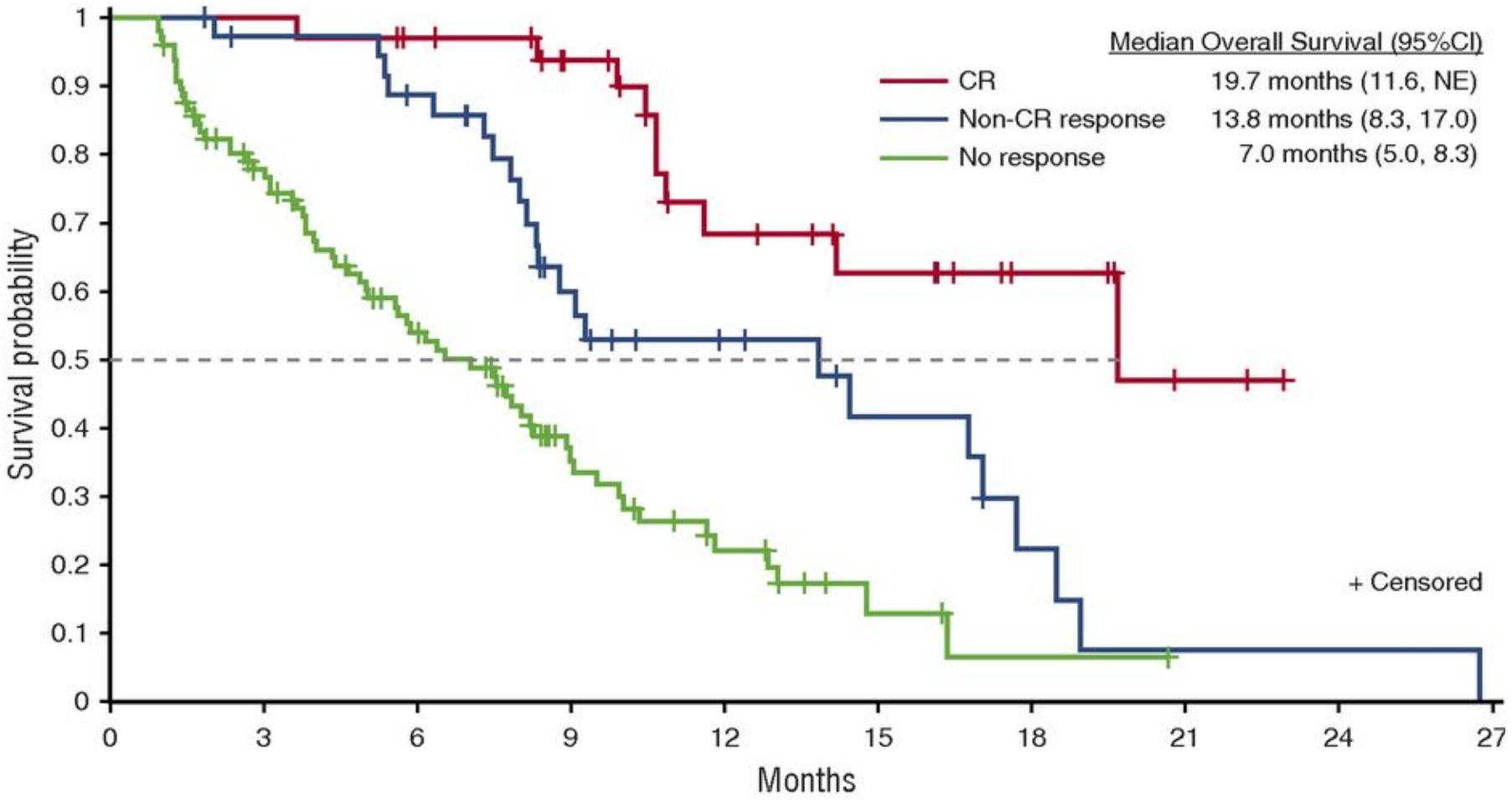





Courtesy of Eytan M Stein, MD

Stein EM, Dinardo CD, et al, Blood 2017

# Overall Survival Stratified by Best Response






Courtesy of Eytan M Stein, MD

Stein EM, Dinardo CD, et al, Blood 2017

# IDHentify – Randomized Enasidenib versus SOC

## Update on Phase 3 IDHENTIFY Trial in Patients with Relapsed or Refractory Acute Myeloma Leukemia

08/25/2020

CATEGORY: Corporate/Financial News

PRINCETON, N.J.—(BUSINESS WIRE)– (NYSE:BMY) The Phase 3 IDHENTIFY study evaluating enasidenib plus best supportive care (BSC) versus conventional care regimens, which include best supportive care (BSC) only, azacitadine plus BSC, low-dose cytarabine plus BSC or intermediate-dose cytarabine plus BSC, did not meet the primary endpoint of overall survival (OS) in patients with relapsed or refractory acute myeloid leukemia (R/R AML) with an isocitrate dehydrogenase-2 (IDH2) mutation. The safety profile of enasidenib was consistent with previously reported findings. The company will complete a full evaluation of the enasidenib data and work with investigators to present detailed results at a future medical meeting.

# IVOsidenib (IDH1 inhibitor) – Relapsed/Refractory AML

# Ivosidenib – Response and Response Duration

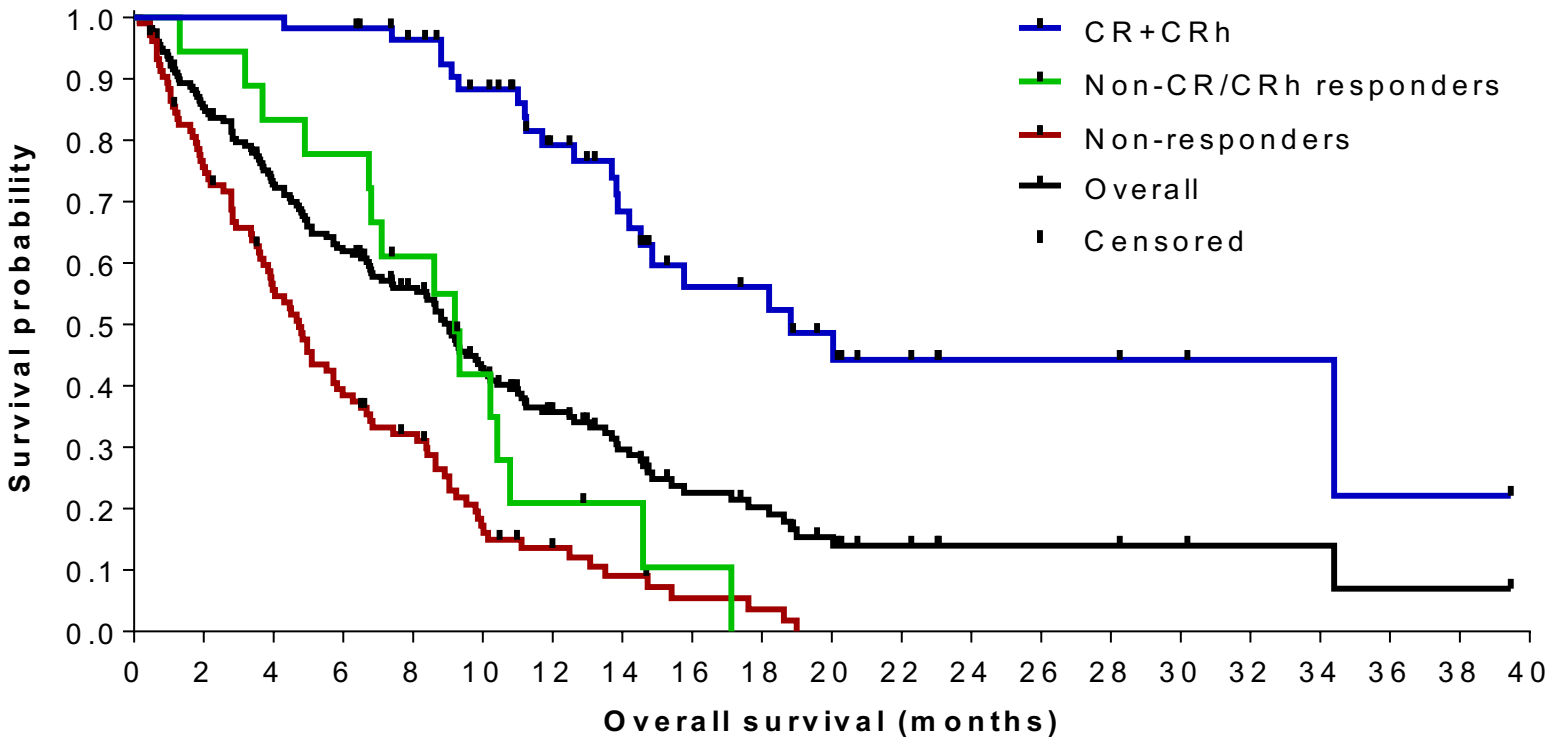
| Response | Primary Efficacy Population (N=125) | Relapsed or Refractory AML (N=179) |
|---|---|---|
| CR or CRh | | |
| No. of patients | 38 | 54 |
| % (95% CI) | 30.4 (22.5–39.3) | 30.2 (23.5–37.5) |
| Median time to CR or CRh (range) — mo | 2.7 (0.9–5.6) | 2.0 (0.9–5.6) |
| Median duration of CR or CRh (95% CI) — mo | 8.2 (5.5–12.0) | 6.5 (5.5–11.1) |
| CR | | |
| No. of patients | 27 | 39 |
| % (95% CI) | 21.6 (14.7–29.8) | 21.8 (16.0–28.6) |
| Median time to CR (range) — mo | 2.8 (0.9–8.3) | 2.8 (0.9–8.3) |
| Median duration of CR (95% CI) — mo | 9.3 (5.6–18.3) | 9.3 (5.6–12.5) |
| Overall response | | |
| No. of patients | 52 | 70 |
| % (95% CI) | 41.6 (32.9–50.8) | 39.1 (31.9–46.7) |
| Median time to first response (range) — mo§ | 1.9 (0.8–4.7) | 1.9 (0.8–4.7) |
| Median duration of response (95% CI) — mo | 6.5 (4.6–9.3) | 6.5 (4.6–9.3) |



Courtesy of Eytan M Stein, MD

CD Dinardo, EM Stein, S deBotton et. al. N Engl J Med 2018.

# Overall Survival by Best Response in R/R AML 500 mg (n=179)



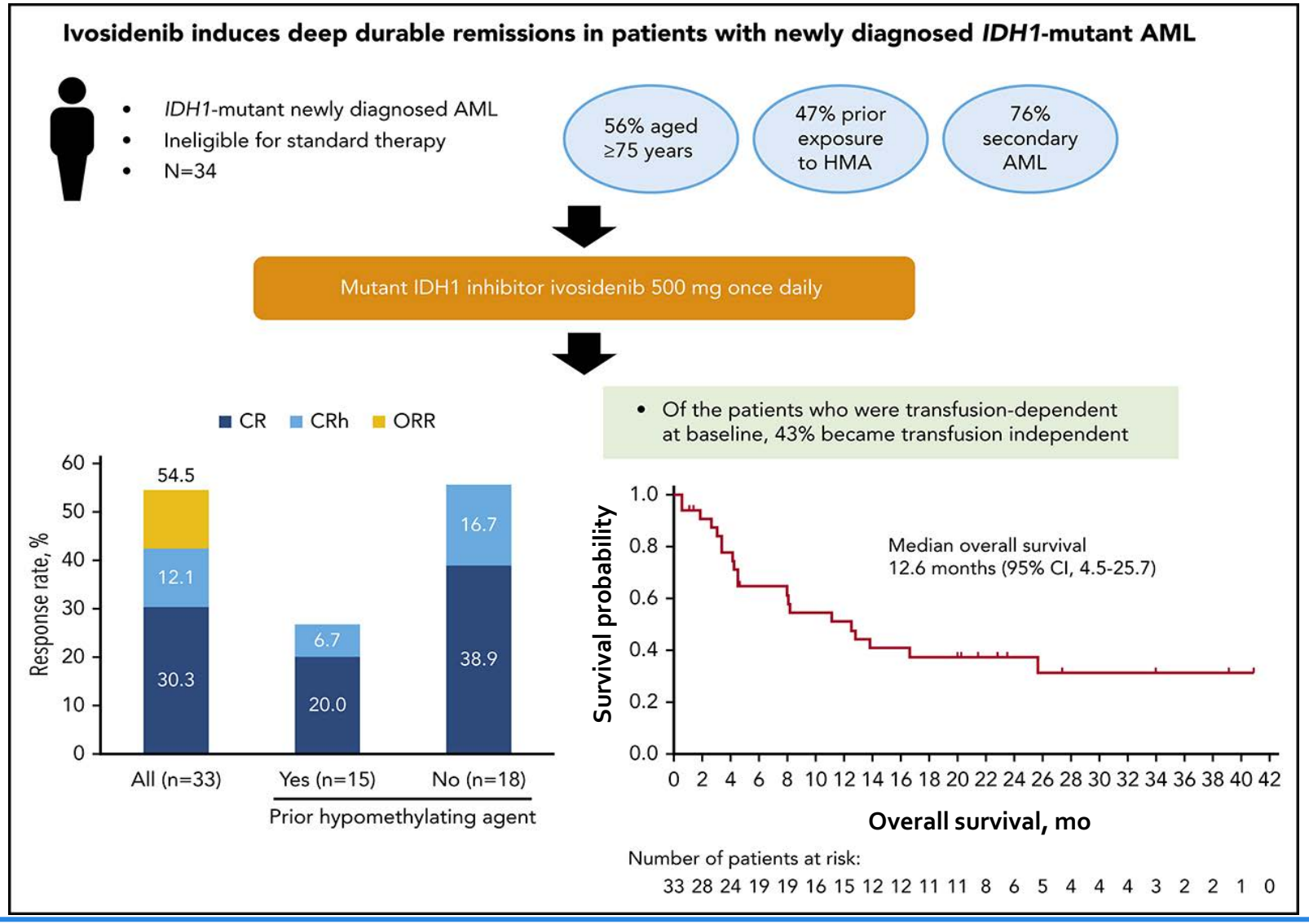

| | Months |
|---|---|
| Overall survival, median [95% CI] | |
| CR+CRh | 18.8 [14.2, NE] |
| Non-CR/CRh responders | 9.2 [6.7, 10.8] |
| Non-responders | 4.7 [3.7, 5.7] |
| All | 9.0 [7.1, 10.0] |
| Overall follow-up, median (range) | 15.3 (0.2–39.5) |

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

# Ivosidenib – Newly Diagnosed AML






Courtesy of Eytan M Stein, MD

Roboz G, et. Al, Blood 2020

# Differentiation Syndrome

**WARNING: DIFFERENTIATION SYNDROME**

**Patients treated with enasidenib have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.**



Courtesy of Eytan M Stein, MD

# Signs and Symptoms Consistent with IDH-DS (Enasidenib)

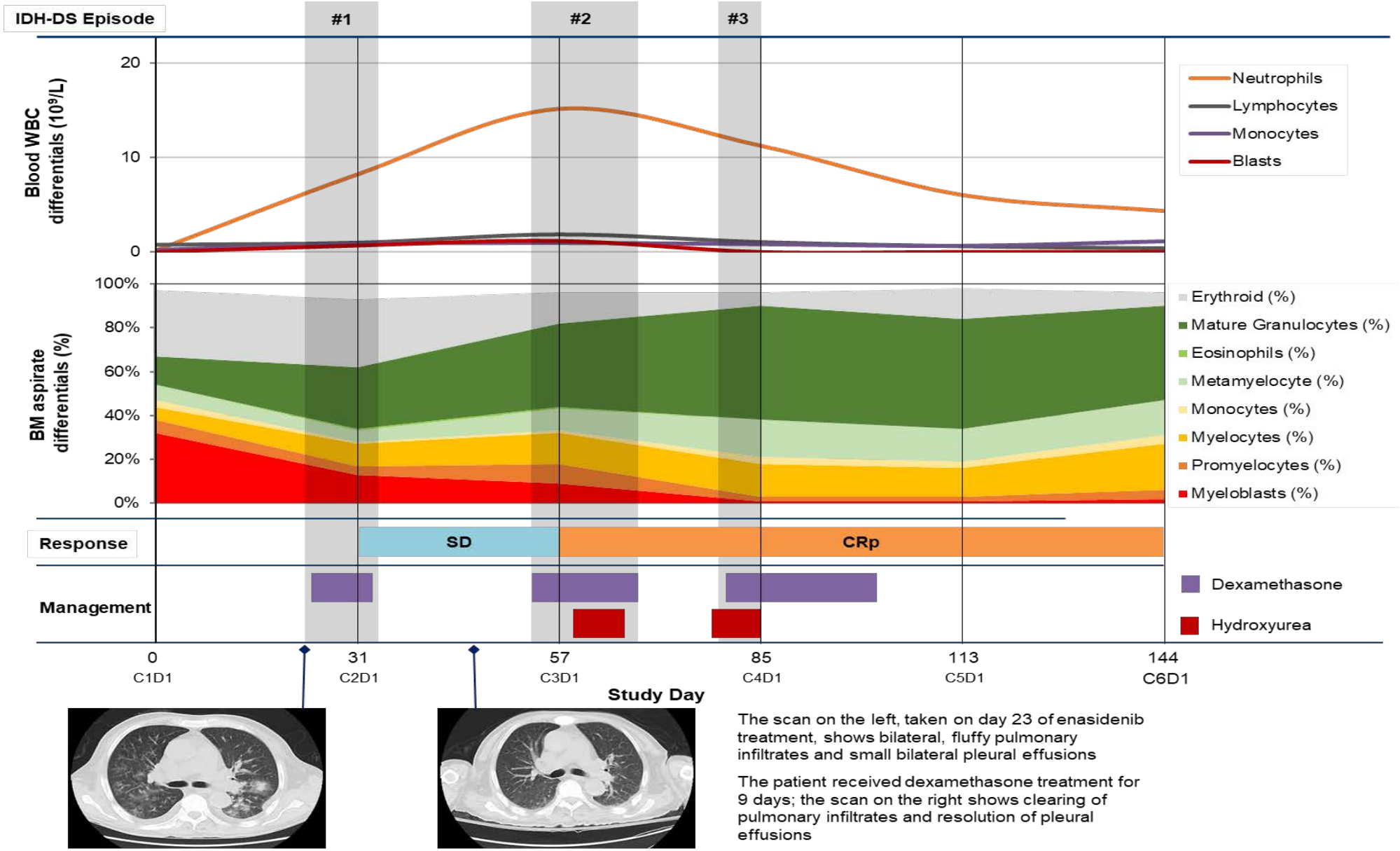
Table 1. Frequency of Signs and Symptoms Consistent With IDH-DS

| Sign or Symptom | Patients With IDH-DS, No. (%) (n = 33) |
|---|---|
| Dyspnea | 28 (85) |
| Unexplained fever (body temperature of 38.0°C for 2 d) | 26 (79) |
| Pulmonary infiltrates | 24 (73) |
| Hypoxia | 19 (58) |
| Acute kidney injury (CTCAE grade ≥2) | 14 (42) |
| Pleural effusion | 14 (42) |
| Bone pain or arthralgia | 9 (27) |
| Lymphadenopathy | 8 (24) |
| Rash | 8 (24) |
| Disseminated intravascular coagulopathy | 7 (21) |
| Edema or weight gain of >5 kg from screening | 7 (21) |
| Pericardial effusion | 5 (15) |



Courtesy of Eytan M Stein, MD

Fathi A, Dinardo CD, et al, JAMA Oncology 2018








The scan on the left, taken on day 23 of enasidenib treatment, shows bilateral, fluffy pulmonary infiltrates and small bilateral pleural effusions

The patient received dexamethasone treatment for 9 days; the scan on the right shows clearing of pulmonary infiltrates and resolution of pleural effusions

# Response Among Patients With and Without IDH-DS

**Table 2. Response Among Patients With and Without IDH-DS**

| Patient Response | IDH-DS, No. (%) (n = 33)[a] | No IDH-DS, No. (%) (n = 248) |
|---|---|---|
| Overall response[b] | 15 (45.5) | 93 (37.5) |
| CR | 6 (18.2) | 49 (19.8) |
| CRi/CRp | 6 (18.2) | 16 (6.5) |
| PR | 2 (6.1) | 14 (5.7) |
| MLFS | 1 (3.0) | 14 (5.7) |
| Stable disease[c] | 16 (48.5) | 121 (48.8) |
| Disease progression | 1 (3.0) | 14 (5.7) |




Courtesy of Eytan M Stein, MD

Fathi A, Dinardo CD, et al, JAMA Oncology 2018

# IDH Inhibitor Combinations with Standard of Care Therapy

# Ivosidenib with Aza – Newly Diagnosed AML

**TABLE 3.** Hematologic Response, Time to Response, and Response Duration (N = 23)

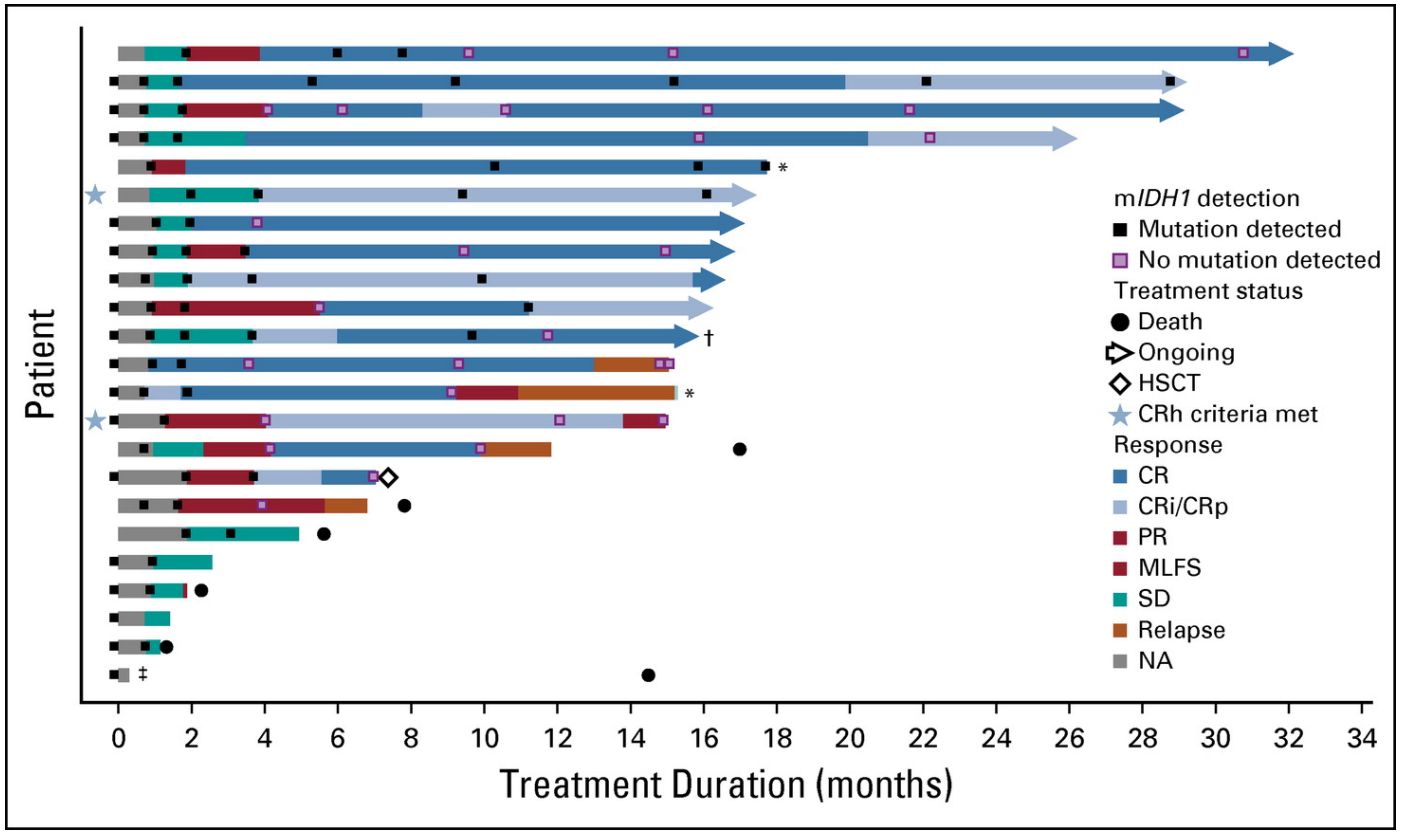
| Response Category | Response |
|---|---|
| CR + CRh,[a] No. (%) [95% CI] | 16 (69.6) [47.1 to 86.8] |
| Median time to CR/CRh, months (range) | 2.8 (0.8-11.5) |
| Median duration of CR/CRh, months [95% CI] | NE [12.2 to NE] |
| CR, No. (%) [95% CI] | 14 (60.9) [38.5 to 80.3] |
| Median time to CR, months (range) | 3.7 (0.8-15.7) |
| Median duration of CR, months [95% CI] | NE [9.3 to NE] |
| CRh,[a] No. (%) | 2 (8.7) |
| ORR,[b] No. (%) [95% CI] | 18 (78.3) [56.3 to 92.5] |
| Median time to response, months (range) | 1.8 (0.7-3.8) |
| Median duration of response, months [95% CI] | NE [10.3 to NE] |
| Best response,[c] No. (%) | |
| CR | 14 (60.9) |
| CRi/CRp | 2 (8.7) |
| MLFS | 2 (8.7) |
| SD | 4 (17.4) |
| NA | 1 (4.3) |

Abbreviations: CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; NA, not assessed; NE, not estimable; PR, partial response; ORR, objective response rate.

[a]CRh derived by sponsor.

[b]ORR comprises CR + CRi + CRp + PR + MLFS.

[c]Modified International Working Group criteria.

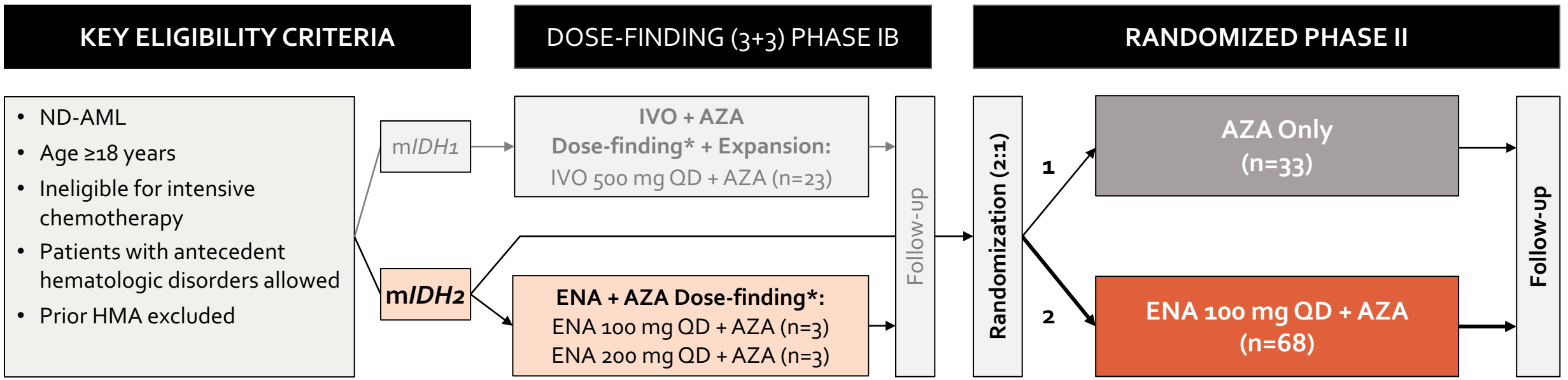



Memorial Sloan Kettering Cancer Center

Courtesy of Eytan M Stein, MD

*Dinardo C et. al, Journal of Clinical Oncology* 2020
DOI: 10.1200/JCO.20.01632]

# Aza With and Without Enasidenib – Newly Diagnosed AML

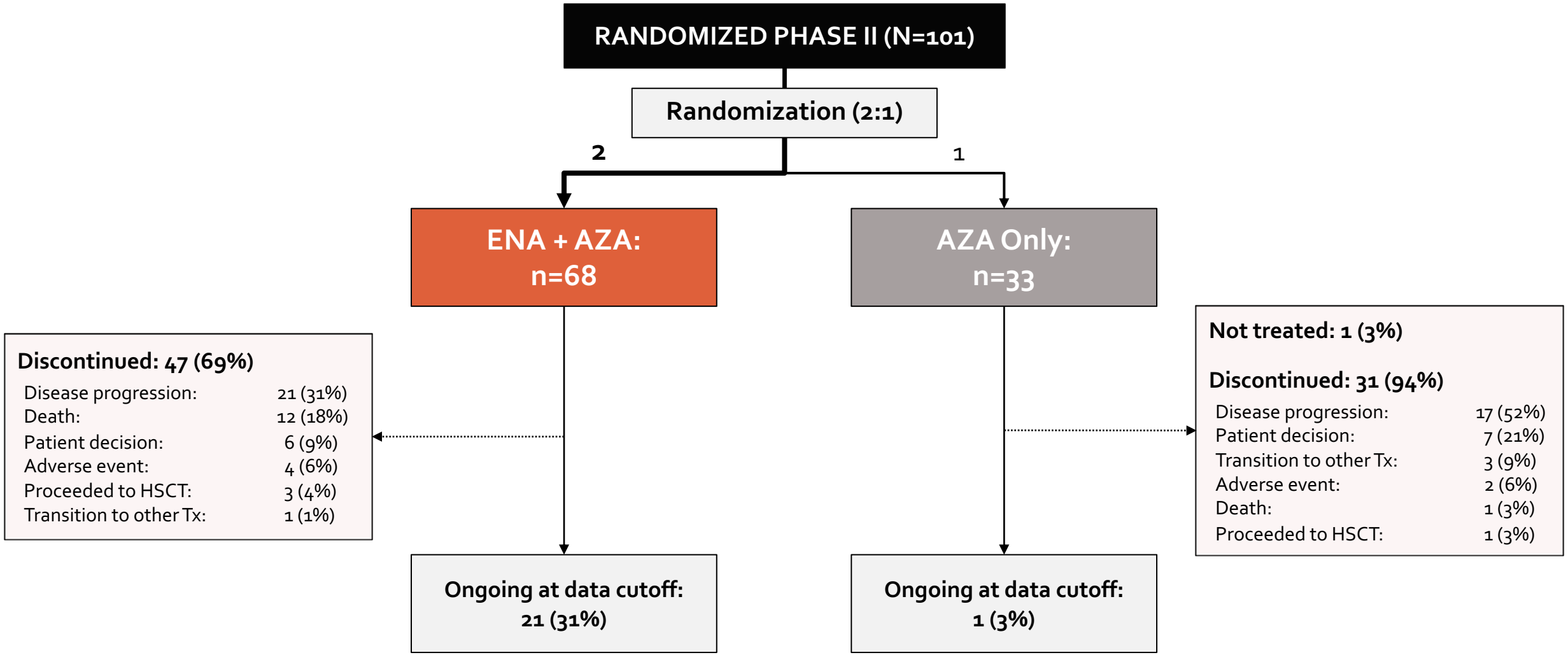



AZA Dosing: 75 mg/m²/day SC x 7 days/ 28-day cycle (all study phases)

**Primary Endpoint: ORR**

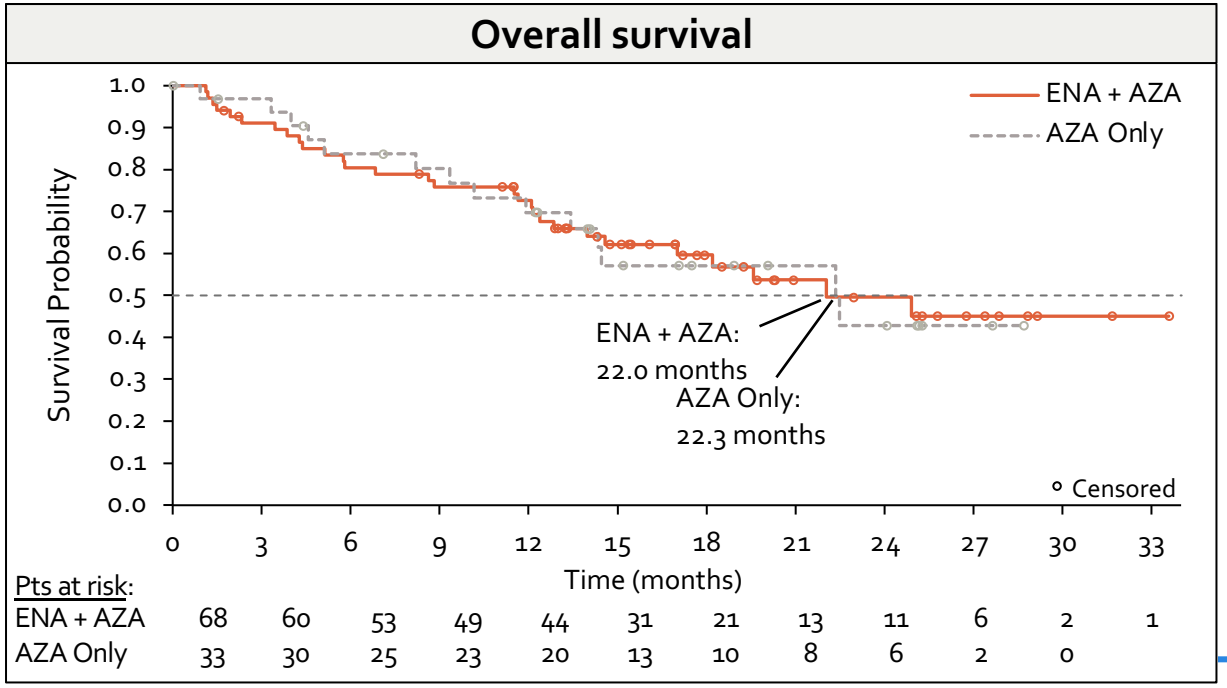
**Key Secondary Endpoints:** CR rate, safety, overall survival (OS), event-free survival (EFS)

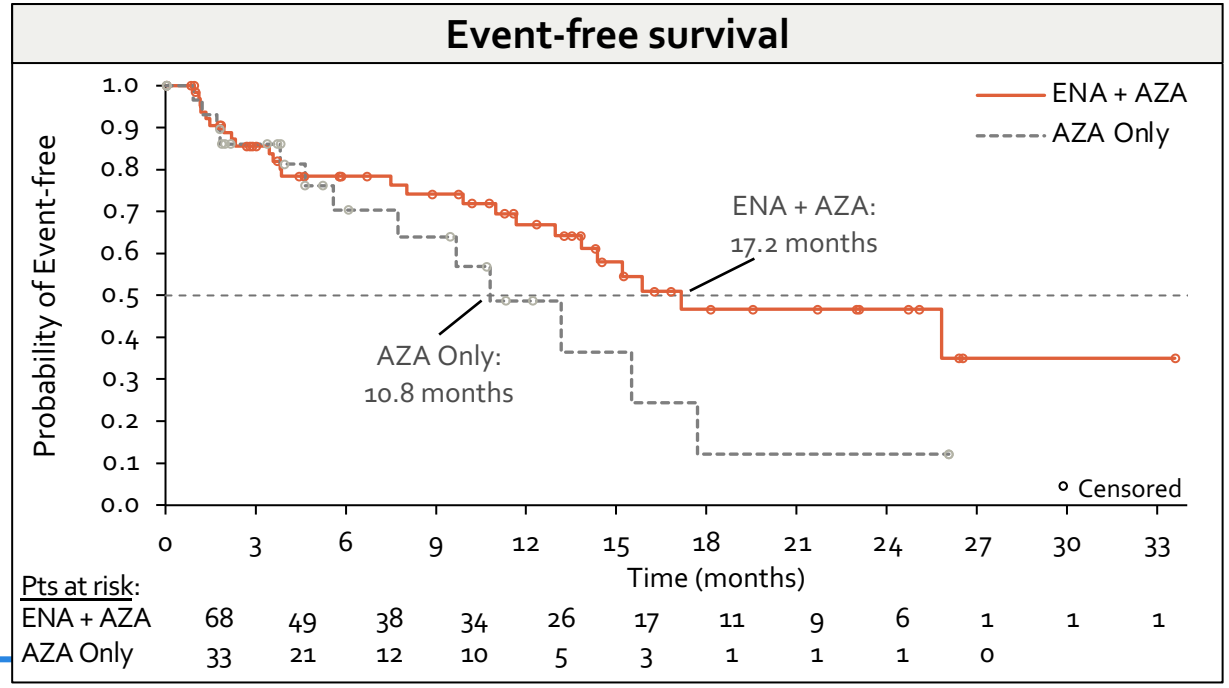
# Aza With and Without Enasidenib – Newly Diagnosed AML



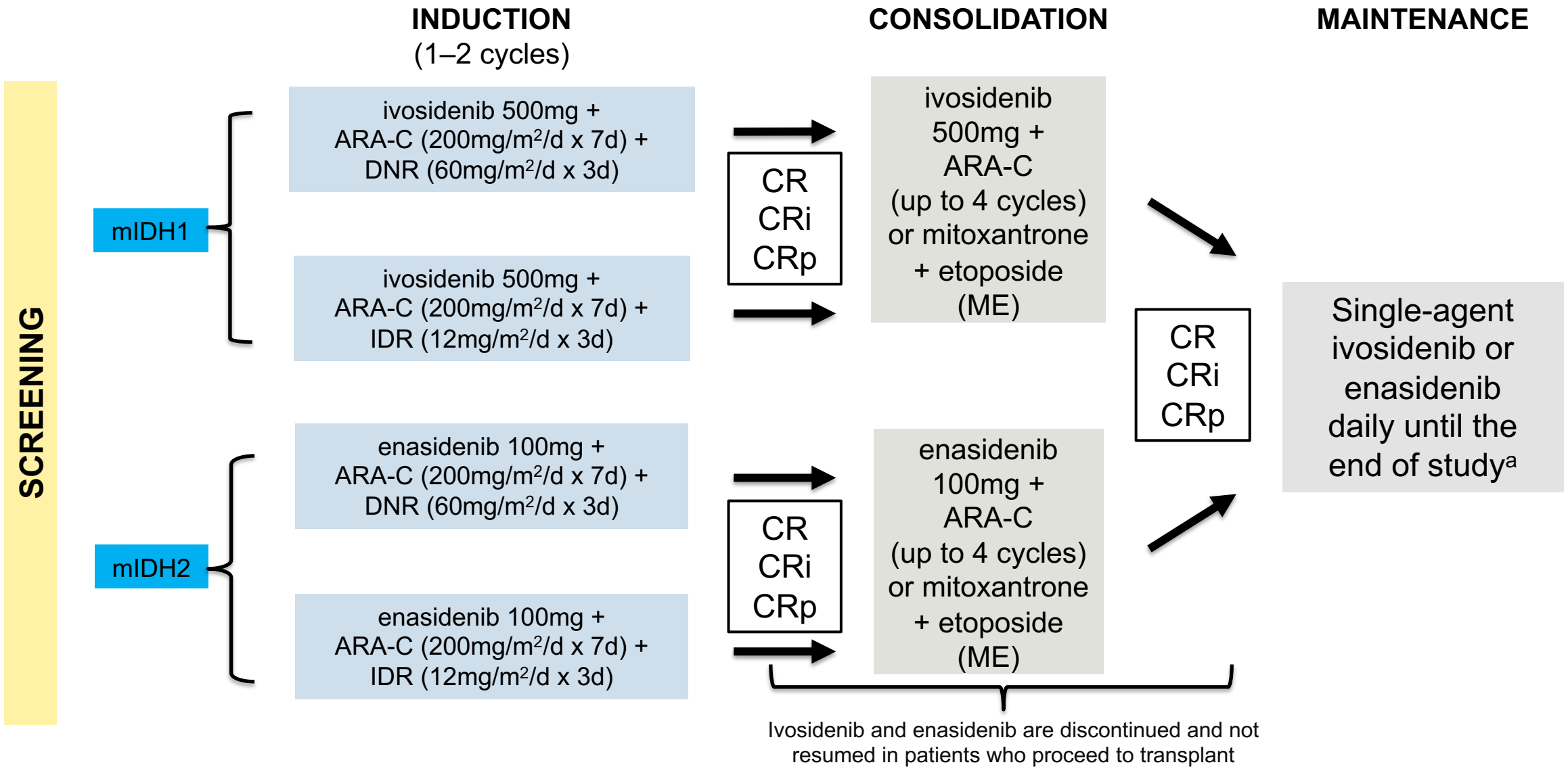
# Aza With and Without Enasidenib – Newly Diagnosed AML

- Median follow-up was 14 months in both treatment arms
- Median OS was 22.0 months in the ENA + AZA group and 22.3 months in the AZA Only group (HR 0.99 [95%CI 0.52, 1.87]; *P*=0.9686)
  - **Among pts in the ENA + AZA arm who achieved CR, median OS was not reached and 1-year survival was over 90%**
- Median EFS was 17.2 months with ENA + AZA, *vs.* 10.8 months with AZA Only (HR 0.59 [95%CI 0.30, 1.17]; *P*=0.1278)
- In the AZA Only arm, 7 patients (21%) received subsequent treatment with enasidenib monotherapy



# Enasidenib/Ivosidenib with Induction Chemotherapy




ARA-C = cytarabine; DNR = daunorubicin; IDR = idarubicin



Courtesy of Eytan M Stein, MD

# Enasidenib/Ivosidenib with Induction Chemotherapy

**Table 3. Best overall responses at any time during the study in the FAS**

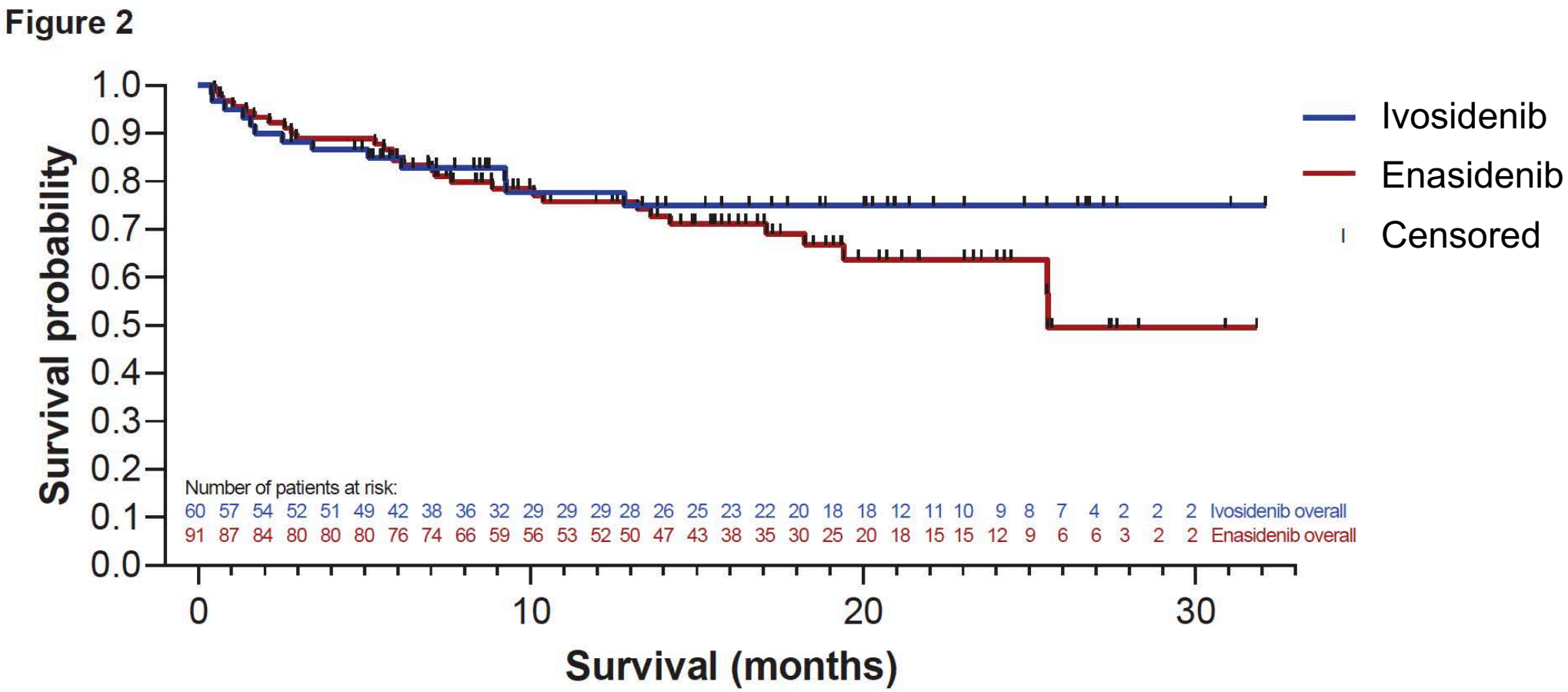
| Response category | Ivosidenib 500 mg + chemotherapy, n (%) | | | Enasidenib 100 mg + chemotherapy, n (%) | | |
|---|---|---|---|---|---|---|
| | All, N = 60 | De novo AML, n = 42 | Secondary AML, n = 18 | All, N = 91* | De novo AML, n = 56 | Secondary AML, n = 35 |
| CR/CRi/CRp | 46 (77) | 37 (88) | 9 (50) | 67 (74) | 45 (80) | 22 (63) |
| CR | 41 (68) | 32 (76) | 9 (50) | 50 (55) | 36 (64) | 14 (40) |
| CRi/CRp | 5 (8) | 5 (12) | — | 17 (19) | 9 (16) | 8 (23) |
| MLFS | 4 (7) | 3 (7) | 1 (6) | 10 (11) | 5 (9) | 5 (14) |
| PR | 2 (3) | — | 2 (11) | 2 (2) | 1 (2) | 1 (3) |
| Treatment failure† | 8 (13) | 2 (5) | 6 (33) | 12 (13) | 5 (9) | 7 (20) |



Courtesy of Eytan M Stein, MD

Stein EM, et al, Blood 2020

# Enasidenib/Ivosidenib with Induction Chemotherapy






Courtesy of Eytan M Stein, MD

# Case #1

- 86 year old woman with newly diagnosed AML associated with mutations in IDH2, RUNX1 and DNMT3A.
- Physical exam is normal. Peformance status is 1.
- Labs notable for pancytopenia with platelets of WBC of 3 (ANC of 0.5), Hgb of 8 and platelets of 13.
- Started on treatment with aza/ven. Achieves a complete remission with the presence of MRD after one cycle of therapy
- Develops COVID pneumonia, 3 week hospitalization, survives.
- Receives another cycle of aza/ven and relapses with 30% blasts
- Started on enasidenib 100 mg daily. Has brief onset of differentiation syndrome a month into therapy, with lower extremity edema and shortness of breath. Steroids given.
- Achieves an MRD negative complete remission at cycle 3 day 1.



Courtesy of Eytan M Stein, MD

# Case #2

- 76 year old woman presents with fatigue, shortness of breath, petechiae.
- Exam shows scattered bruising and a petechial rash.
- Labs notable for WBC of 6, hgb of 6.4, platelets of 5.
- Bone marrow biopsy confirms a diagnosis of AML with 55% blasts and mutations in IDH1 and DNMT3A.
- Patient wants to take oral medication – does not want aza or aza/ven– and is started on ivosidenib 500mg qd.
- At cycle 4 day 1, achieves an MRD negative complete remission.
- Is now in a continuous MRD negative complete remission at cycle 60 (5 years!).



Courtesy of Eytan M Stein, MD