Approach to MDS/AML – Focus on Targeted Therapies

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Title Restated: How Should We Treat MDS or AML with 10-30% Blasts

- Does the percentage of blasts matter when choosing a targeted treatment strategy in AML?
- Do patients with the same genetic background (e.g. NPM1 mutations) have the same outcomes with the same treatments when blast percentages are different (e.g. 70% versus 15%)?
- More fundamentally, should treatment be based on how we name the disease (e.g. MDS) vs. some other disease characteristic?

Example of How Nomenclature can Influence Treatment

Table 1
FAB Classification of MDS [7].

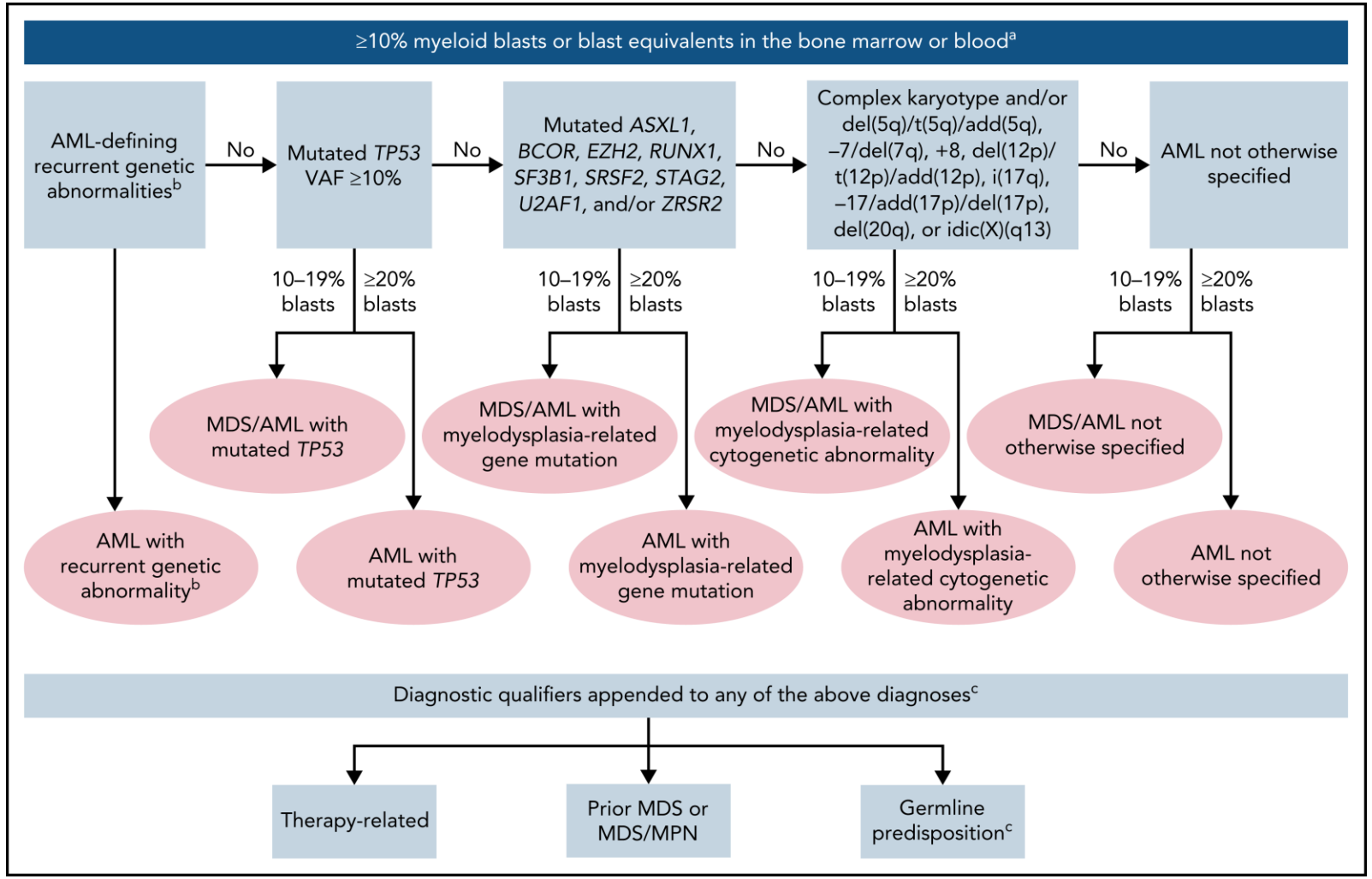
Category	Dysplasia	% BM blasts	% PB blasts
Refractory anemia (RA)	Erythroid	<5	<1
Refractory anemia with ring sideroblasts (RARS)	Erythroid	<5	<1
Refractory anemia with excess blasts (RAEB)	2 or more lineages	5–20	0–4
Refractory anemia with excess blasts in transformation (RAEB-T)	Usually 2 or more lineages	21–30	≥5
Chronic myelomonocytic leukemia (CMML)	Variable $\geq 1 \times 10^9$/L monocytes	<20	

Should we have treated RAEB-T as AML or MDS?

Vardiman J, 2005

Definitions of the Population and Problems with the Definition

Needs at least 10% blasts



Dohner H. et al, Blood 2022

Definitions of the Population and Problems with the Definition

WHO Definition of AML: Defining genetic Abnormality with ANY blast percentage

Table 7. Acute myeloid leukaemia.

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML*::*RARA* fusion
Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
Acute myeloid leukaemia with *DEK*::*NUP214* fusion
Acute myeloid leukaemia with *RBM15*::*MRTFA* fusion
Acute myeloid leukaemia with *BCR*::*ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation

Khoury J, et. al. Leukemia 2023

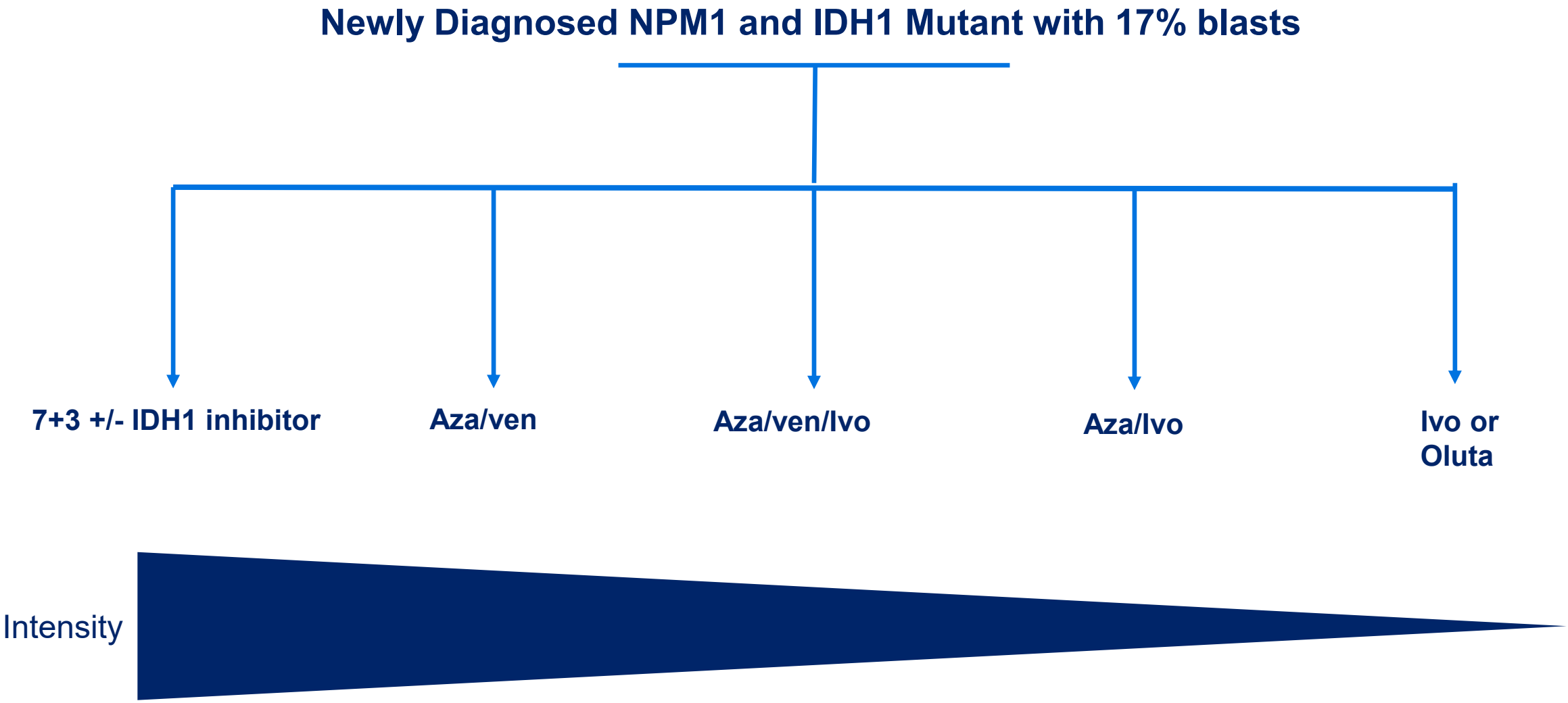
A Case from My Practice (Monday, April 21, 2025)

- 70-year-old man with prior medical history significant for hypertension, diabetes mellitus type 2 and hyperlipidemia presents for newly diagnosed “AML” with 17% blasts. Patient has a normal karyotype and mutations in NPM1 and IDH1. FLT3 is wild-type. The patient has a performance status of 0 and recently returned from a hiking trip in Zion National Park. He plays squash three times a week.

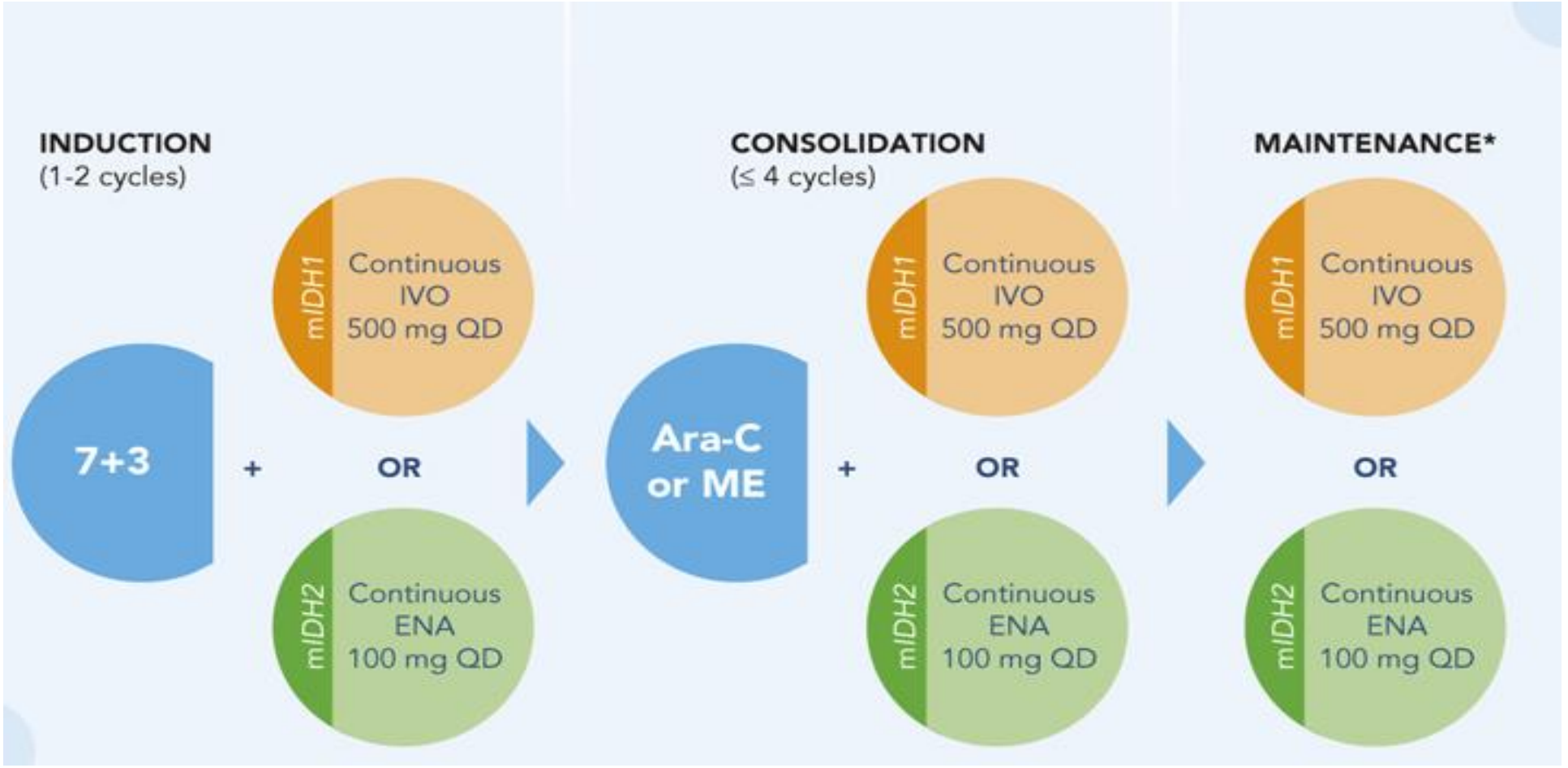
- He says (and this is a direct quote), “I can handle the strong stuff doc. Don’t give me weak treatment because I’m 70 years old.”

- What are the potential options (FDA approved and non-approved) to treat this patient and what is the optimal therapy?

Options to Treat Newly Diagnosed IDH1 Mutant AML

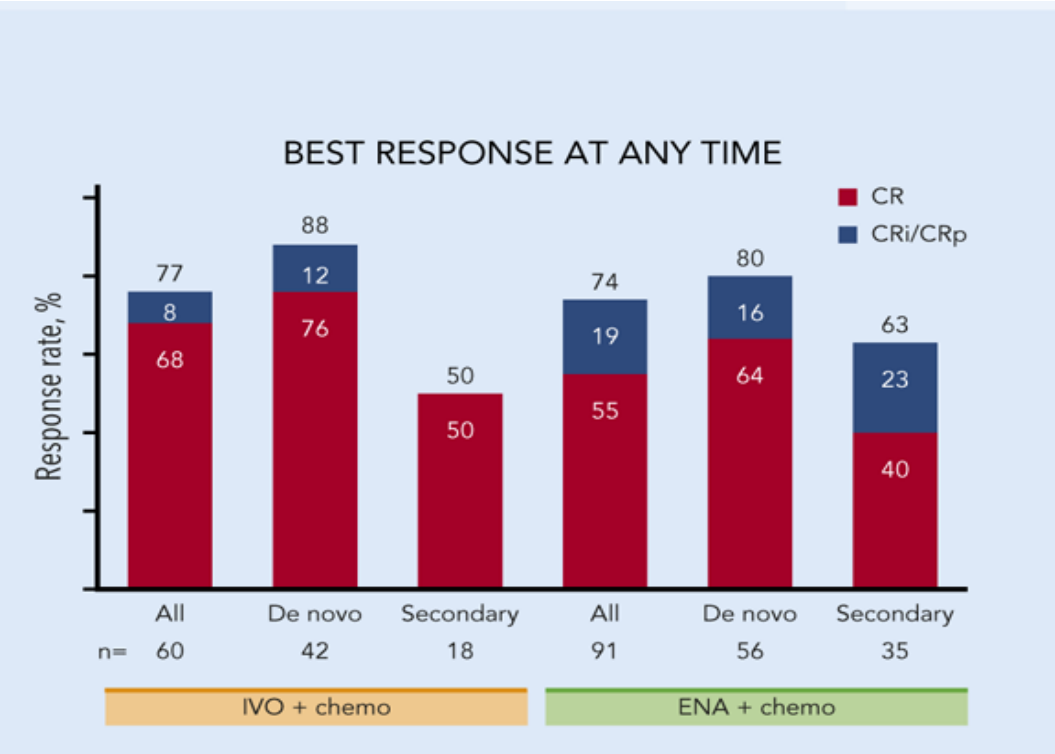


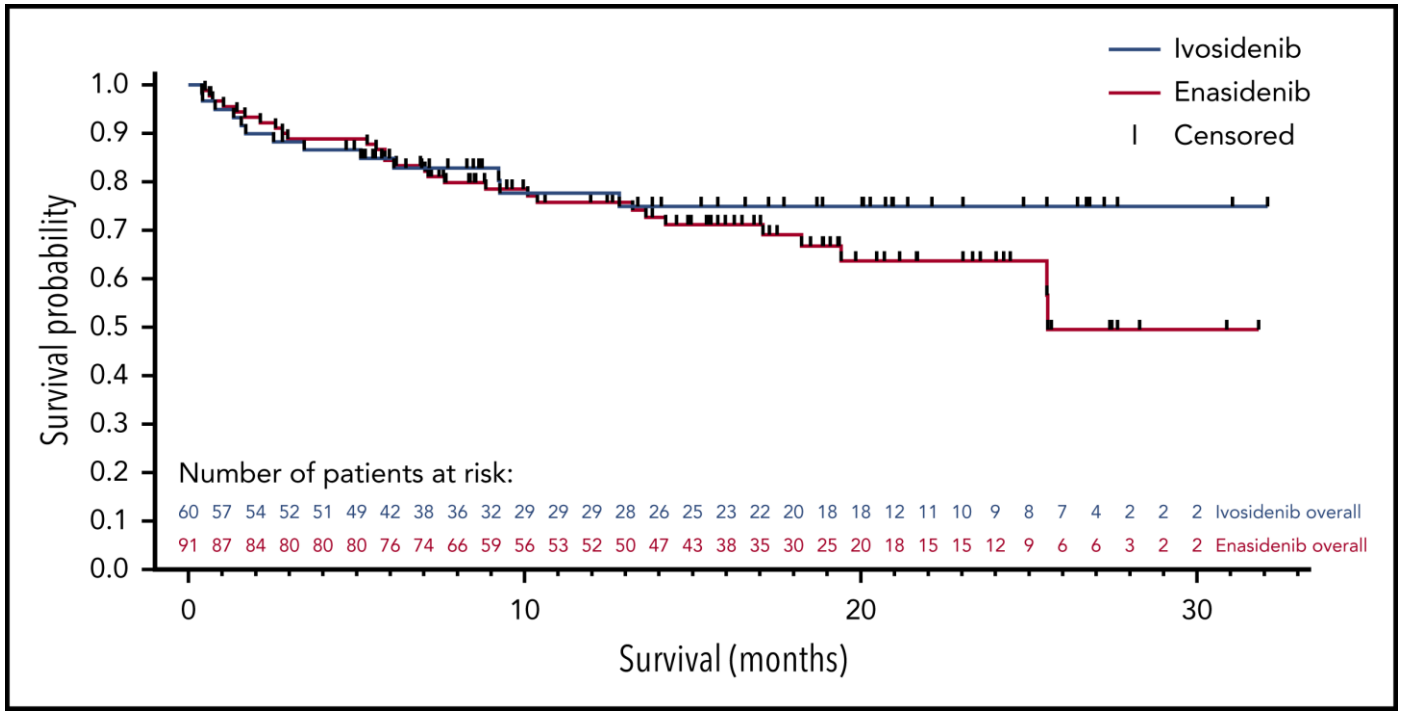
Intensive Chemotherapy in IDH1 Mutant AML



Stein EM, Dinardo CD et. al. Blood 2021

Intensive Chemotherapy in IDH1 Mutant Disease



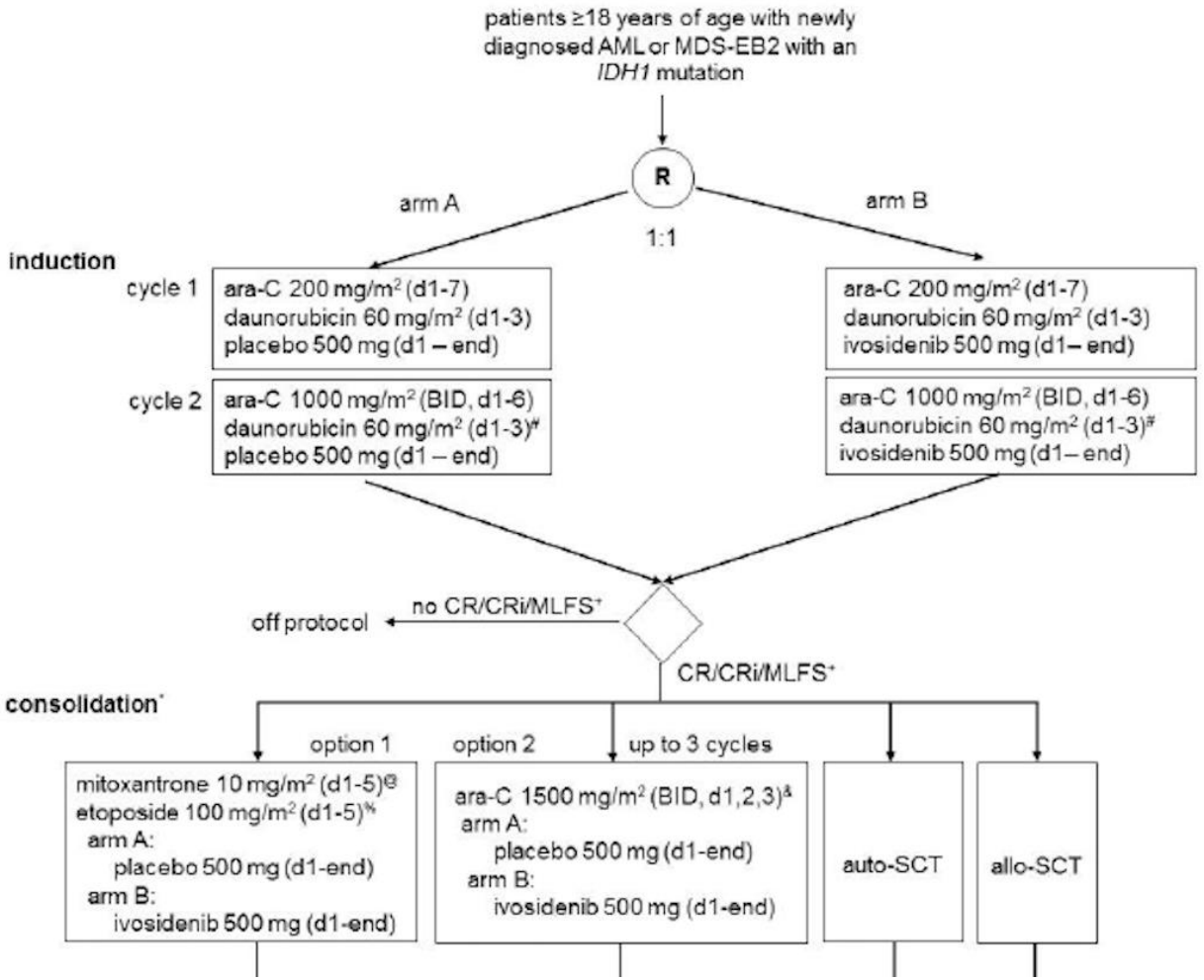


- **Response rate of 77%**
- **Overall Survival of 80% at 2 years**
- **Some of these patients can be cured without a transplant (e.g. NPM1/IDH1 co-mutant)**

Stein EM, Dinardo CD et. al. Blood 2021

Will we get a Definitive Answer to Benefit of Chemo with IDH Inhibitors?

IDH1 cohort (randomization ivosidenib vs placebo)



HOVON HO150 AML

Closed

GO TO ECRF

Main info

Identifier:	HOVON 150 AML / AMLSG 29-18
Sponsor:	HOVON
Working group party:	Leukemia
Age:	>= 18
Stage:	1st Line
Echelon:	Level C-HIC&C-SCT

Included patients: 974 (of 971)

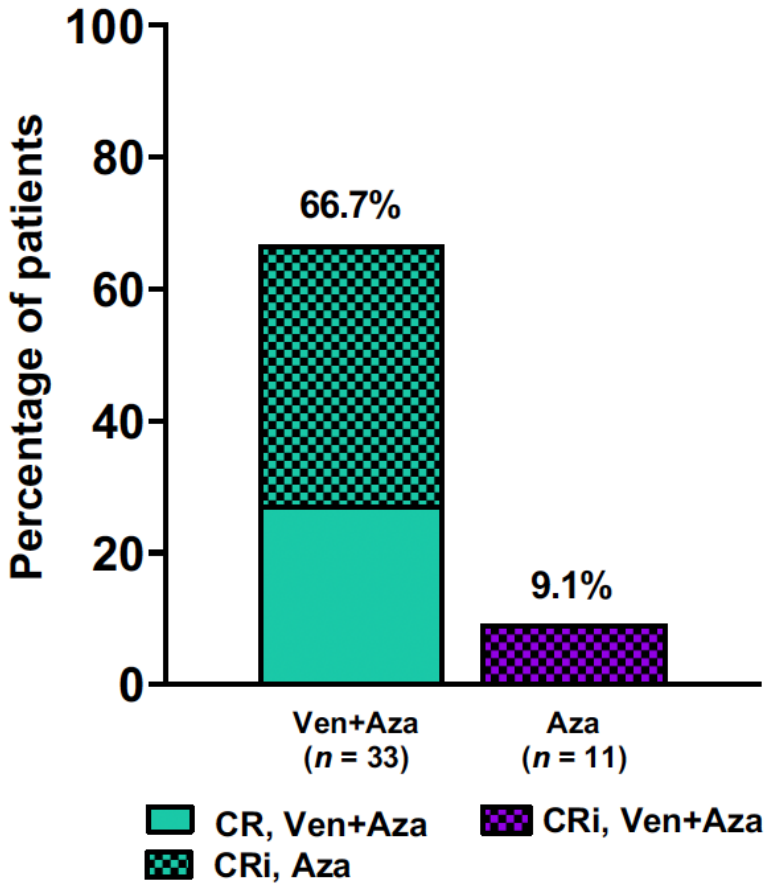
Active sites: 191 (of 219)

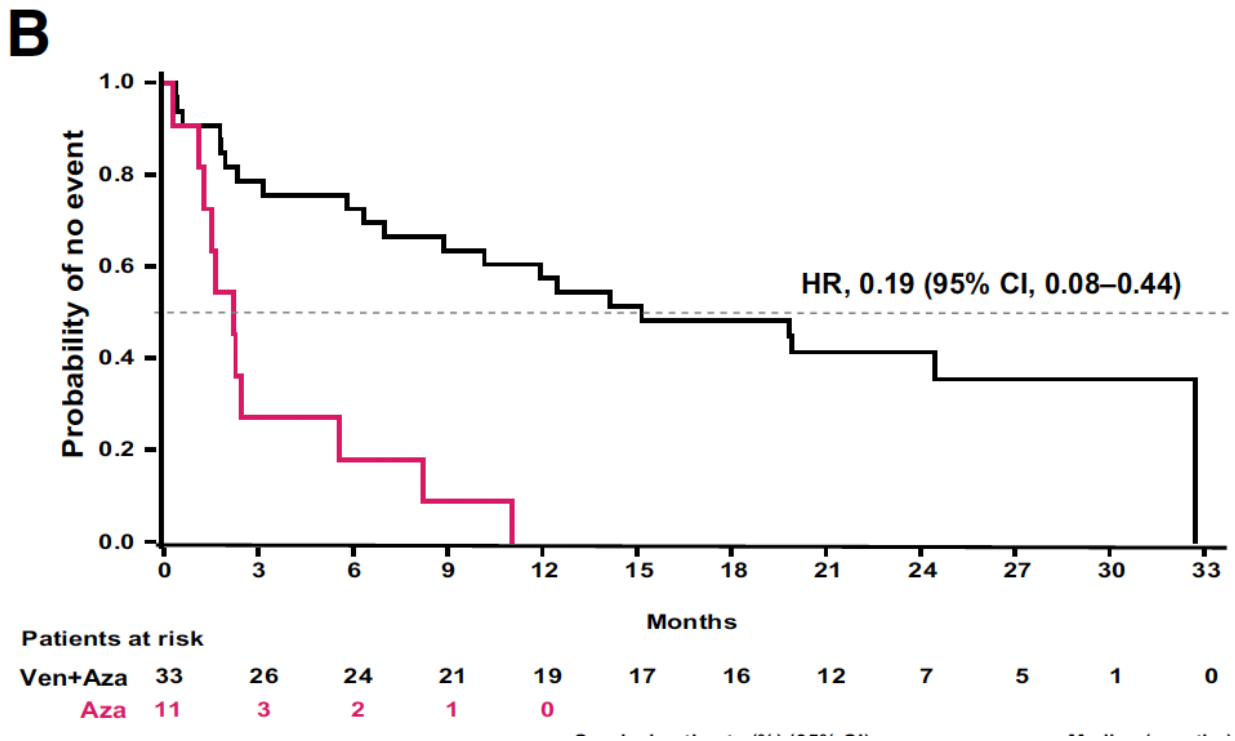
1 sites are pending

Title:
A phase 3, multicenter, double-blind, randomized, placebo-controlled study of ivosidenib or enasidenib in combination with induction therapy and consolidation therapy followed by maintenance therapy in patients with newly diagnosed acute myeloid leukemia or myelodysplastic syndrome with excess blasts-2, with an IDH1 or IDH2 mutation, respectively, eligible for intensive chemotherapy.

https://hovon.nl/en/trials/ho150, accessed April 21, 2025

Azacitidine/Venetoclax in IDH1 Mutant AML





- The aza monotherapy curve is not consistent with other data or clinical experience
- Does this suggest that the IDH1 mutant curve is also underestimating survival?

Pollyea DA, et. al, Clin Cancer Res 2022;28:2753–61

Toxicity of Aza/Ven for IDH Mutant AML

Table 6. Laboratory utilization, transfusions, and toxicities of responders before and after CR/CRi.

	Before CR/CRi	After CR/CRi	*P*
CBC Draws Per Cycle, median (IQR)	18 (16)	12 (11)	0.04
RBC Transfusions Per Cycle, median (IQR)	3 (6.3)	0 (0.9)	0.002
PLT Transfusions Per Cycle, median (IQR)	2.1 (5.8)	0 (0.8)	0.1
Growth Factor Use, % of Cycles	3	4	0.72
Febrile Neutropenia*, % of Cycles	36	2.3	<0.001
Neutropenia*, % of Cycles	100	85	<0.001
Anemia*, % of Cycles	68	25	<0.001
Thrombocytopenia*, % of Cycles	76	39	<0.001
ED / Unplanned Hospitalization, % of Cycles	39	24	0.12

Chin KK, et. al, Leukemia and Lymphoma 2025

Ven/Aza for High Risk MDS

Patients and Methods

Adult patients with de novo treatment-naive, HR MDS per IPSS (≥1.5)/IPSS-R (>3), BM blasts <20% at baseline, and ECOG PS ≤2

Dose Escalation + Safety Expansion
Ven 14-Days/Cycle Dosing

Ven 400 mg + Aza
n = 107

Selected RP2D

Garcia J, et. al. Blood 2025

Aza/Ven for High Risk MDS

Table 2. Patient demographics and disease characteristics

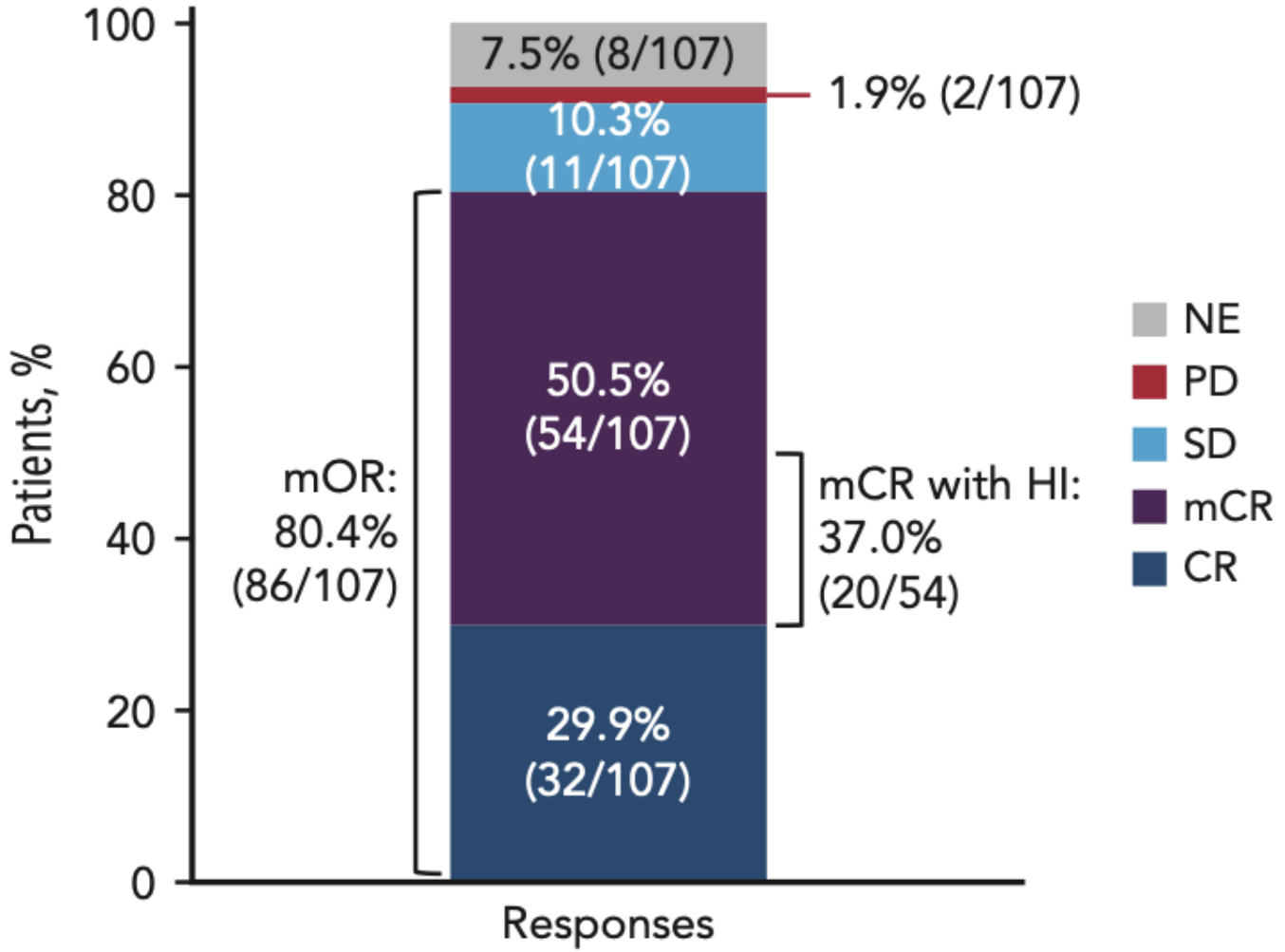
Characteristic	Venetoclax 400 mg (14 d/cycle) + azacitidine 75 mg/m^2 (7 d/cycle) N = 107
Age, median (range), y	68 (26-87)
<65, n (%)	35 (32.7)
≥65, n (%)	72 (67.3)
≥75, n (%)	27 (25.2)
Male, n (%)	74 (69.2)
Race, n (%)	
White	98 (92.5)
Black or African American	1 (0.9)
Asian	7 (6.6)
Missing	1 (0.9)
Ethnicity, n (%)	
Hispanic or Latino	4 (3.8)
Not Hispanic or Latino	102 (96.2)
Missing	1 (0.9)

Table 2. Patient demographics and disease characteristics

Characteristic	Venetoclax 400 mg (14 d/cycle) + azacitidine 75 mg/m^2 (7 d/cycle) N = 107
IPSS-R prognostic score, n (%)†	
Low	1 (0.9)
Intermediate	14 (13.1)
High	40 (37.4)
Very high	52 (48.6)
BM blast category, n (%)	
≤5%	11 (10.3)
>5 to ≤10%	32 (29.9)
>10%	64 (59.8)
BM blast count, median (range), %	11.0 (1-19.5)

Garcia J, et. al. Blood 2025

Aza/Ven for High Risk MDS



Garcia J, et. al. Blood 2025

Aza/Ven for High Risk MDS

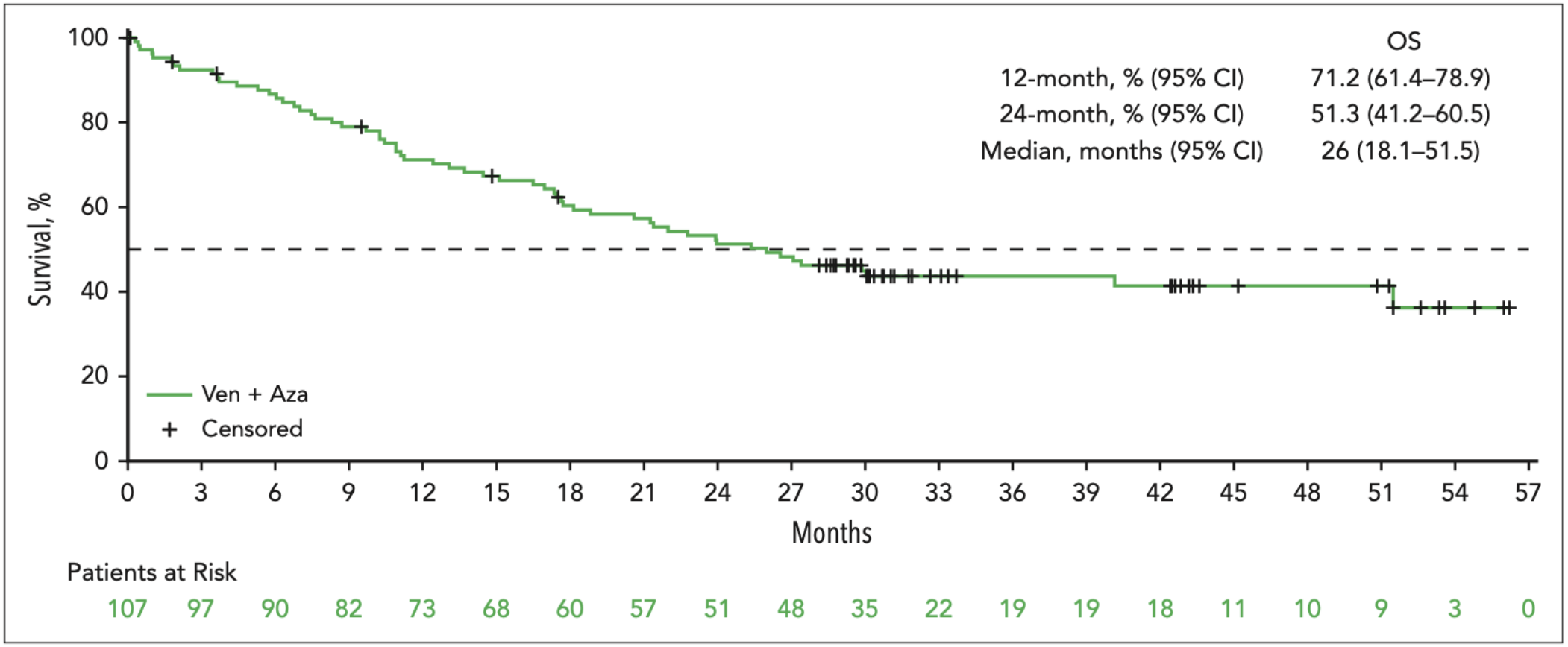


Figure 3. OS. OS was defined as the number of months from the date of the first dose of study drug to the date of death of any cause. If a patient had not died, the data were censored at the date the patient was last known to be alive on or before the cutoff date. AZA, azacitidine; VEN, venetoclax.

Garcia J, et. al. Blood 2025

VERONA Trial – Aza vs. Aza/Ven for High Risk MDS

June 16, 2025

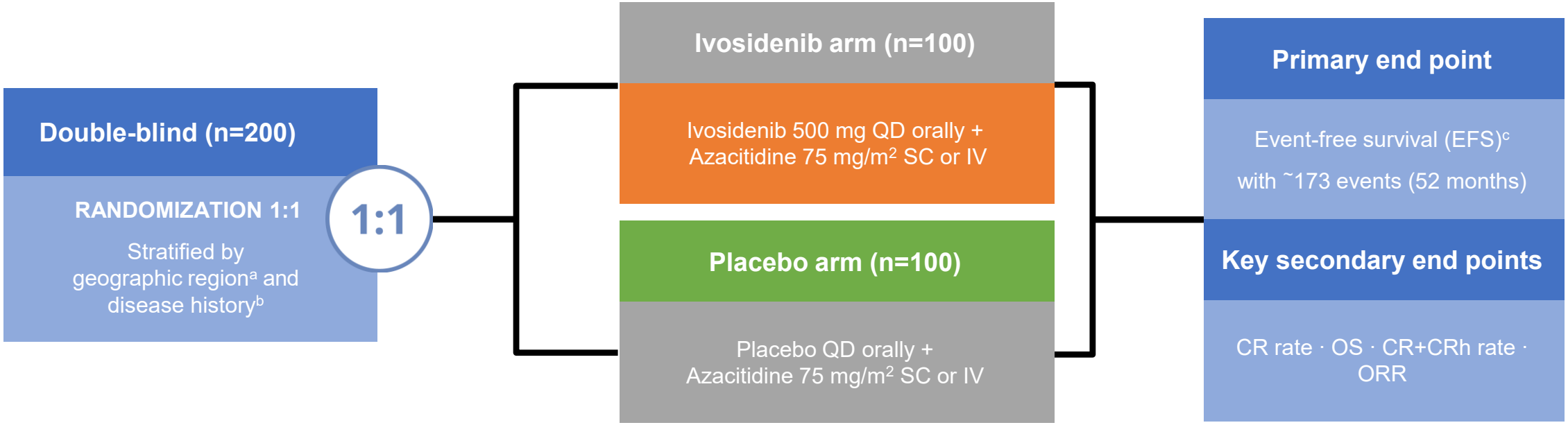
AbbVie Provides Update on VERONA Trial for Newly Diagnosed Higher-Risk Myelodysplastic Syndromes

NORTH CHICAGO, Ill., June 16, 2025 /PRNewswire/ -- AbbVie (NYSE: ABBV) announced the global Phase 3 VERONA trial evaluating venetoclax in combination with azacitidine in the treatment of newly diagnosed higher-risk myelodysplastic syndrome (HR-MDS) did not meet the primary endpoint of overall survival (OS) with a hazard ratio (HR) of 0.908; stratified log-rank, p=0.3772. No new safety signals were observed.[1] Results from the VERONA trial will be available in a future medical congress and/or publication. Any patients who received venetoclax in combination with azacitidine through participation in the MDS clinical trials will be informed by their treating physician.

These data do not impact any current approved indications for venetoclax.

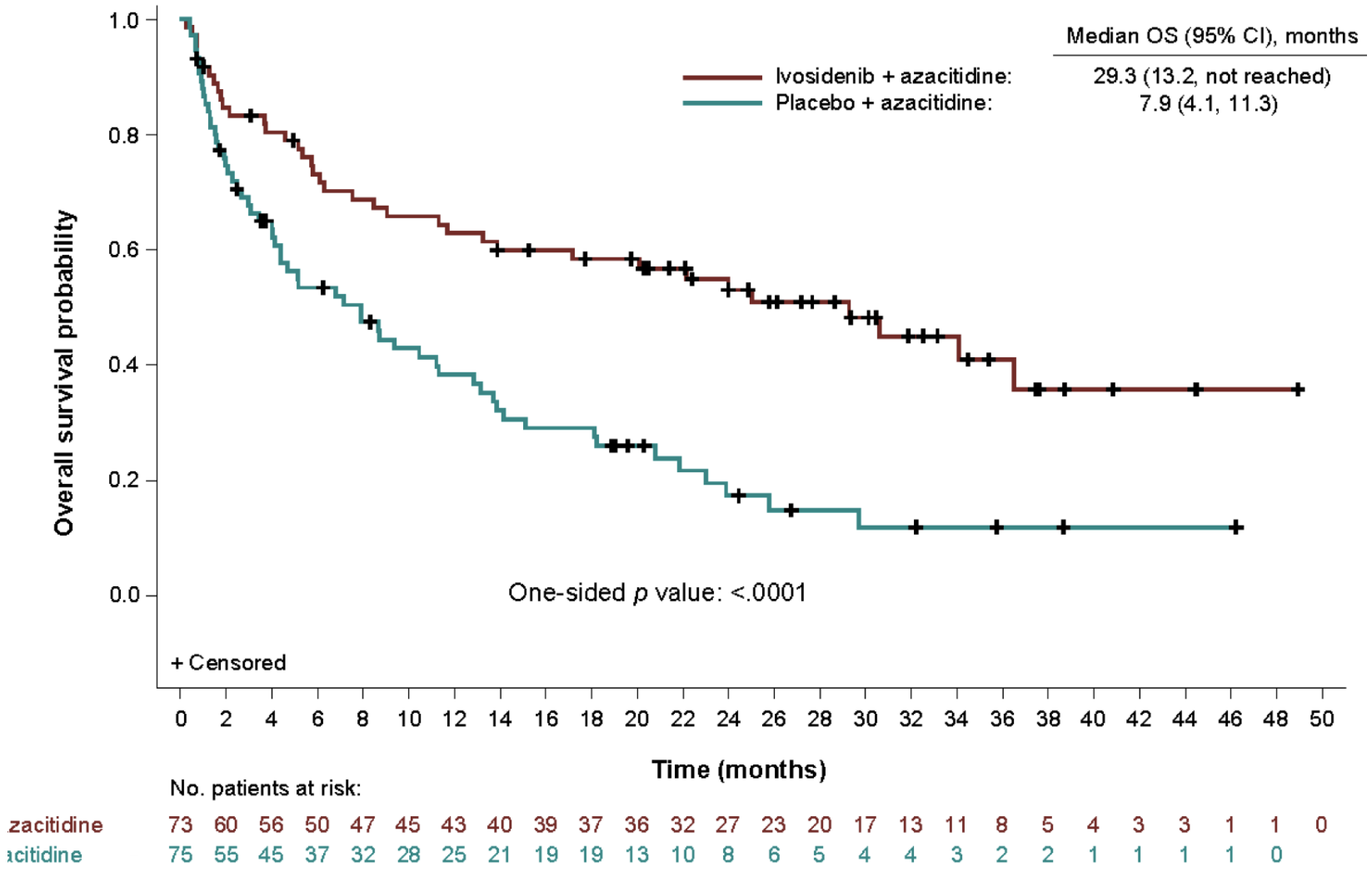
Being Presented Today at 3:11PM Central Time at SOHO Annual Meeting

Azacitidine with Ivosidenib in IDH1 Mutant AML



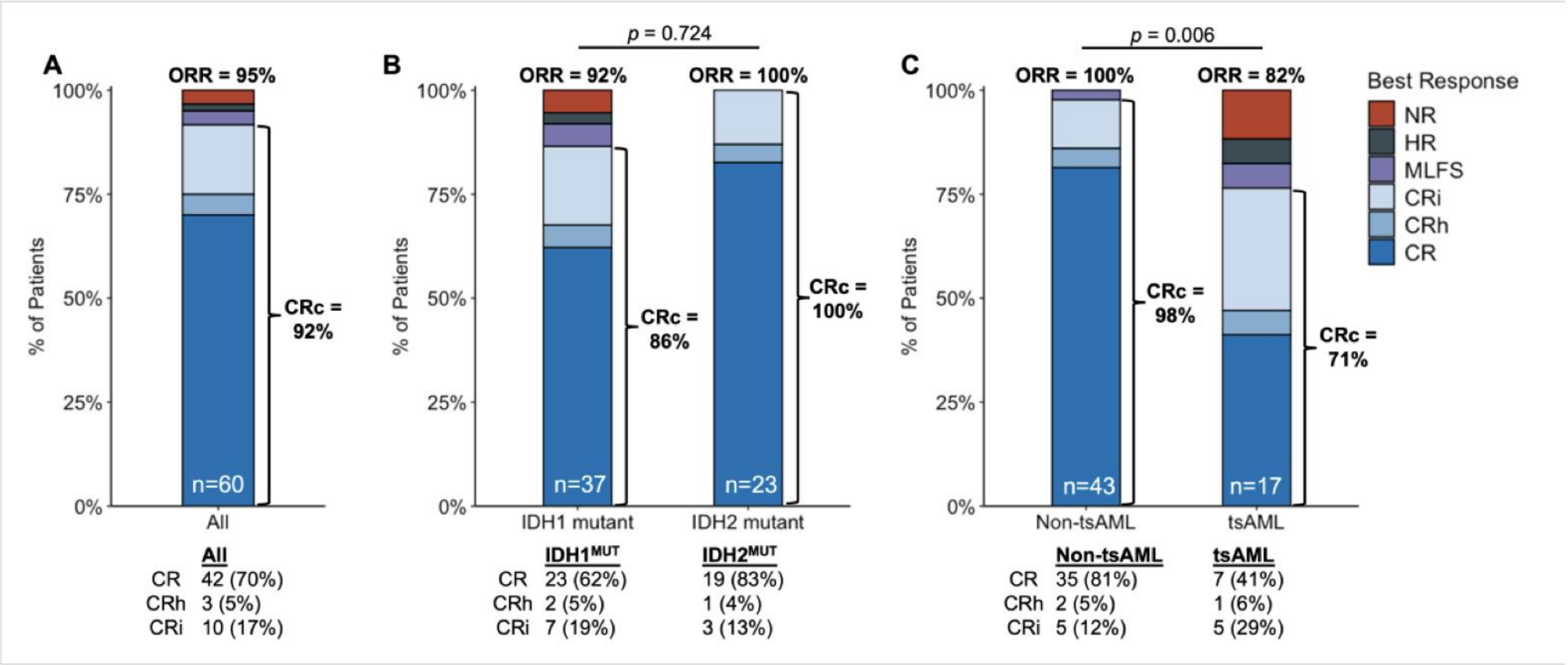
Dohner H et. al, ASH 2021

Ivosidenib in Combination with Azacitidine



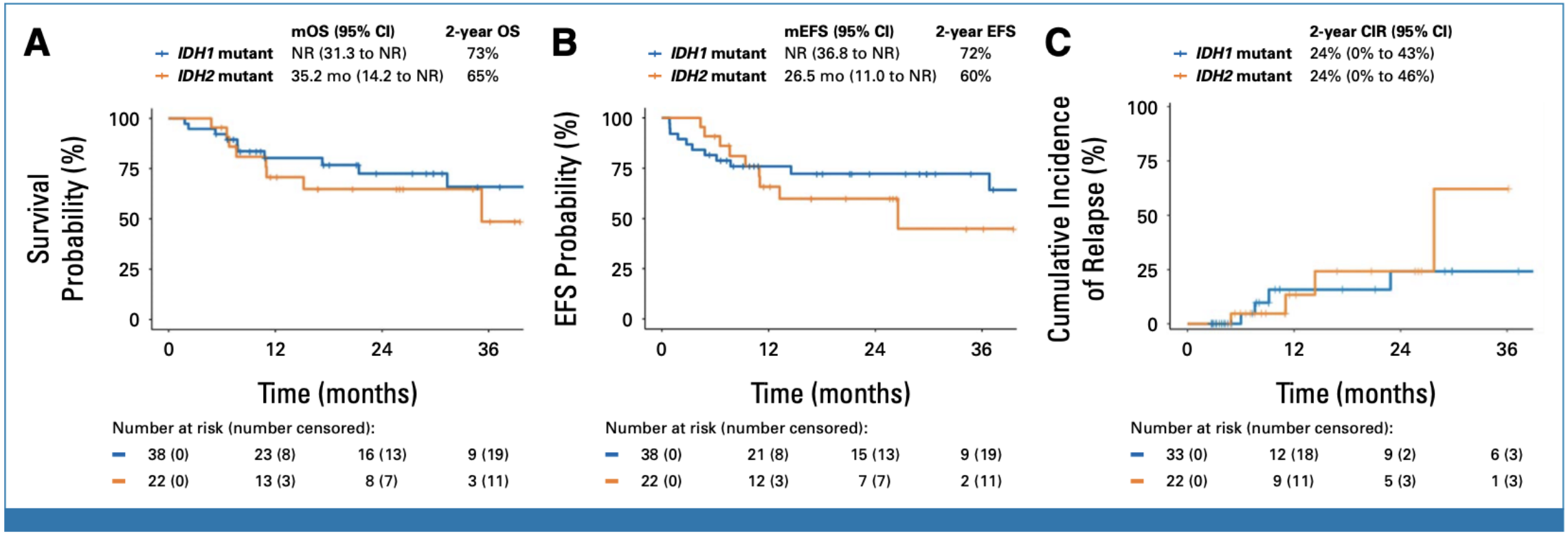
Montesinos P. et. al. Blood Advances 2025

Triplet of Azacitidine/Ivosidenib/Venetoclax



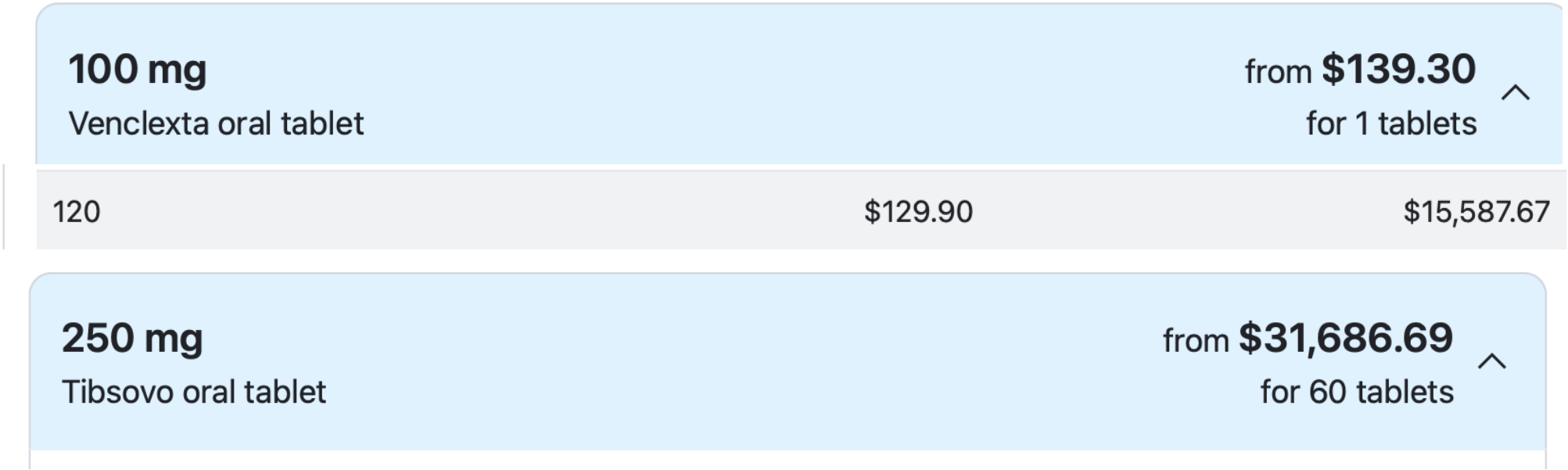
Dinardo CD, et al JCO 2025

Triplet of Azacitidine/Ivosidenib/Venetoclax



Dinardo CD, et al JCO 2025

Cost of Triplet Therapy



100 mg
Venclexta oral tablet

from **$139.30**
for 1 tablets

120	$129.90	$15,587.67

250 mg
Tibsovo oral tablet

from **$31,686.69**
for 60 tablets

Cost for one year of treatment (not including cost of aza) = $567,292.32

Drugs.com, accessed Aug 20, 2023

Ivosidenib – Newly Diagnosed AML

Table 1. Baseline characteristics of patients with newly diagnosed AML

Characteristic	Ivosidenib 500 mg, N = 34
Age, median (range), y	76.5 (64-87)
Age category, n (%), y	
60 to <75	15 (44)
≥75	19 (56)
Women/men, n	15/19
ECOG PS at baseline, n (%)	
0	8 (24)
1	20 (59)
2	5 (15)
3	1 (3)

Table 1. Baseline characteristics of patients with newly diagnosed AML

Characteristic	Ivosidenib 500 mg, N = 34
Nature of AML, n (%)	
De novo	8 (24)
Secondary	
History of MDS	18 (53)
History of MPD	4 (12)
Treatment-related	3 (9)
Other	1 (3)
Prior hypomethylating agent, n (%)	16 (47)
Cytogenetic risk status by investigator, n (%)	
Intermediate	24 (71)
Poor	9 (26)
Unknown	1 (3)

Ivosidenib as a Single Agent in Newly Diagnosed AML

Response category	Ivosidenib 500 mg, n = 33*
CR + CRh rate, n (%) [95% CI]	14 (42.4) [25.5-60.8]
Time to CR/CRh, median (range), mo	2.8 (1.9-12.9)
Duration of CR/CRh, median [95% CI], mo	NE [4.6 to NE]
CR rate, n (%) [95% CI]	10 (30.3) [15.6-48.7]
Time to CR, median (range), mo	2.8 (1.9-4.6)
Duration of CR, median [95% CI], mo	NE [4.2 to NE]
CRh rate, n (%) [95% CI]	4 (12.1) [3.4-28.2]
Time to CRh, median (range), mo	3.7 (1.9-12.9)
Duration of CRh, median [95% CI], mo	6.5 [2.8 to NE]
ORR by IWG, n (%) [95% CI]†	18 (54.5) [36.4-71.9]
Time to first response, median (range), mo	1.9 (0.9-3.6)
Duration of response, median [95% CI], mo	NE [4.6 to NE]
Best response by IWG, n (%)	
CR	10 (30.3)
CRi or CRp	6 (18.2)
PR	1 (3.0)
MLFS	1 (3.0)
SD	10 (30.3)
PD	3 (9.1)
Not assessed	2 (6.1)

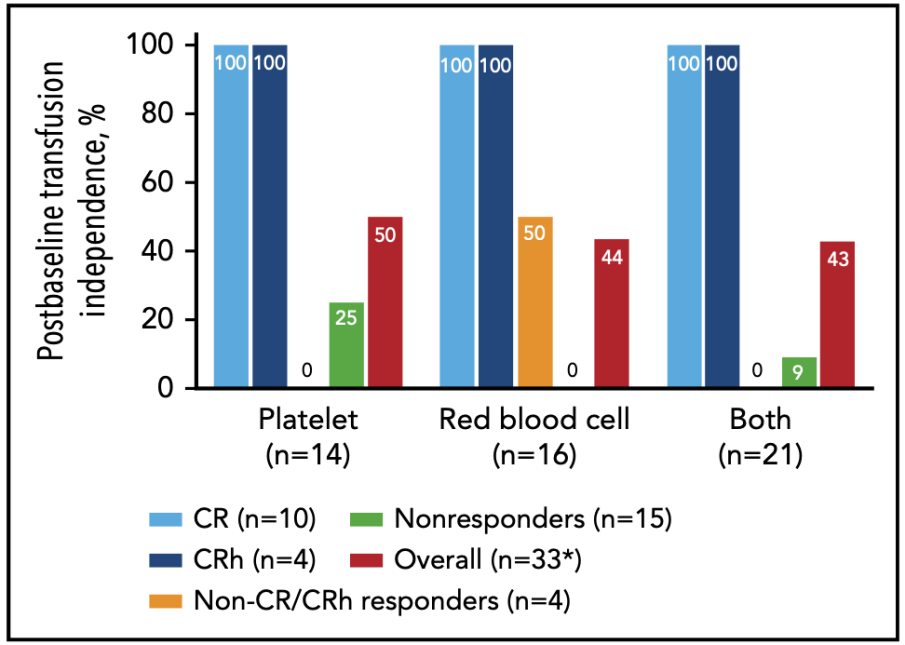
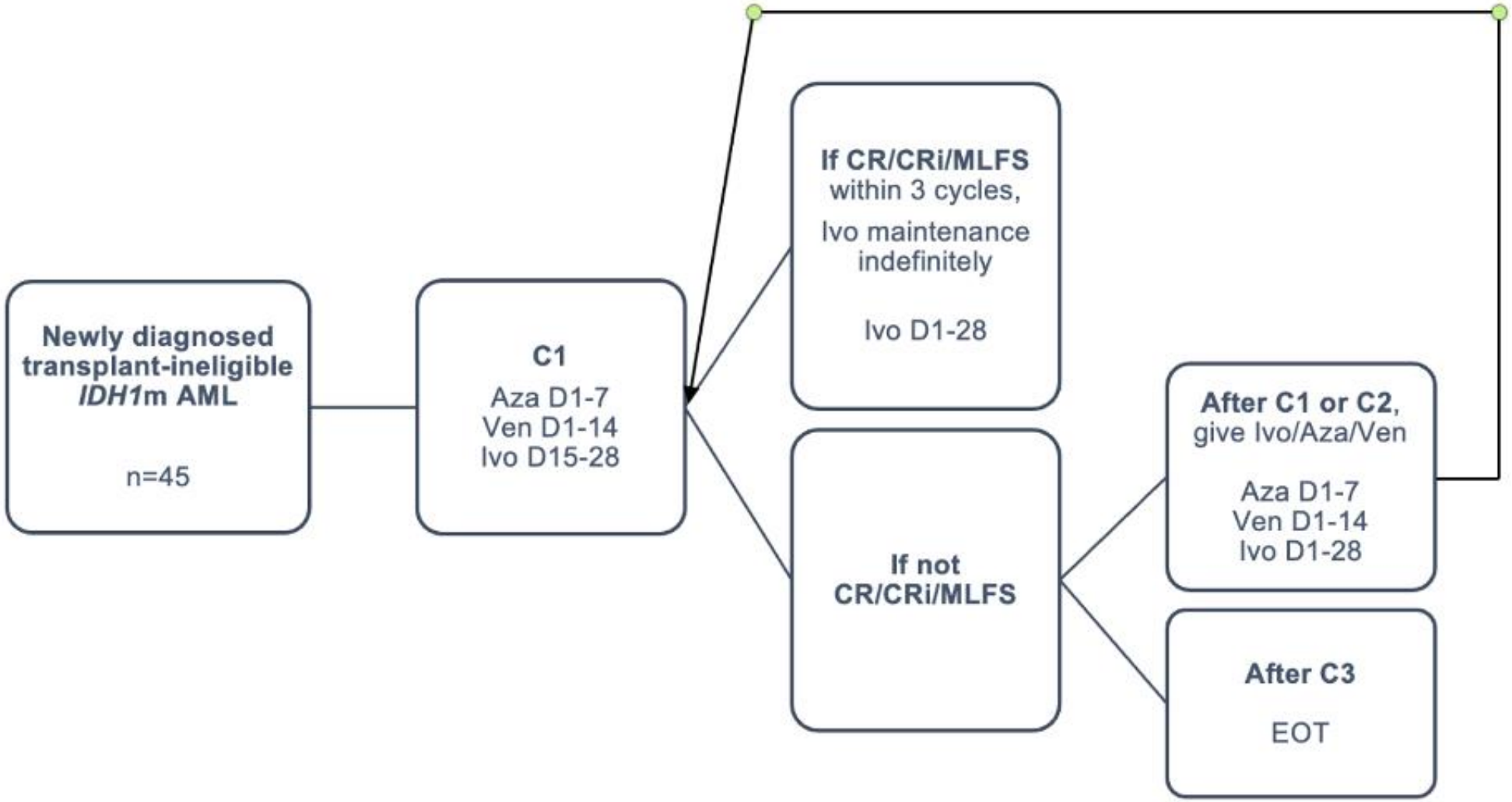


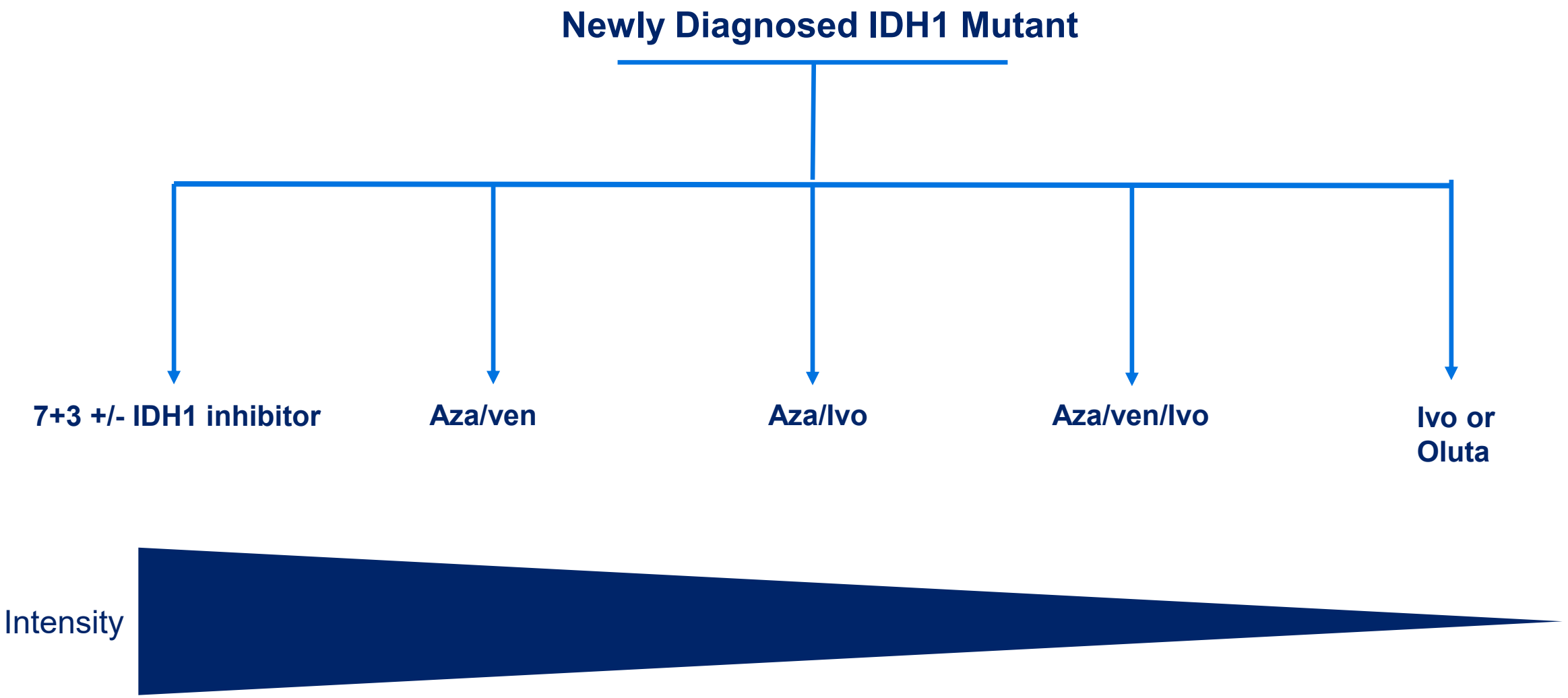
Figure 3. Transfusion independence in patients who were transfusion dependent at baseline. Non-CR/CRh responders include patients with CR with incomplete hematologic recovery/incomplete platelet recovery and morphologic leukemia-free state not meeting the criteria for CRh, and patients with PR. Nonresponders include patients with stable disease and progressive disease. *One patient enrolled in dose-escalation phase was positive for the *IDH1*-D54N mutation by local testing and was not positive for the *IDH1*-R132 mutation by the companion diagnostic test; this patient was therefore excluded from the efficacy analyses.

How do we Achieve the Best of Both Worlds? Triplet Induction → Ivo Maintenance



MSKCC multicenter protocol 24-246

Options to Treat Newly Diagnosed IDH1 Mutant AML



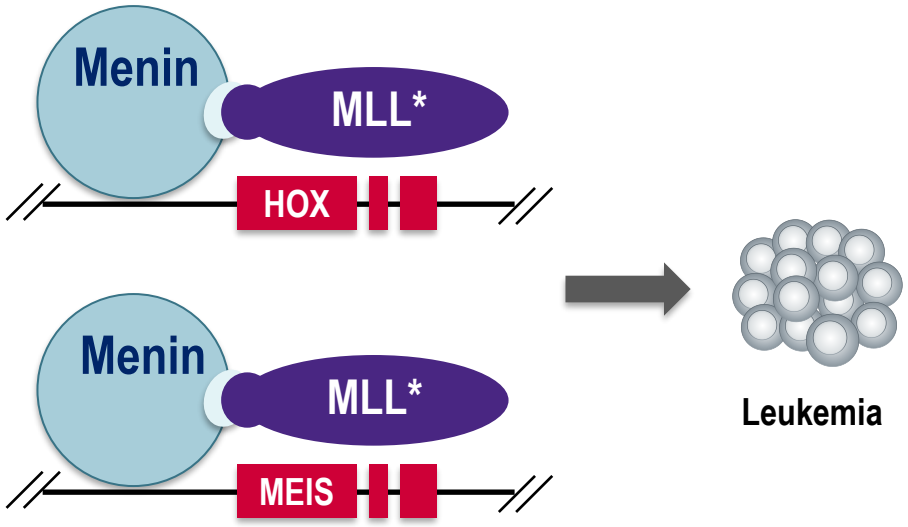
A Case from My Practice (Monday, April 21, 2025)

- 70-year-old man with prior medical history significant for hypertension, diabetes mellitus type 2 and hyperlipidemia presents for newly diagnosed “AML” with 17% blasts. Patient has a normal karyotype and mutations in NPM1 and IDH1. He receives aza/ven/ivo as a triplet on a clinical trial and then transitions to ivo maintenance. He remains in remission for one year and relapses. At relapse, NPM1 is mutant, IDH1 is wild type. No new mutations. Options?

- 1. Chemo
- 2. Restart Aza/Ven
- 3. Restart Aza/Ven/Ivo
- 4. Menin Inhibitor

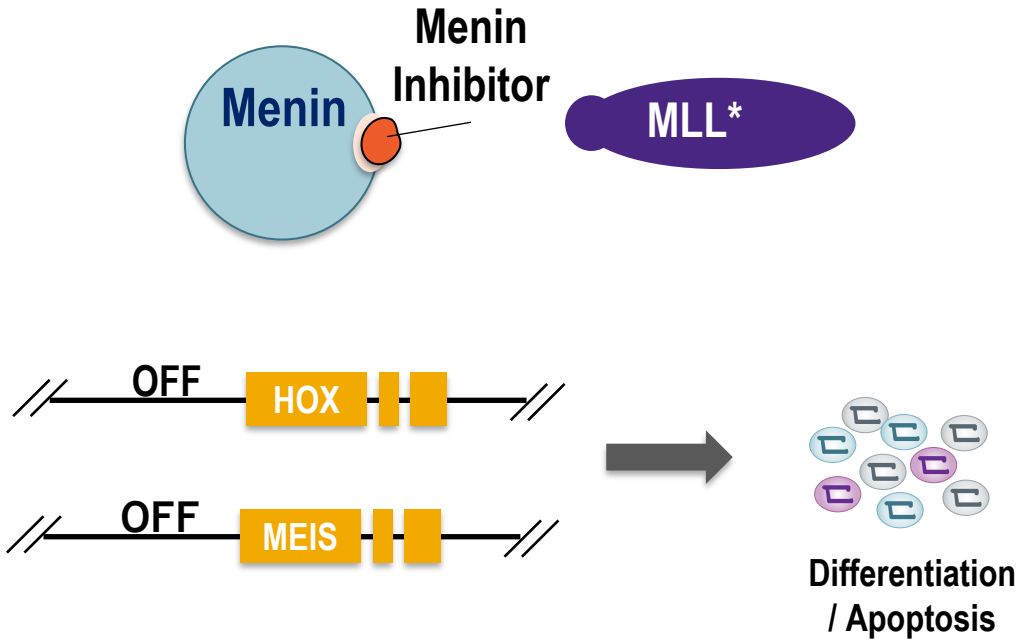
Menin Inhibitors turn off leukemic transcriptional programs by binding to Menin and displacing MLL complexes in Leukemia Dependent on HOX gene dysregulation

MLLr Acute Leukemias



Gene transcription ON

Menin Inhibitor



Gene transcription OFF

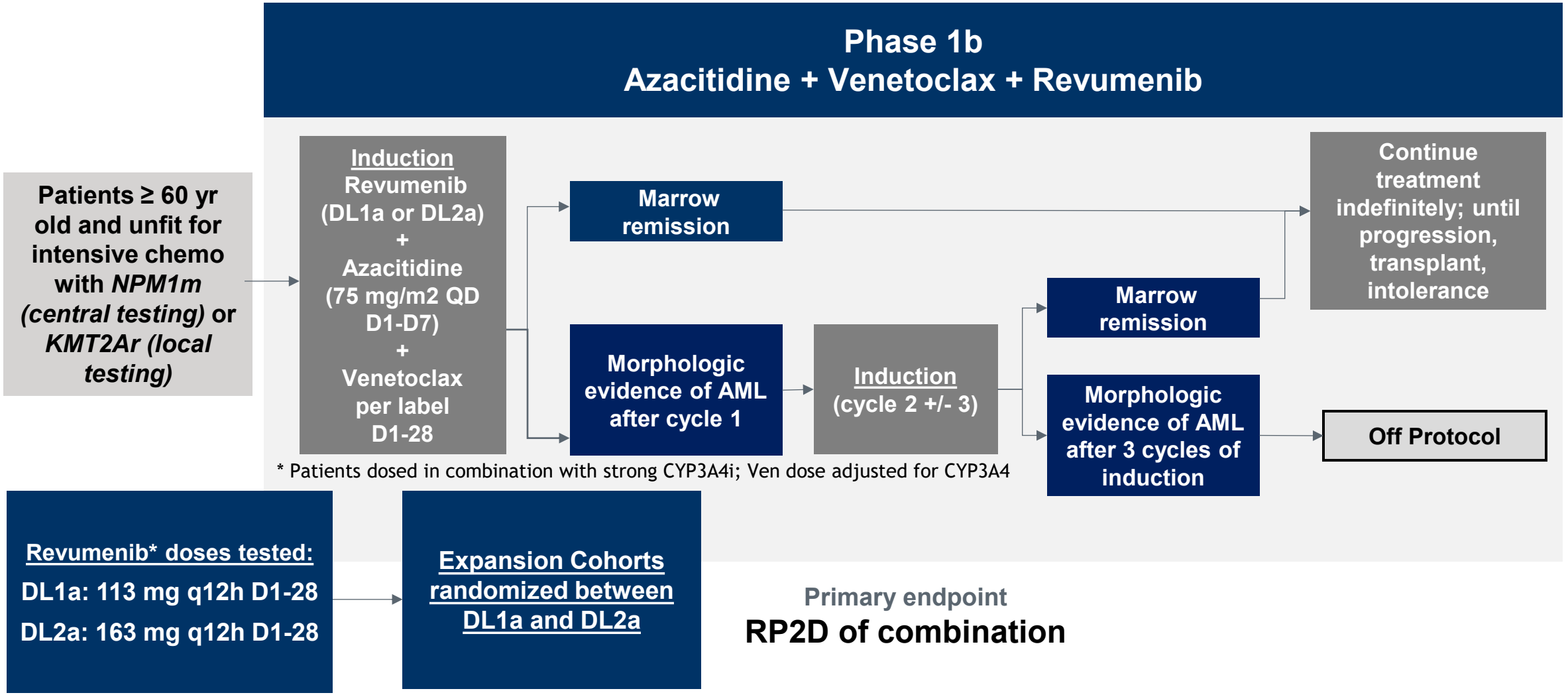
MLL* = MLLr or MLL1 wildtype; Adopted from: Uckelmann HJ, et al. Presented at ASH Annual Meeting, 2018

Single Agent Menin Inhibitors for Relapsed and Refractory Acute Leukemia

Name	Company	Patient Population	Response Rates for KMT2Ar	Response Rates for NPM1	Duration of CR/CRh (median)	Toxicity
Revumenib**	Syndax	KMT2A NPM1 NUP98r	ORR – 63% CR/CRh – 21.2%	ORR 48% CR/CRh (26%)	KMT2A - 6.4 months	QT prolongation DS
Ziftomenib	Kura	NPM1	ORR – 33% CR/CRh – 15%	ORR - 33% CR/CRh 23%	NPM1 3.7 months (mean)	DS
Bleximinib	J and J	KMT2A NPM1	CR/CRh – 33.3%	CR/CRh - 33.3%	6.5 months	DS
Enzomenib	Sumitomo	KMT2A NPM1	ORR – 65.2 CR/CRh – 30.4%	ORR – 58.8% CR/CRh - 47.1%	NPM1 - 7.0 months	DS (10.7%)

Issa et al, JCO 2024, Fathi A, et al, EHA 2025, Jabbour E, et al, ASH 2023 Zeidner, EHA 2024

Beat AML Study Design- Phase 1b Study of Aza/Ven + Revumenib in Newly Dx AML



Zeidner J, et. al EHA 2025

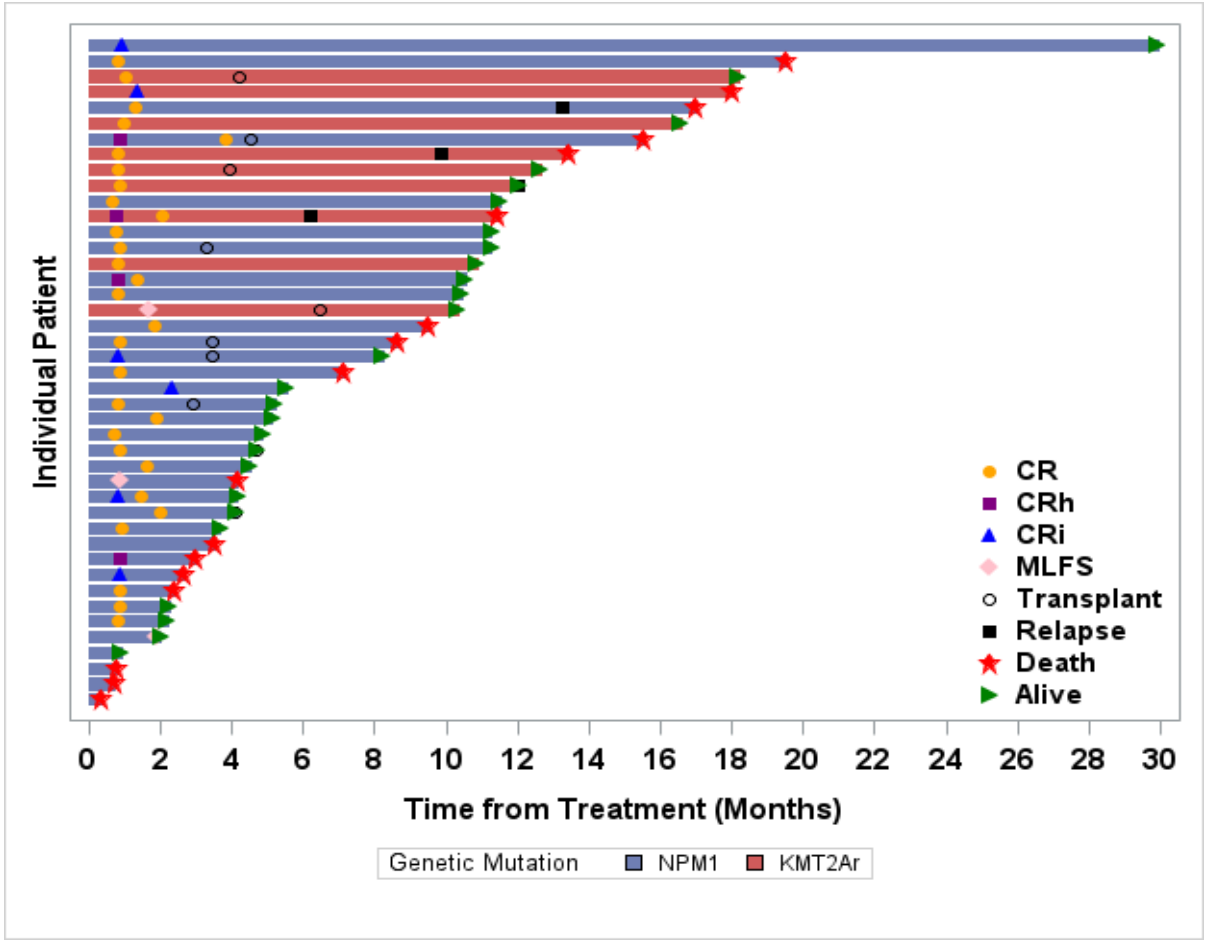
Clinical Outcomes of Aza/Ven/Revumenib

Clinical Outcomes	Dose Level 1	Dose Level 2	All		
	(n=21)	(n=22)	*KMT2Ar* (n=9)	*NPM1m* (n=34)	All (n=43)
Best Response, no. (%)					
CR	13 (61.9)	16 (72.7)	7 (77.8)	22 (64.7)	29 (67.4)
CRh	0 (0.0)	1 (4.5)	0 (0.0)	1 (2.9)	1 (2.3)
CRi	4 (19.0)	1 (4.5)	1 (11.1)	4 (11.8)	5 (11.6)
MLFS	2 (9.5)	1 (4.5)	1 (11.1)	2 (5.9)	3 (7.0)
Not Evaluable[1]	2 (9.5)	3 (13.6)	0 (0.0)	5 (14.7)	5 (11.6)
ORR (CR/CRh/CRi/MLFS)	19 (90.5%)	19 (86.4%)	9 (100%)	29 (85.3%)	38 (88.4%)
CRc (CR/CRh/CRi)	17 (81.0%)	18 (81.8%)	8 (88.9%)	27 (79.4%)	35 (81.4%)

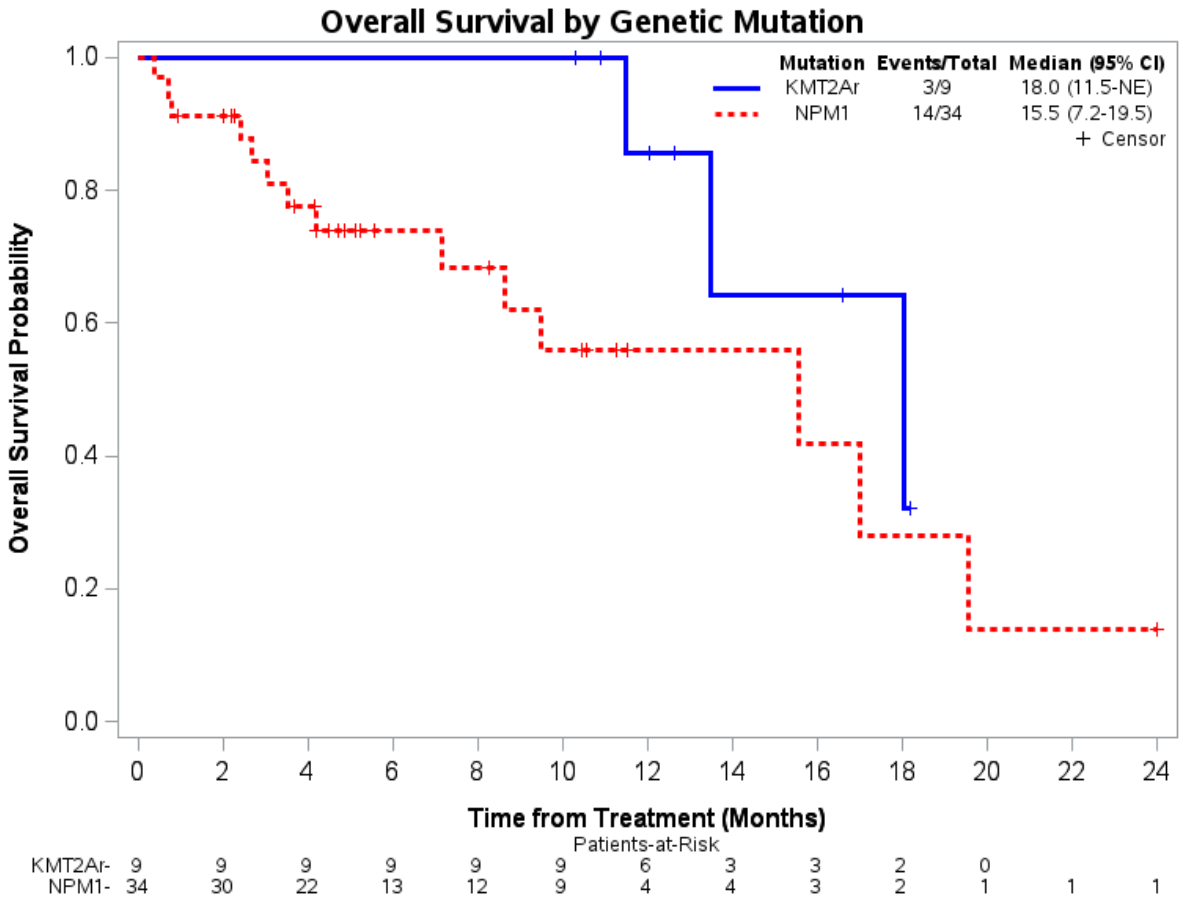
- **No patient had refractory disease after 1-2 cycles**
- **84% of evaluable patients achieved remission within 1st cycle of therapy**
- **100% of evaluable pts achieved flow MRD-negative remission (sensitivity 0.02%)**
  - **76% after cycle 1; 89% after cycle 2**
- **31% achieved *NPM1m* NGS-negative remission (sensitivity 0.005%)**

1 Not Evaluable = 5 pts had either early death (n=3) or withdrew from study (n=2) prior to end of cycle 1 BM Bx

Survival Outcomes of Aza/Ven/Revumenib



- 10 pts (23%) received an allogeneic stem cell transplant
- 4 pts relapsed (*KMT2Ar*: n=3; *NPM1m*: n=1)



- Median F/U = 6.9 months
- 1 year OS = 63% (*KMT2Ar*: 83% vs. *NPM1m*: 55%)

Summary and Thoughts

- The optimal therapy of a newly diagnosed patient with between 10-30% blasts is unclear.
  - Likely depends on genotype for targeted therapy HOWEVER
  - VERONA shows that blast percentage and kinetics of disease development may be more important than genetics.

- For certain genotypes, intensive chemotherapy may be optimal as cure can be achieved without an allogeneic stem cell transplant (e.g. IDH1/NPM1 co-mutant).

- The triplet of aza/ven/ivo may lead to better survival than an aza/ven doublet, but a randomized study is needed (in development in Europe).

- For non-transplant eligible patients an up-front induction approach followed by maintenance therapy may balance efficacy with toxicity.

- Menin inhibitors are effective in R/R NPM1 mutant AML and may have utility in newly diagnosed AML in combination with aza/ven.

Thank You!

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