Memorial Sloan Kettering Cancer Center

IDH Inhibitors

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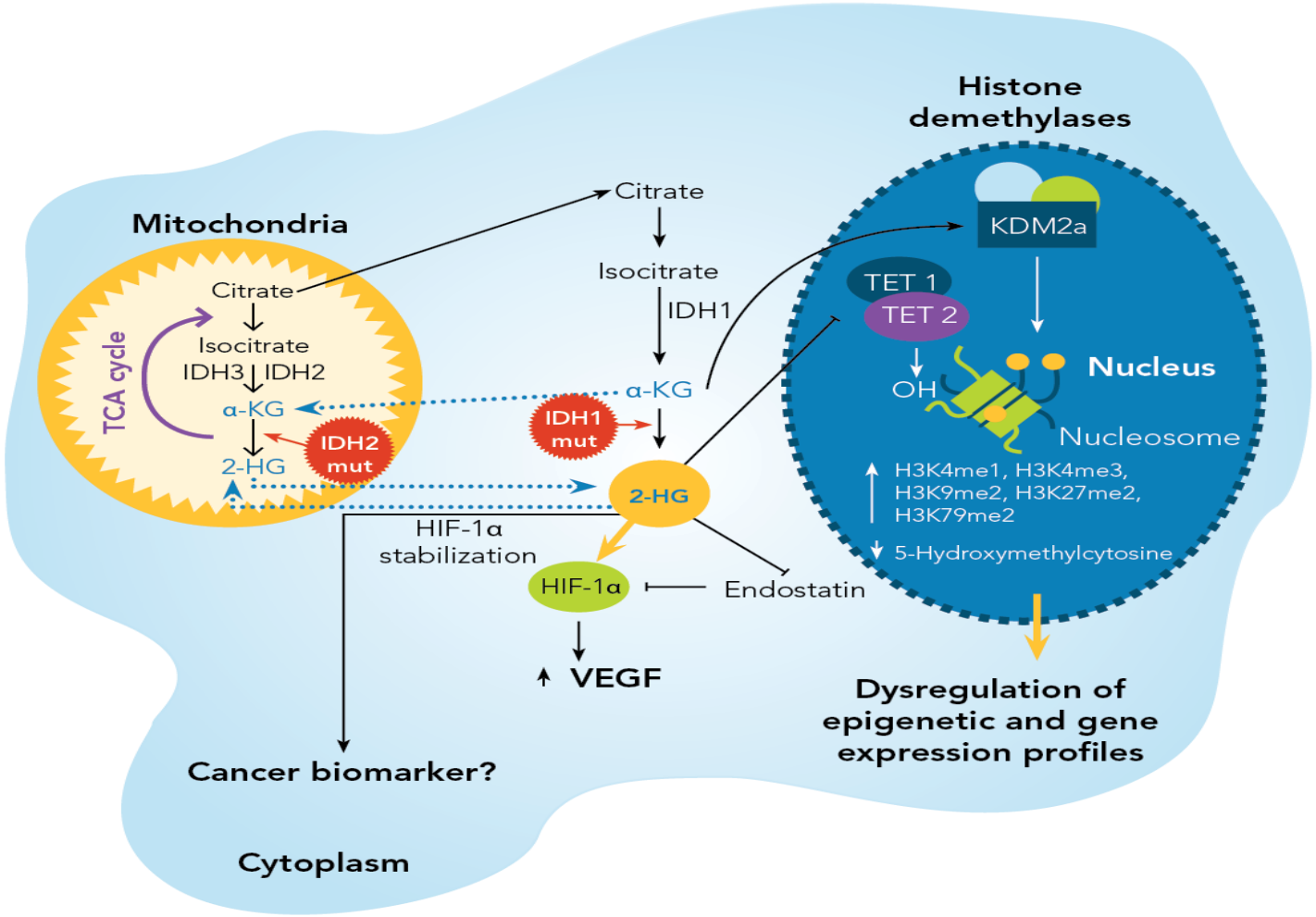
Disclosures

Advisory Board: Novartis, PinotBio, Janssen, Bristol Myers Squibb, Agios, Jazz, Menarini, Genentech, Genesis, Abbvie, Neoleukin, Gilead, Syndax, OnCusp, CTI Biopharma, Foghorn, Servier, Calithera, Daiichi, Aptose, Syros, Astellas, Ono Pharma, Blueprint *Honoraria:* Kura. *Safety Monitoring:* Epizyme, Cellectis. *Research Funding*: Eisai, Bristol Myers Squibb *Equity*: Auron.

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)[2]	3-5%
	Type II D-2HG Aciduria (inborn error of metabolism)	100%
IDH1m	Low-grade glioma & 2^{ary} GBM[1]	70%
	Chondrosarcoma	>50%
	AML	7.5%
	MDS/MPN	5%
	Intrahepatic cholangiocarcinoma	20%
	Others (colon, melanoma, lung)[2]	1-2%

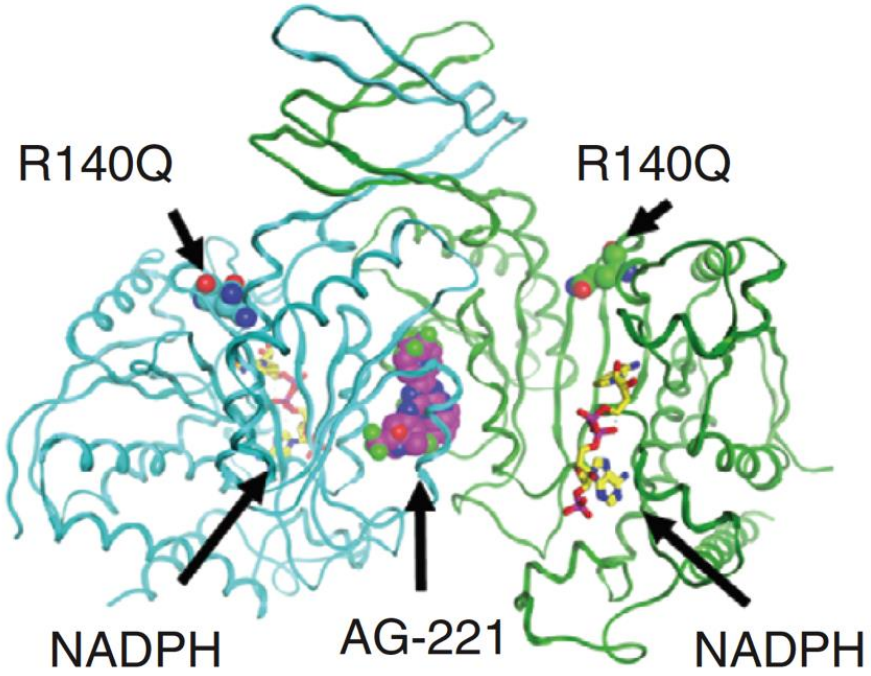
Pathogenesis of IDH Mutant AML



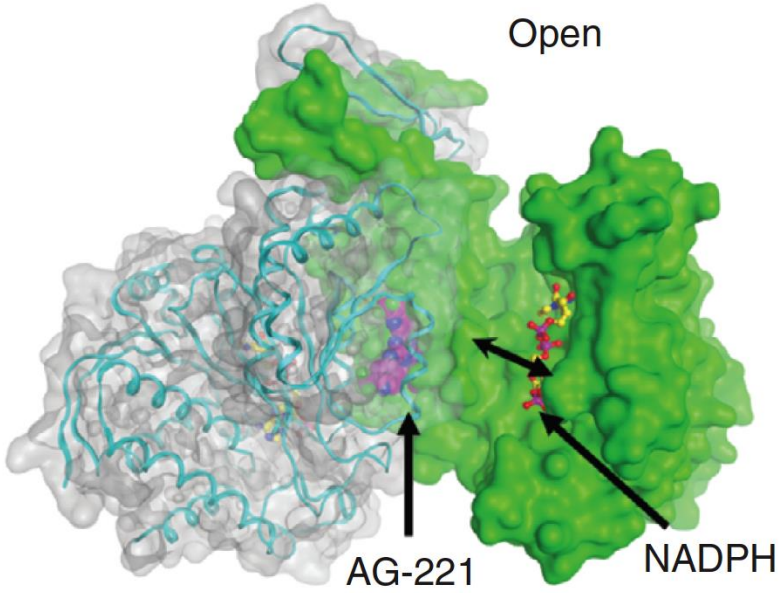
- IDH1 in cytoplasm and IDH2 in mitochondria
- Cancer-associated IDHm produces 2-hydroxyglutarate (R-2-HG)

Prensner and Chinnaiyan Nature, 2011

Enasidenib is an Allosteric Inhibitor of Mutant IDH2



Allosteric inhibitor
Binds to dimer interface



IDH inhibitors Enasidenib stabilizes the catalytically inactive open conformation, blocks production of 2HG

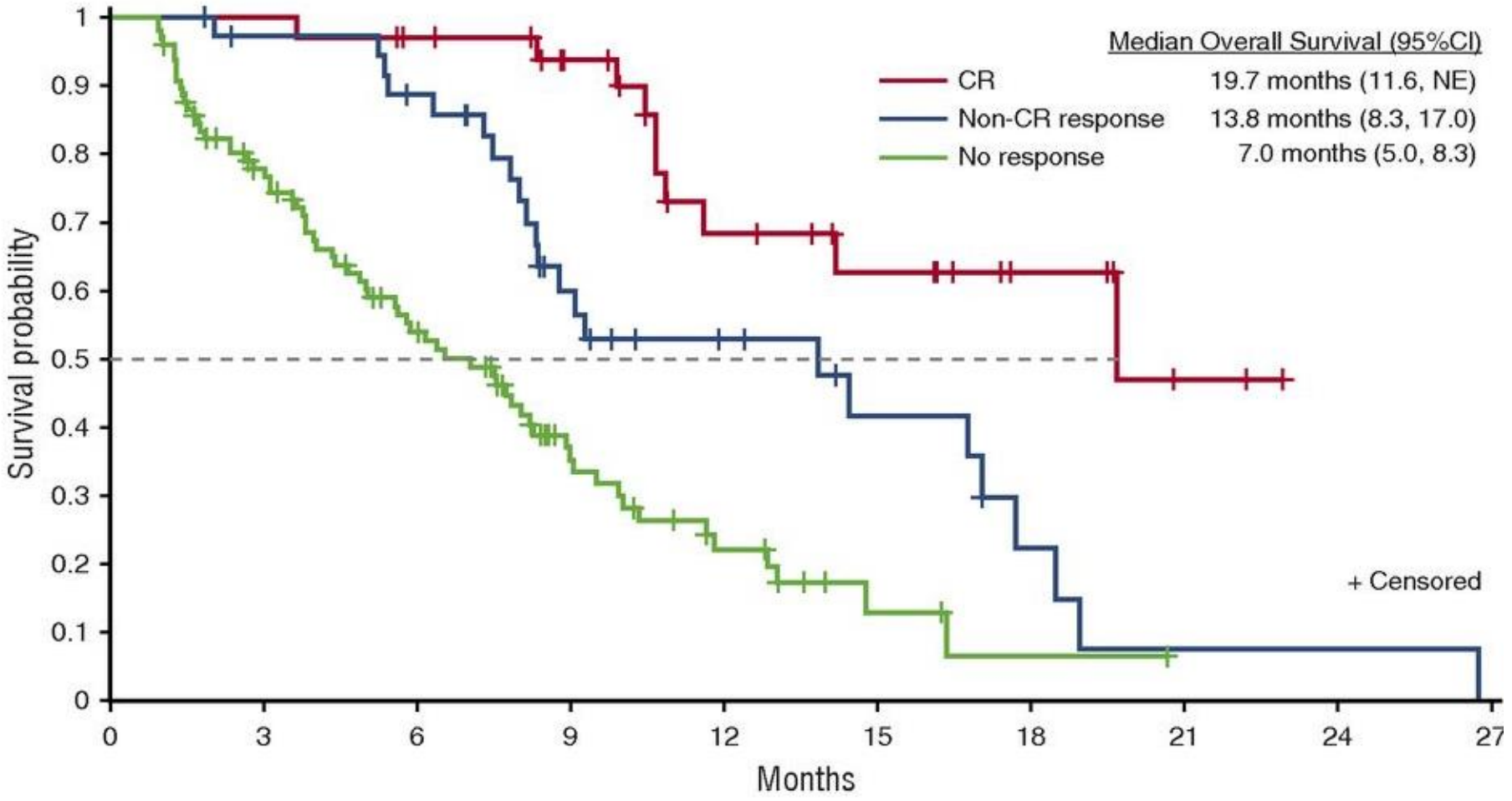
Yen et al, *Cancer Discovery* 2017

Efficacy of Enasidenib in R/R AML

	Relapsed/Refractory AML	
	Enasidenib 100 mg/day (n=214)	**All patients (N=280)**
Overall response rate (ORR),* % (n/N)	**38.8% (83/214)**	**39.6% (111/280)**
[95%CI for ORR]	[32.2%, 45.7%]	[33.9%, 45.6%]
CR + CRi/CRp rate, % (n/N)	29.0% (62/214)	27.9% (78/280)
Best response		
Complete remission (CR), n (%)	42 (19.6)	53 (18.9)
[CR rate 95%CI]	[14.5%, 25.6%]	[14.5%, 24.0%]
CR with incomplete count recovery (CRi/CRp), n (%)	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)
Time to first response, months, median (range)	1.9 (0.5-9.4)	1.9 (0.5-9.4)
Duration of response, months, median [95%CI]	5.6 [3.8, 7.4]	5.6 [4.6, 6.5]
Time to best response, months, median (range)	3.7 (0.6-14.7)	3.7 (0.5-14.7)
Time to CR, months, median (range)	3.7 (0.7-14.7)	3.8 (0.5-14.7)
Overall survival, months, median [95%CI]	8.8 [7.7, 9.6]	8.8 [7.8, 9.9]
Event-free survival,§ months, median [95%CI]	4.7 [3.7, 5.6]	4.6 [3.7, 5.6]

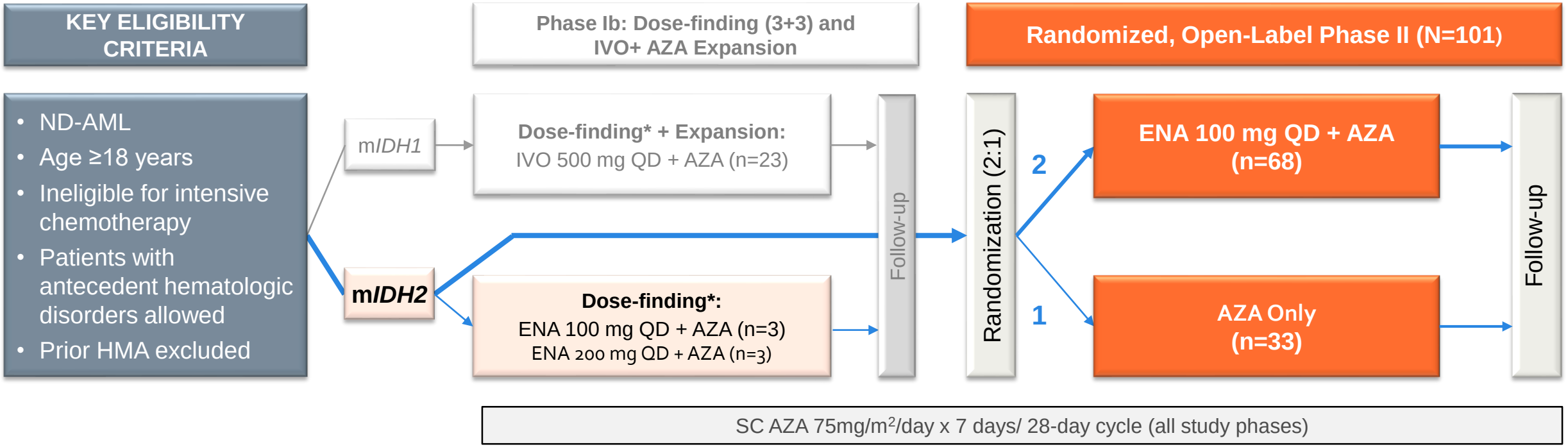
Stein EM, Dinardo CD, Blood 2017

Overall Survival Stratified by Best Response



Stein EM, Dinardo CD, et al, Blood 2017

Enasidenib (IDH2) and Aza versus Aza

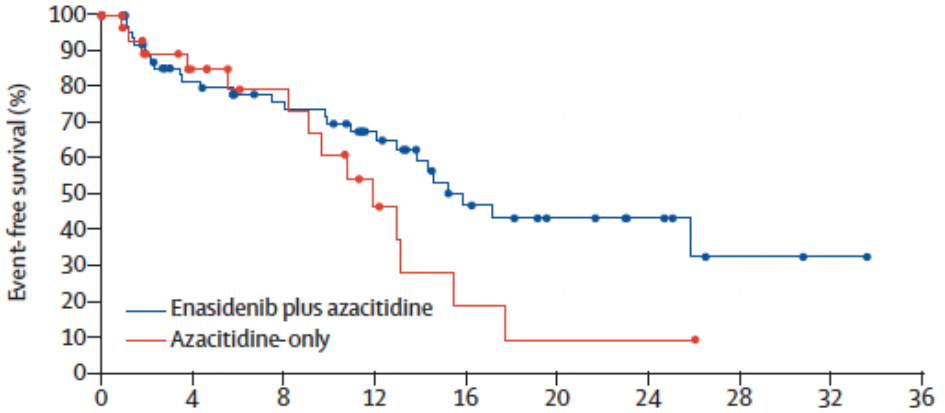


Primary Endpoint: ORR

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

Enasidenib/Aza vs. Aza

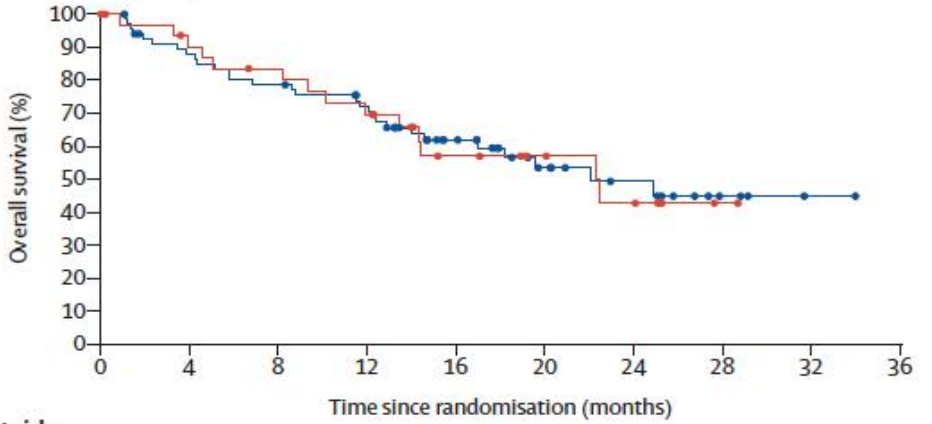
	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)
Events	27 (40%)	14 (42%)
Censored	41 (60%)	19 (58%)
Median event-free survival, months	15·9 (95% CI 13·0–NR)	11·9 (95% CI 8·2–15·5)
Hazard ratio	0·59 (95% CI 0·30–1·13)	
Log-rank p value	0·11	



Number at risk (number censored)										
Enasidenib plus azacitidine	68 (0)	45 (12)	37 (17)	27 (23)	14 (29)	9 (33)	6 (36)	2 (39)	1 (40)	0 (41)
Azacitidine only	33 (0)	18 (11)	13 (15)	6 (17)	2 (18)	1 (18)	1 (18)	0 (19)	..	..

Event Free Survival

	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)
Events	29 (43%)	14 (42%)
Censored	39 (57%)	19 (58%)
Median overall survival, months	22·0 (95% CI 14·6–NR)	22·3 (95% CI 11·9–NR)
Hazard ratio	0·99 (95% CI 0·52–1·87)	
Log-rank p value	0·97	



Number at risk (number censored)										
Enasidenib plus azacitidine	68 (0)	57 (3)	51 (3)	44 (6)	28 (16)	16 (25)	11 (29)	4 (35)	1 (38)	0 (39)
Azacitidine only	33 (0)	27 (3)	24 (4)	20 (4)	12 (9)	9 (12)	6 (13)	1 (18)	0 (19)	..

Overall Survival

Dinardo CD, et. al, Lancet Oncology 2020

IVOsidenib (IDH1 inhibitor)

IDH1 Inhibitor – Ivosidenib – Study Design

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

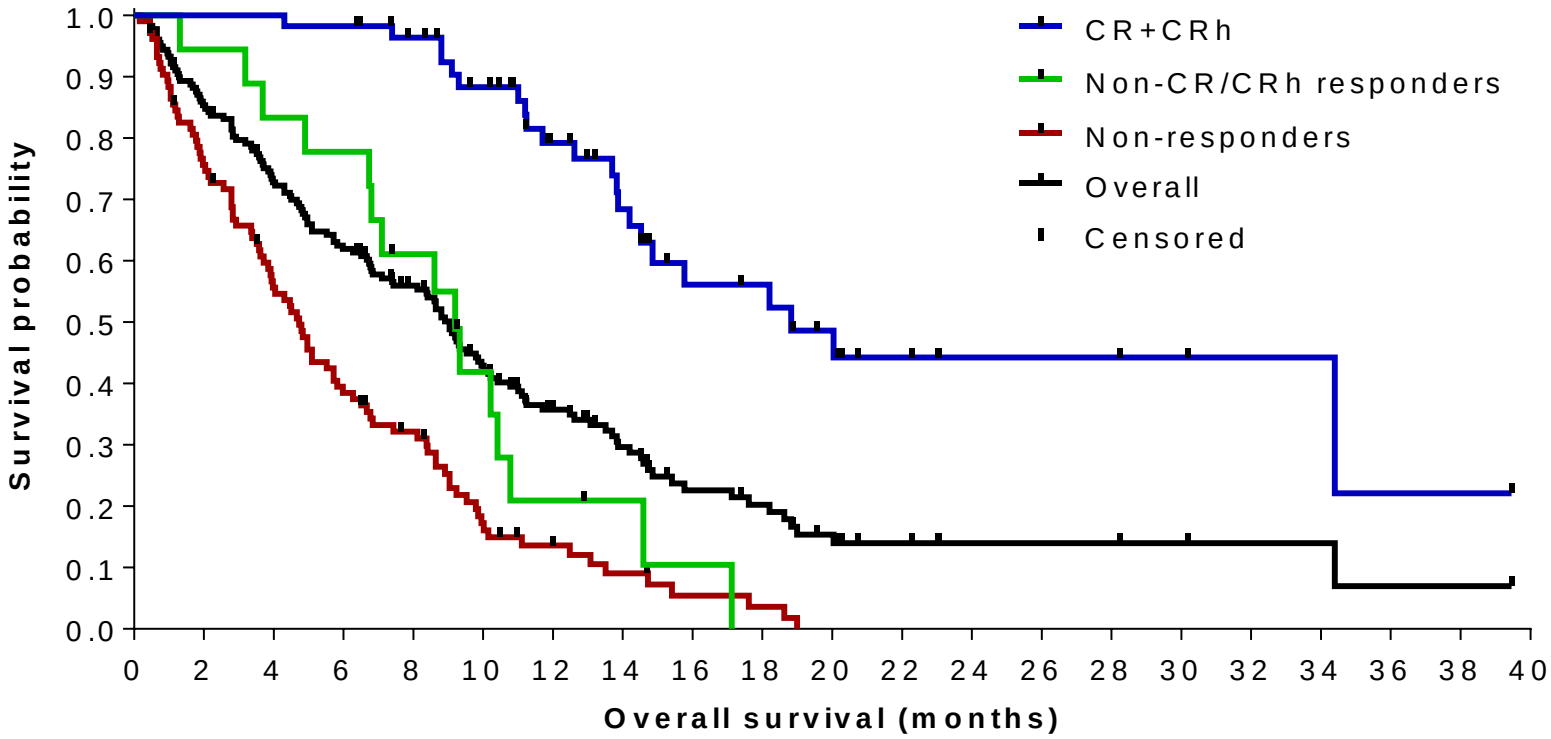
1. R/R AML in 2nd+ relapse, relapse after SCT, refractory to induction or reinduction, or relapse within 1 year, **n=126**
2. Untreated AML not eligible for SOC, **n=25**
3. Other non-AML mIDH1 R/R advanced hematologic malignancies, **n=11**
4. Other R/R AML not eligible for Arm 1, **n=18**

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)

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)

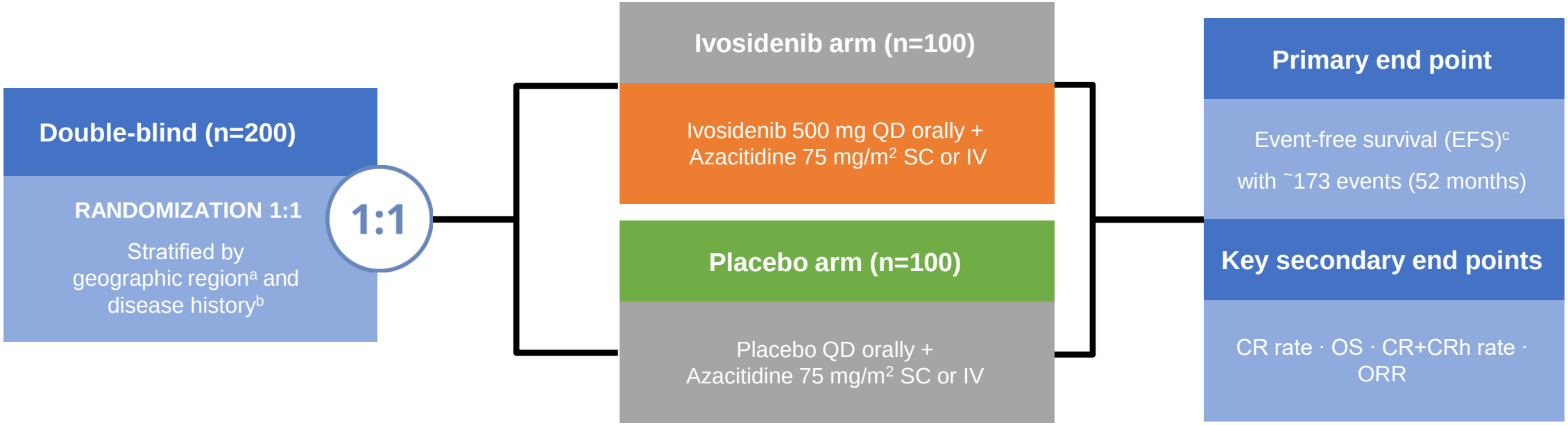
Number of patients at risk:

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

Pollyea D, et al, ASCO 2018

IDH1 Inhibitor Ivosidenib with Azacitidine



Dohner H et. al, ASH 2021

IDH1 Mutant AML – Ivosidenib with Aza

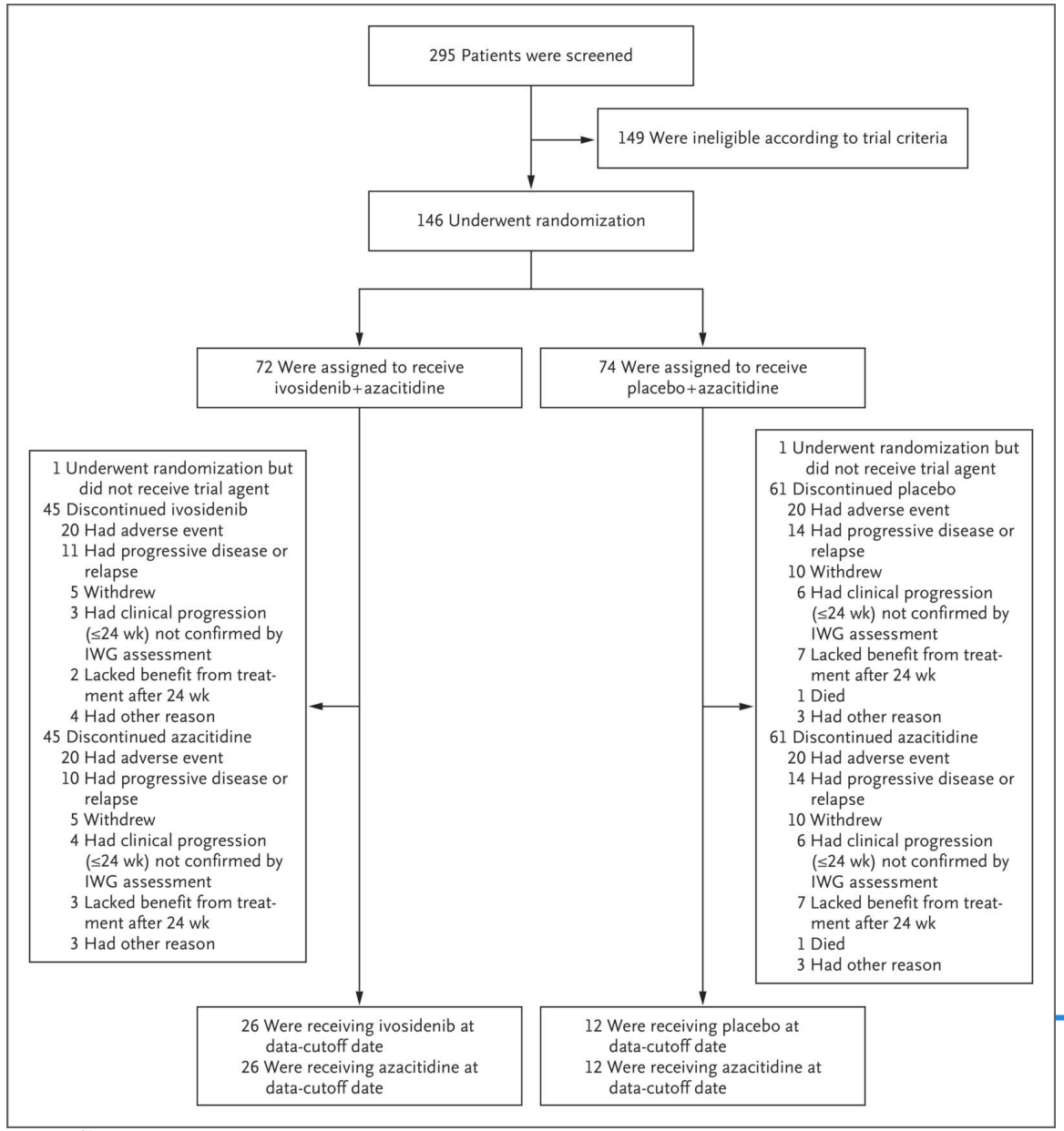


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Ivosidenib + Azacitidine (N = 72)	Placebo + Azacitidine (N = 74)
Median age (range) — yr	76.0 (58.0–84.0)	75.5 (45.0–94.0)
Sex — no. (%)		
Male	42 (58)	38 (51)
Female	30 (42)	36 (49)
Race or ethnic group — no. (%)†		
Asian	15 (21)	19 (26)
White	12 (17)	12 (16)
Black	0	2 (3)
Other or not reported	45 (62)	41 (55)
ECOG performance-status score — no. (%)‡		
0	14 (19)	10 (14)
1	32 (44)	40 (54)
2	26 (36)	24 (32)
Disease history according to investigator — no. (%)		
Primary AML	54 (75)	53 (72)
Secondary AML§	18 (25)	21 (28)
History of myeloproliferative neoplasms	4 (6)	8 (11)
World Health Organization classification — no. (%)		
AML with recurrent genetic abnormalities	16 (22)	24 (32)
AML with myelodysplasia-related changes	28 (39)	26 (35)
Therapy-related myeloid neoplasms	1 (1)	1 (1)
IDH1 mutation type — no. (%)¶		
R132C	45 (62)	51 (69)
R132H	14 (19)	12 (16)
R132G	6 (8)	4 (5)
R132L	3 (4)	0
R132S	2 (3)	6 (8)
Median variant allele frequency of *IDH1* mutations in bone marrow aspirate (range) — %‖	36.8 (3.1–50.5)	35.5 (3.0–48.5)
Cytogenetic risk status — no. (%)**		
Favorable	3 (4)	7 (9)
Intermediate	48 (67)	44 (59)
Poor	16 (22)	20 (27)
Median bone marrow blast level (range) — %	54.0 (20.0–95.0)	48.0 (17.0–100)

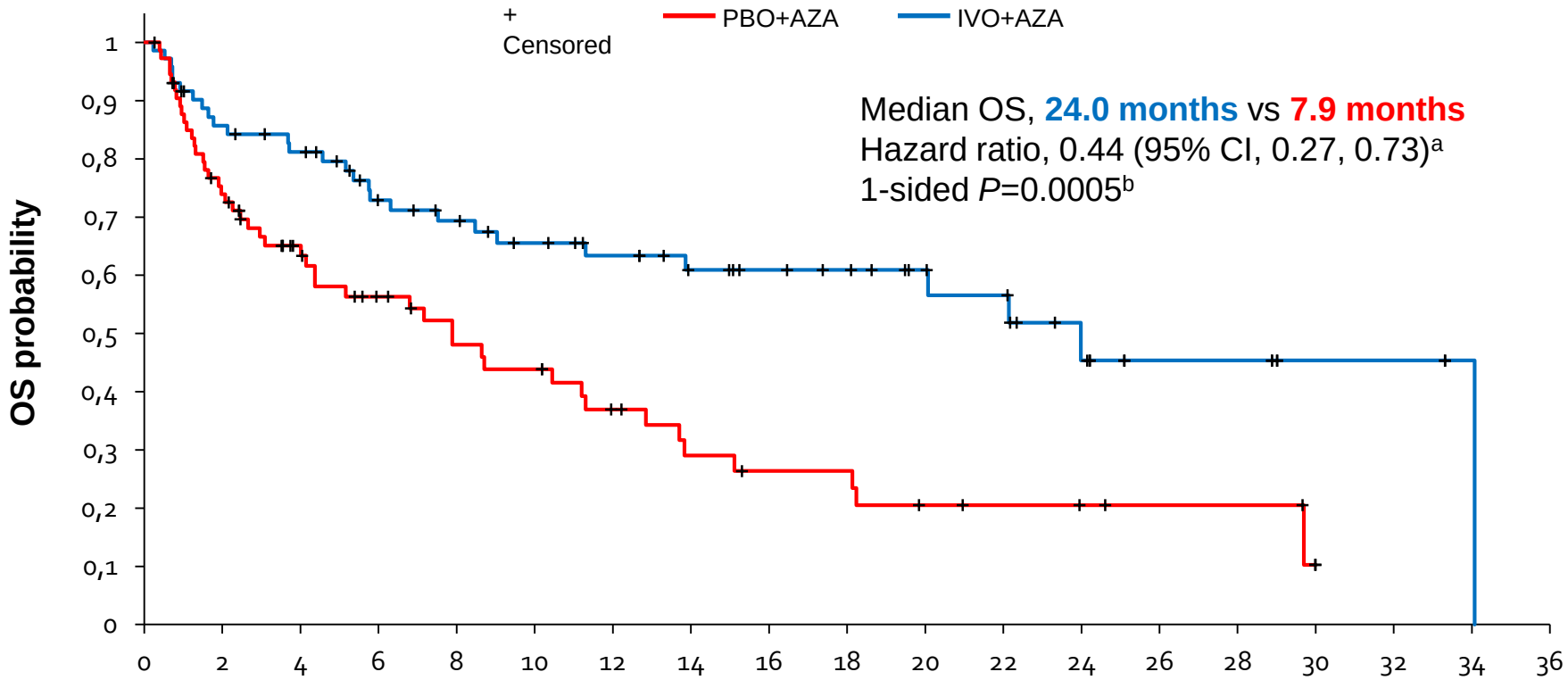
Montesinos P, et. al, NEJM 2022

Targeting Specific Mutations – IDH1 - Response

Table 2. Hematologic Response, Response Duration, and Time to Response (Intention-to-Treat Population).*

Response Category	Ivosidenib + Azacitidine (N = 72)	Placebo + Azacitidine (N = 74)
Best response — no. (%)		
Complete remission	34 (47)	11 (15)
Complete remission with incomplete hematologic or platelet recovery	5 (7)	1 (1)
Partial remission	4 (6)	2 (3)
Morphologic leukemia-free state	2 (3)	0
Stable disease	7 (10)	27 (36)
Progressive disease	2 (3)	4 (5)
Could not be evaluated	1 (1)	2 (3)
Not assessed	17 (24)	27 (36)
Complete remission		
Percentage of patients (95% CI)	47 (35–59)	15 (8–25)
Odds ratio vs. placebo (95% CI); P value	4.8 (2.2–10.5); two-sided P<0.001	
Median duration of complete remission (95% CI) — mo	NE (13.0–NE)	11.2 (3.2–NE)
Median time to complete remission (range) — mo	4.3 (1.7–9.2)	3.8 (1.9–8.5)
Complete remission or complete remission with partial hematologic recovery		
No. of patients	38	13
Percentage of patients (95% CI)	53 (41–65)	18 (10–28)
Odds ratio vs. placebo (95% CI); P value	5.0 (2.3–10.8); two-sided P<0.001	
Median duration of complete remission or complete remission with partial hematologic recovery (95% CI) — mo	NE (13.0–NE)	9.2 (5.8–NE)
Median time to complete remission or complete remission with partial hematologic recovery (range) — mo	4.0 (1.7–8.6)	3.9 (1.9–7.2)
Objective response		
No. of patients	45	14
Percentage of patients (95% CI)	63 (50–74)	19 (11–30)
Odds ratio vs. placebo (95% CI); P value	7.2 (3.3–15.4); two-sided P<0.001	
Median duration of response (95% CI) — mo	22.1 (13.0–NE)	9.2 (6.6–14.1)
Median time to first response (range) — mo	2.1 (1.7–7.5)	3.7 (1.9–9.4)

Ivosidenib in Combination with Azacitidine

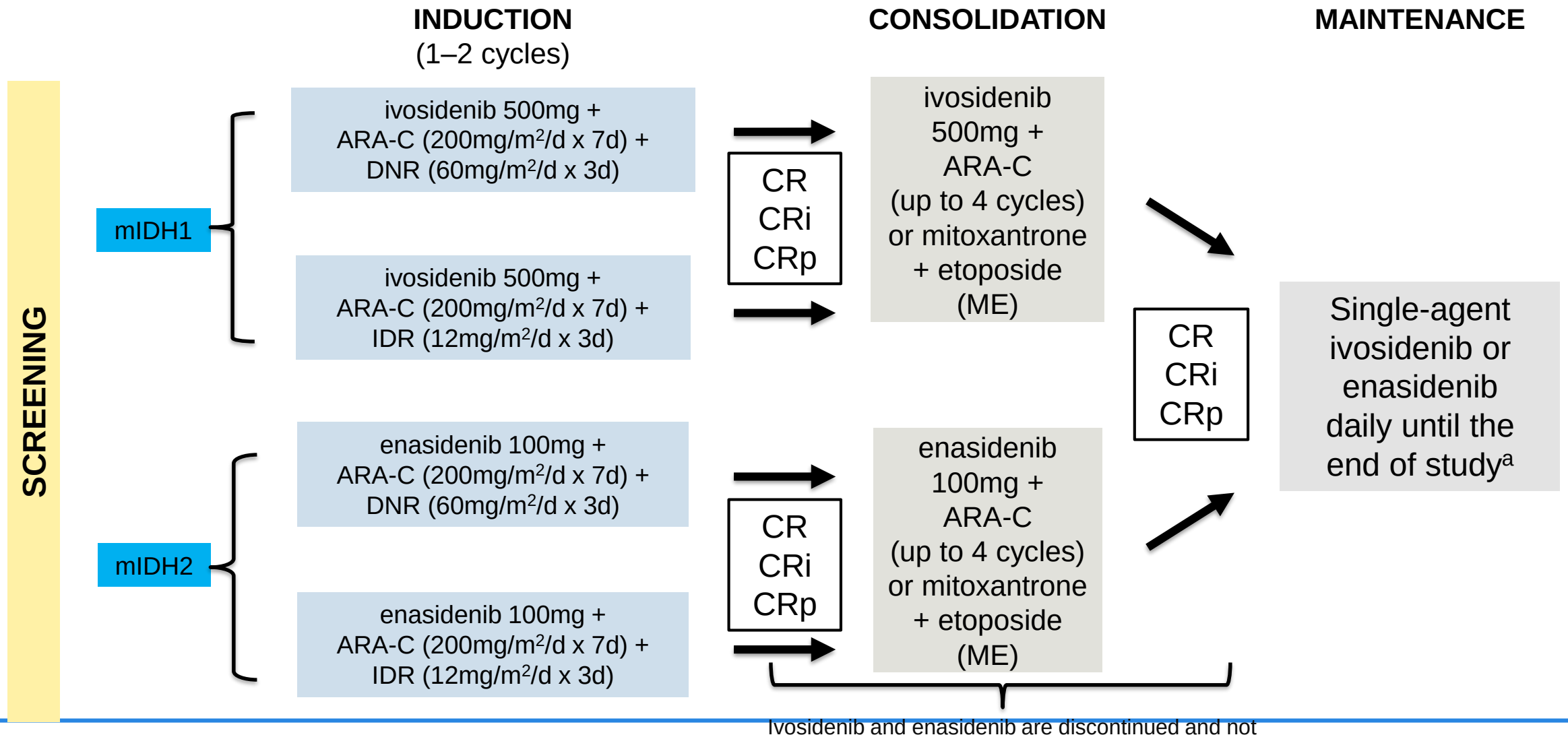


Number of patients at risk:

PBO+AZA	74	53	38	29	23	21	15	11	9	9	6	5	4	3	3	0		
IVO+AZA	72	58	53	42	38	33	29	24	21	19	15	13	7	4	4	2	2	1

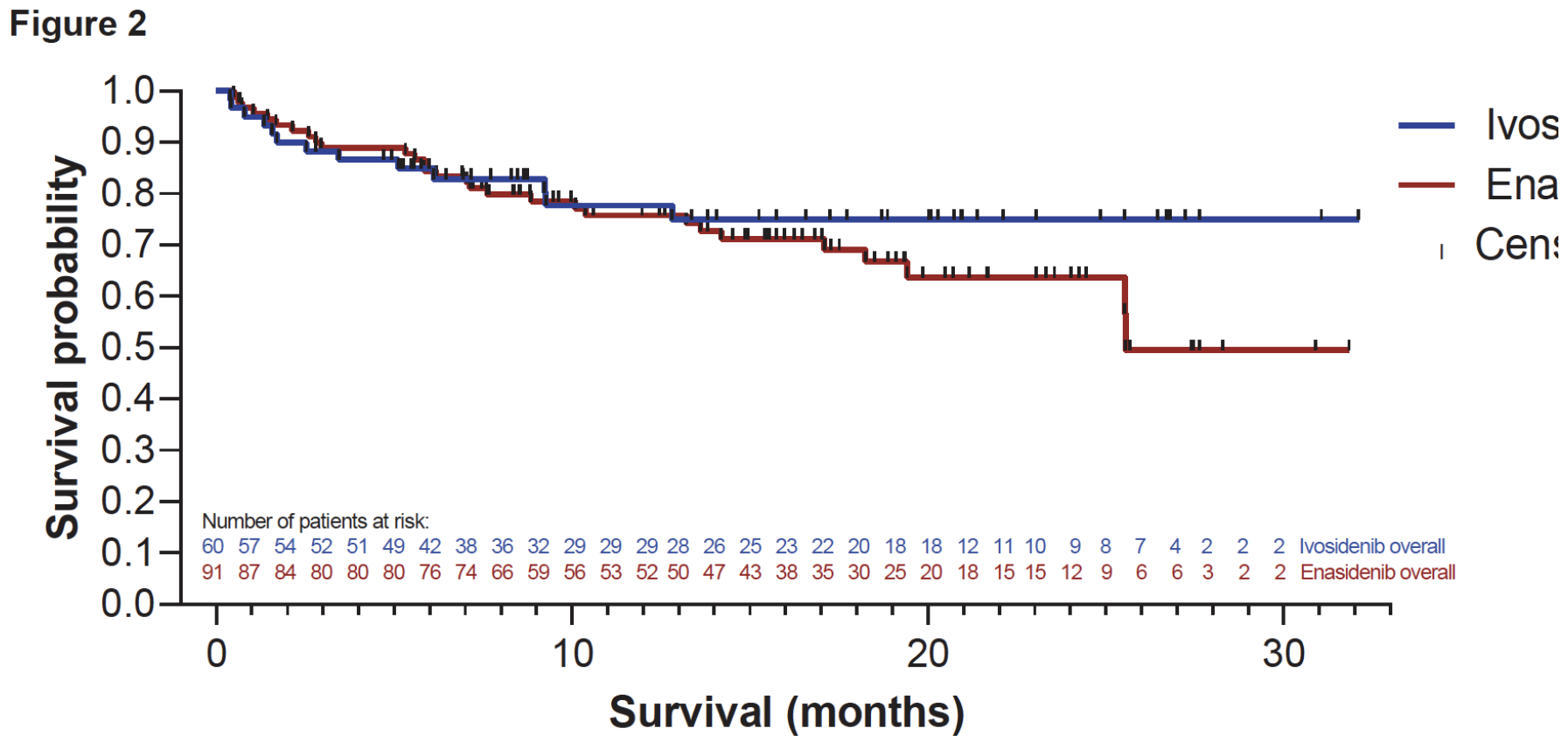
Dohner H et. al, ASH 2021

Enasidenib/Ivosidenib with Induction Chemotherapy



Stein EM, et. al Blood 2021

Enasidenib/Ivosidenib with Induction Chemotherapy



Stein EM, et. al Blood 2021

Conclusions

- The outcomes of patients treated with single agent IDH inhibitors are favorable, with nearly 1/3 of patients in CR having a molecular remission

- The combination of Ivosidenib (IDH1) with aza leads to an OS benefit compared to aza alone
  - However, Enasidenib (IDH2) with aza shows no benefit over aza alone. Trial may have been confounded by crossover and underpowering.

- Whether aza/ven is superior to aza/ivo for newly diagnosed IDH1 mutant AML is unknown. Needs a trial.

- Randomized study of induction chemo with ena/ivo vs induction chemo/placebo (HOVON/AMLSG)

Thank You!

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