Penn Medicine

AML: Where are we now? Where are we going?

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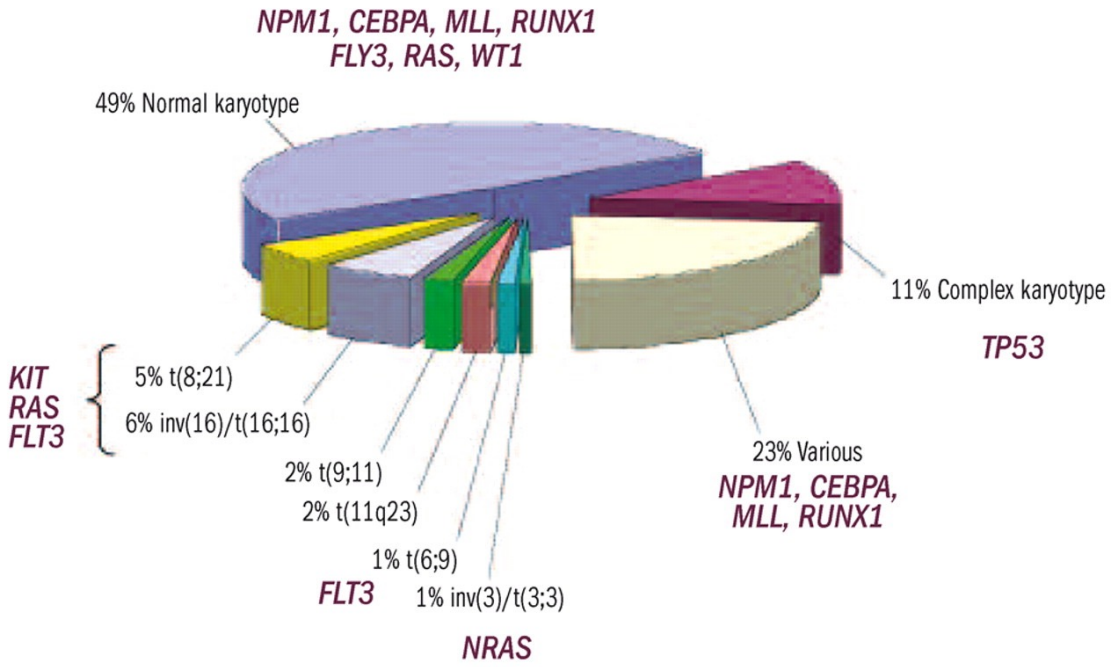
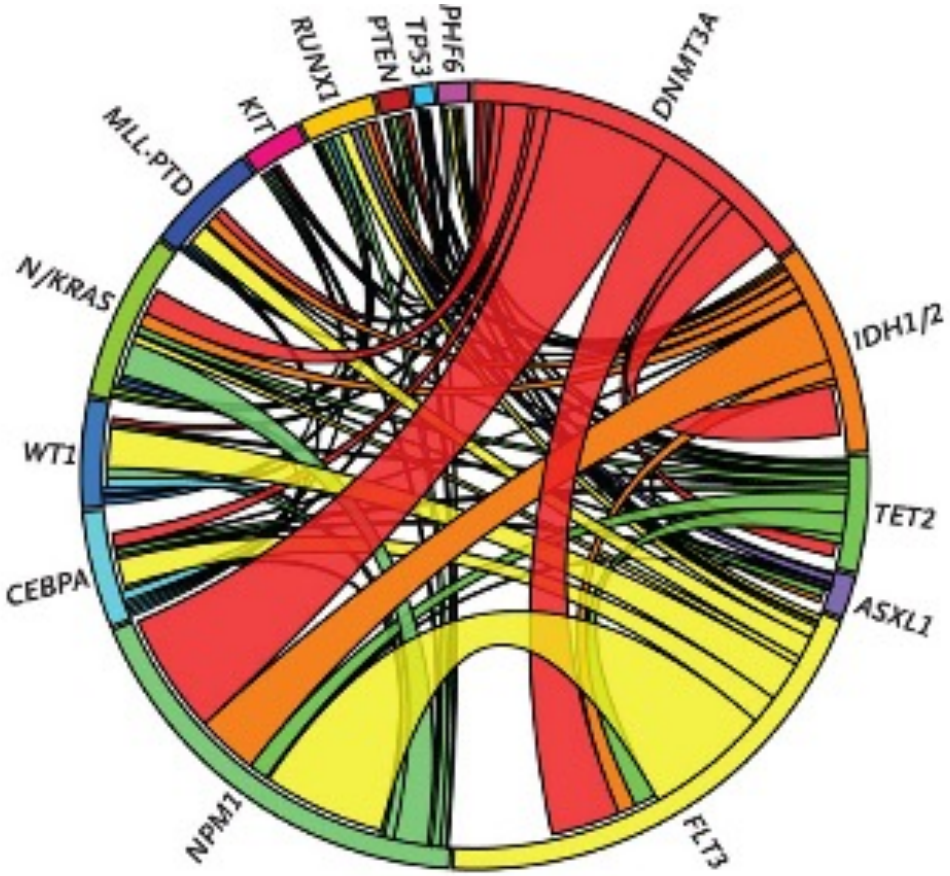
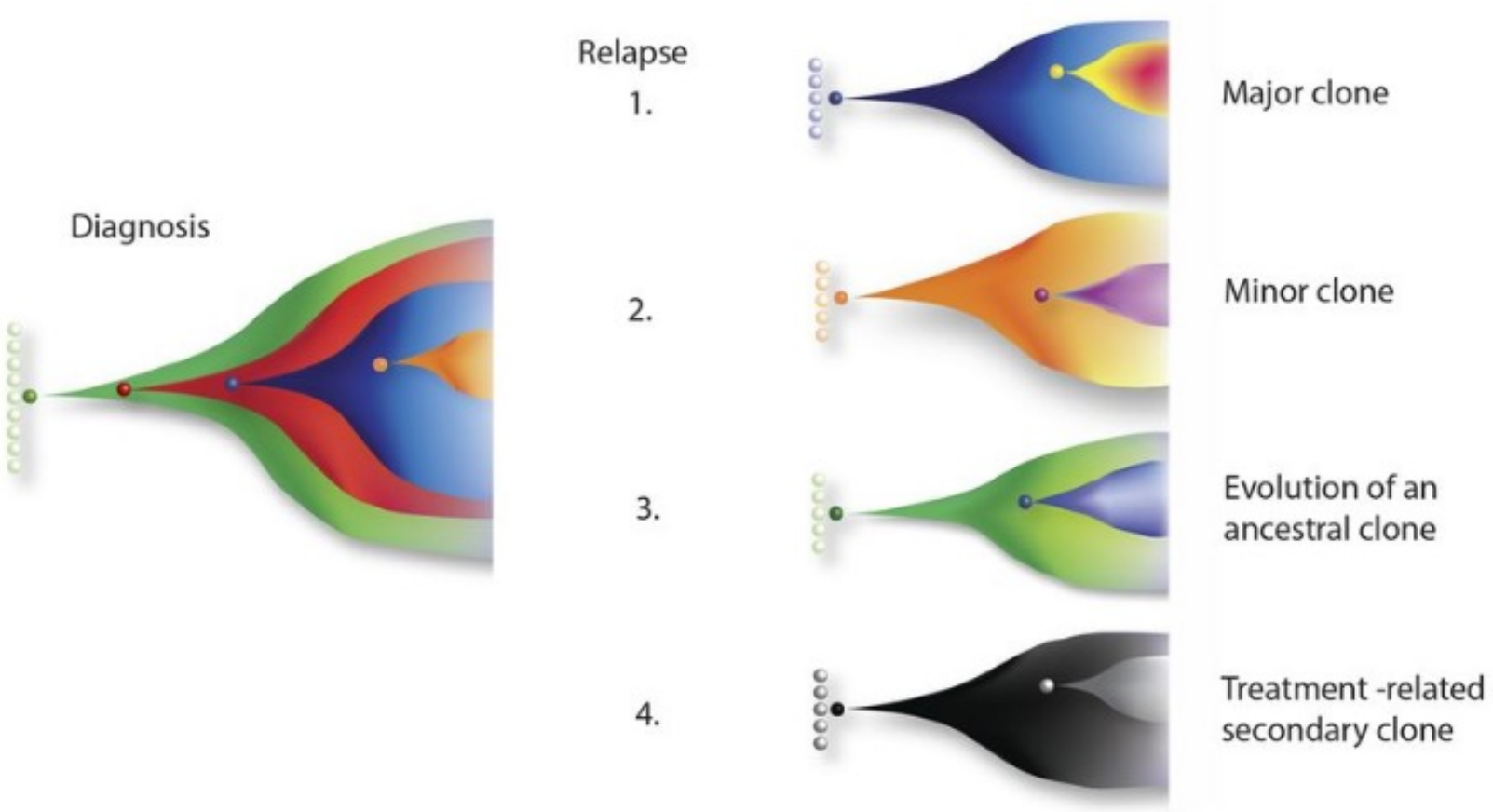
AML is Not One Disease





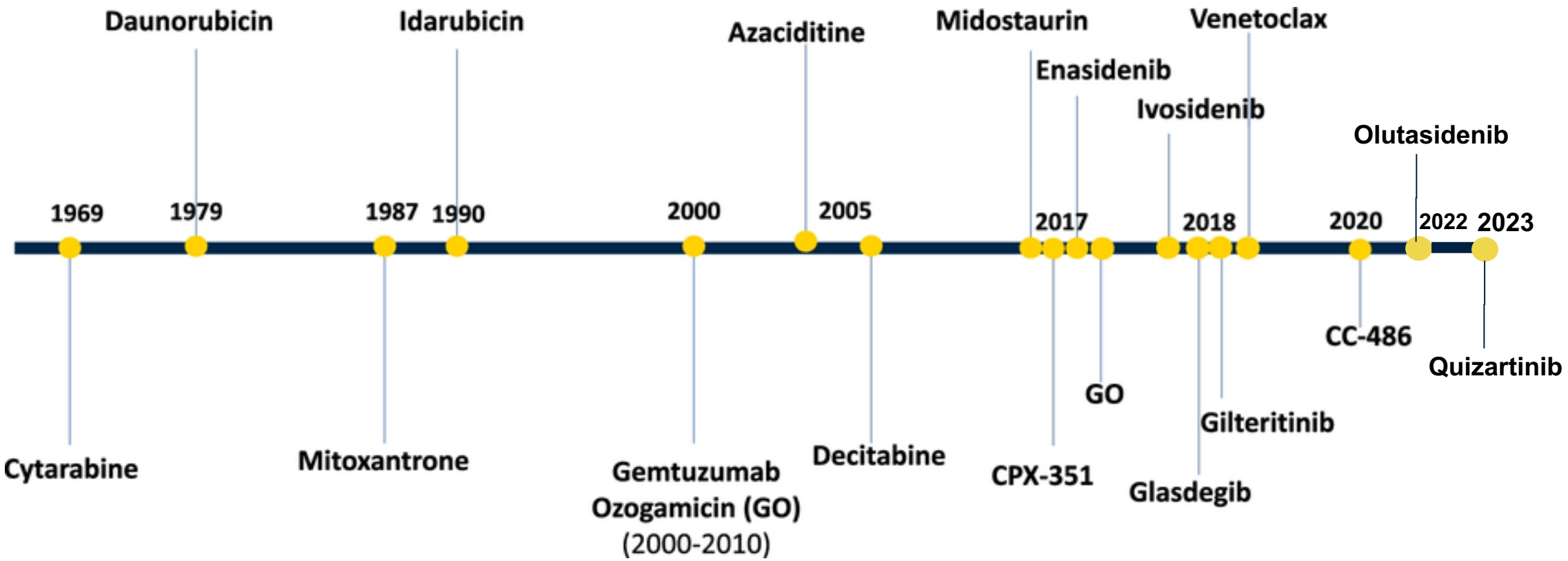
Patel et al. N Engl J Med 2012
Papaemmanuil et al. NEJM 2016

Clonal Evolution Makes Treatment Challenging



Grimwade et al. Blood 2016 127:29-41

What has been accomplished in AML treatment?



Adapted from Ochs et al. Annals of Hematology 2022

FDA Approved Drugs Since 2017

Newly diagnosed

- Midostaurin – April 2017
- CPX-351 – August 2017
- Venetoclax – November 2018
- Glasdegib – November 2018
- Quizartinib – July 2023

Relapsed/refractory

- Enasidenib – August 2017
- Gilteritinib – November 2018
- Olutasidenib – December 2022

Newly diagnosed and Relapsed/Refractory

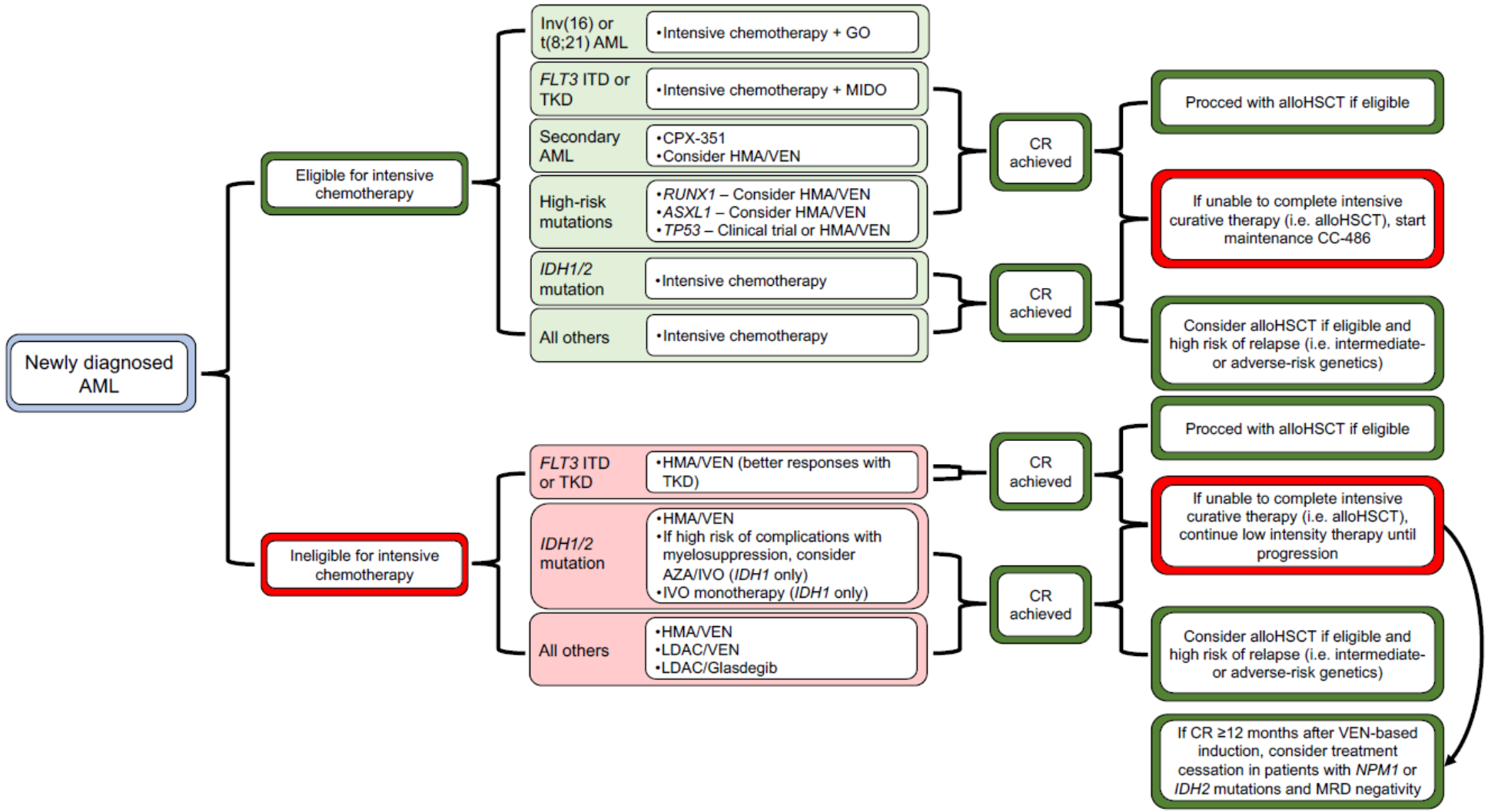
- Gemtuzumab ozogamicin – September 2017
- Ivosidenib – July 2018, May 2019

Maintenance

- CC-486 – September 2020

Historical Standard Approach To Induction Chemotherapy

New Standard Approach to Newly Diagnosed AML



Bhansali, Lai et al. Journal of Hematology & Oncology 2023

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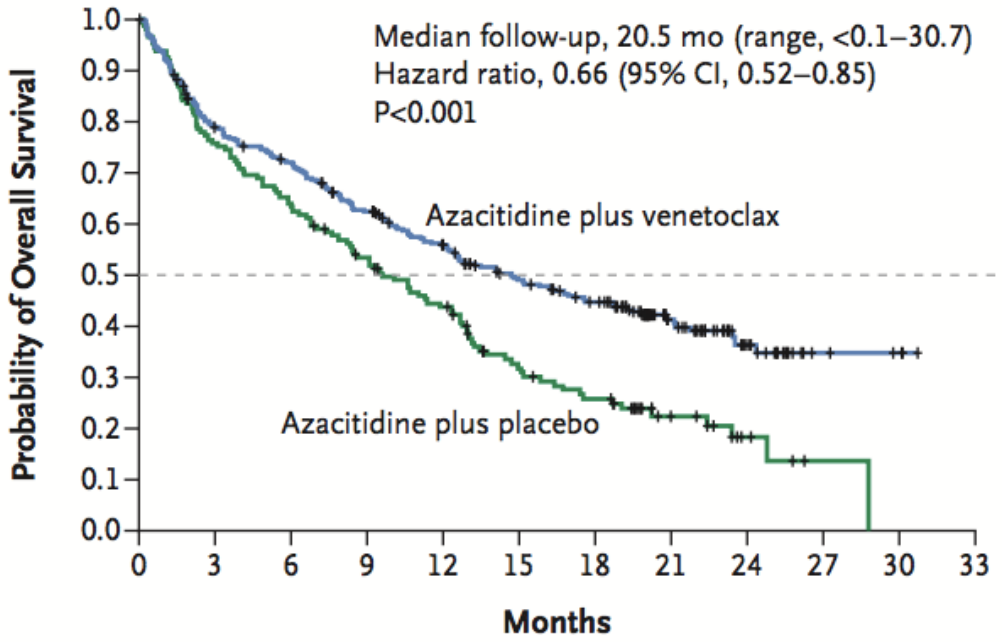
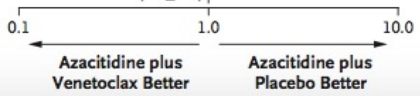
VIALE-A: AZA + Venetoclax Superior to AZA alone



No. at Risk

Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0

Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
All patients	161/286 (56.3)	109/145 (75.2)	0.64 (0.50–0.82)
Sex			
Male	61/114 (53.5)	41/58 (70.7)	0.68 (0.46–1.02)
Female	100/172 (58.1)	68/87 (78.2)	0.62 (0.46–0.85)
Age			
<75 yr	66/112 (58.9)	36/58 (62.1)	0.89 (0.59–1.33)
≥75 yr	95/174 (54.6)	73/87 (83.9)	0.54 (0.39–0.73)
Geographic region			
United States	27/50 (54.0)	21/24 (87.5)	0.47 (0.26–0.83)
Europe	70/116 (60.3)	46/59 (78.0)	0.67 (0.46–0.97)
China	9/24 (37.5)	5/13 (38.5)	1.05 (0.35–3.13)
Japan	10/24 (41.7)	9/13 (69.2)	0.52 (0.20–1.33)
Rest of world	45/72 (62.5)	28/36 (77.8)	0.73 (0.45–1.17)
Baseline ECOG score			
Grade <2	89/157 (56.7)	65/81 (80.2)	0.61 (0.44–0.84)
Grade ≥2	72/129 (55.8)	44/64 (68.8)	0.70 (0.48–1.03)
Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51–0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35–0.91)
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41–0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54–1.12)
Molecular marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)	0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16–0.71)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)	0.34 (0.20–0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36–1.51)
AML with myelodysplasia-related changes			
Yes	56/92 (60.9)	38/49 (77.6)	0.73 (0.48–1.11)
No	105/194 (54.1)	71/96 (74.0)	0.62 (0.46–0.83)
Bone marrow blast count			
<30%	46/85 (54.1)	28/41 (68.3)	0.72 (0.45–1.15)
30 to <50%	36/61 (59.0)	26/33 (78.8)	0.57 (0.34–0.95)
≥50%	79/140 (56.4)	55/71 (77.5)	0.63 (0.45–0.89)



Dinardo et al. NEJM 2020

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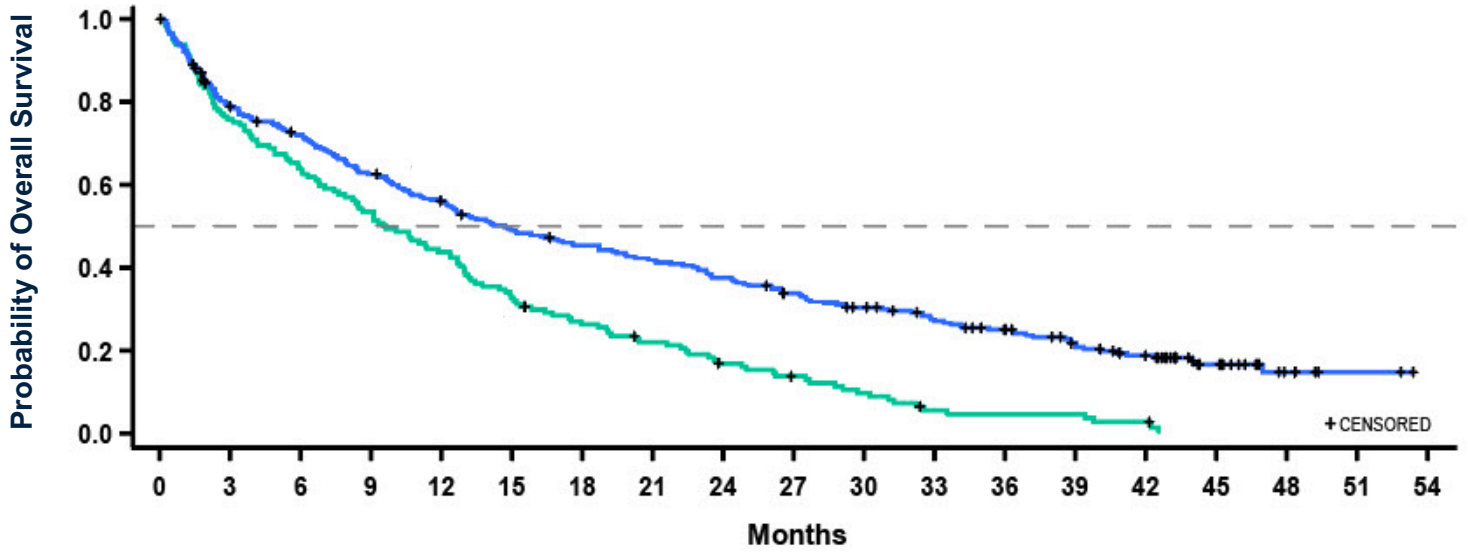
Azacitidine + Venetoclax has Sustained Benefit Over Azacitidine Alone with Long-term Follow Up of VIALE-A

Median follow-up time: 43.2 months (range: < 0.1 - 53.4)



Patients at Risk

Ven+Aza	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0
Pbo+Aza	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0	0	0	0

	No. of events/No. of patients (%)	OS (months) median (95% CI)
Ven+Aza	222/286 (77.6)	14.7 (12.1 - 18.7)
Pbo+Aza	138/145 (95.2)	9.6 (7.4 - 12.7)

Hazard ratio: 0.58 (95% CI, 0.465 - 0.723), P < 0.001

HR reduction from 0.66 (95% CI, 0.52 - 0.85) at 75% OS analysis

Pratz KW et al, ASH 2022, abstract #219

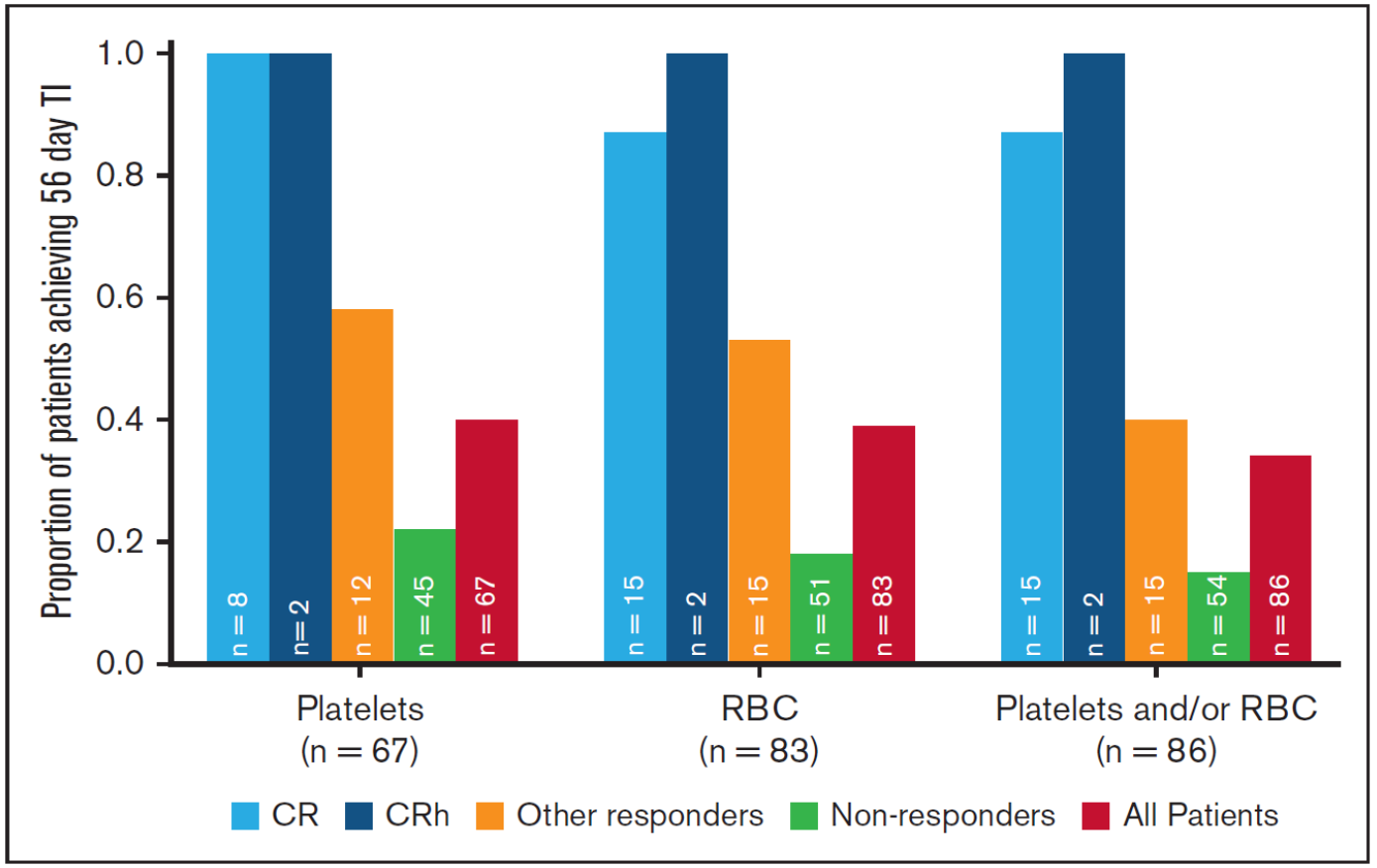
What happened in 2023?

- Olutasidenib approved
  - IDH1 mutated relapsed AML

- Quizartinib approved
  - FLT3 positive newly diagnosed AML

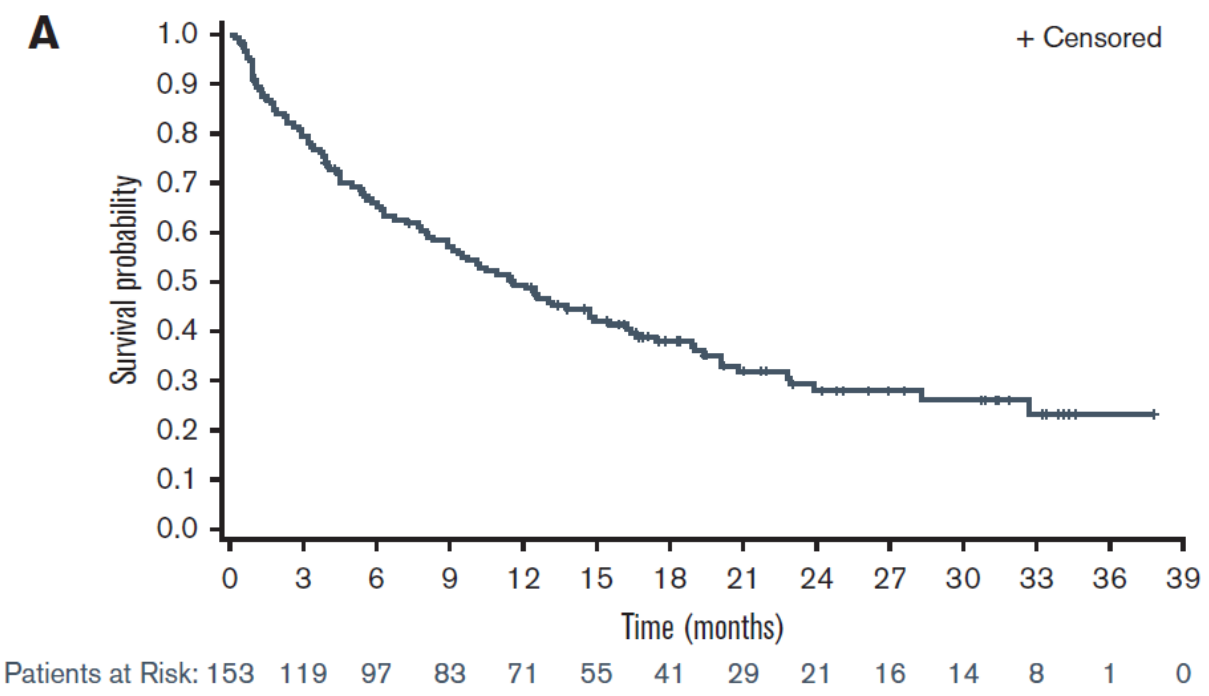
Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed or refractory *IDH1*-mutated AML

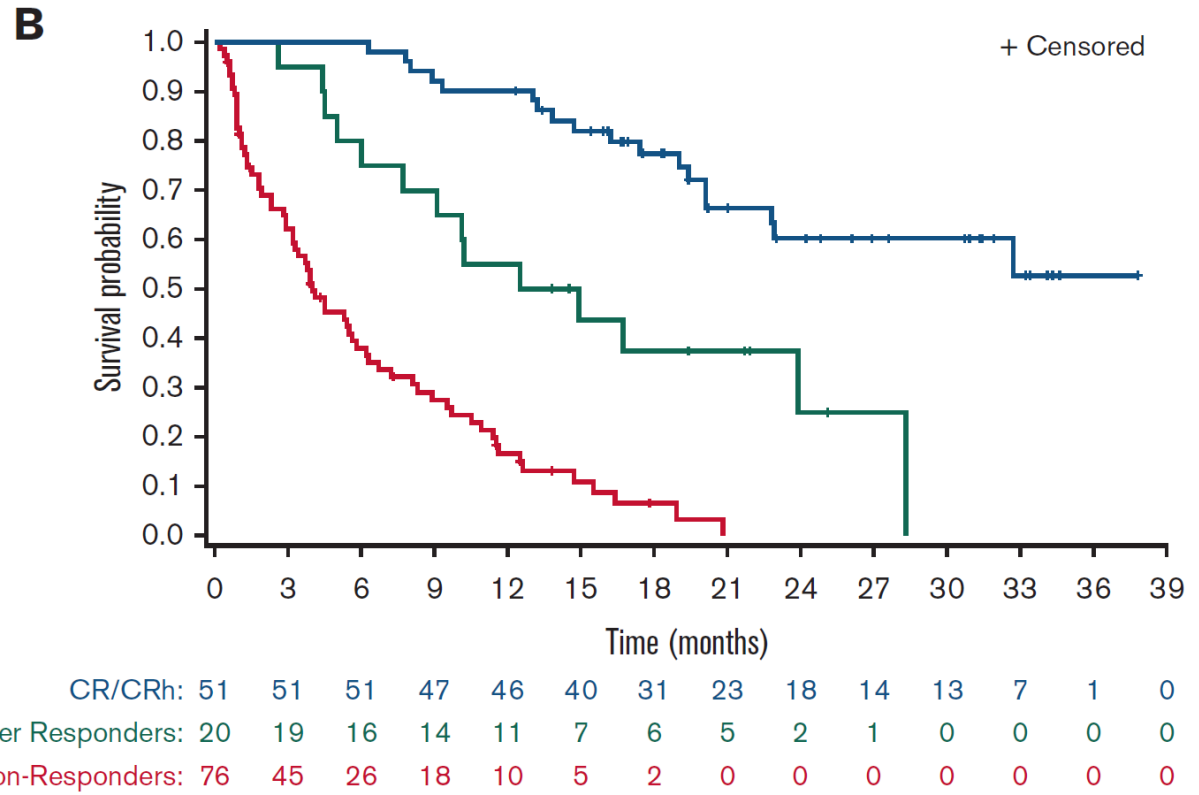
Response rates	Efficacy-evaluable population (n = 147)
CR* or CRh	
n (%) [95% CI]	51 (35) [27.0-43.0]
Median time to CR/CRh, mo (range)	1.9 (0.9-5.6)
CR*	
n (%) [95% CI]	47 (32) [24.5-40.2]
Median time to CR, months (range)	2.8 (0.9-7.4)
Overall response	
N (%) [95% CI]	71 (48) [40.0-56.7]
Median time to first overall response, mo (range)	1.9 (0.9-10.2)
Best overall response, n (%)	
CR*	47 (32)
CRh	4 (3)
CRi	15 (10)
PR	3 (2)
MLFS	2 (1)
SD†	42 (29)
Progressive disease	10 (7)
Not evaluable/not done	6 (4) / 18 (12)



De Botton et al. Blood Advances 2023

Durable response duration and survival in responders





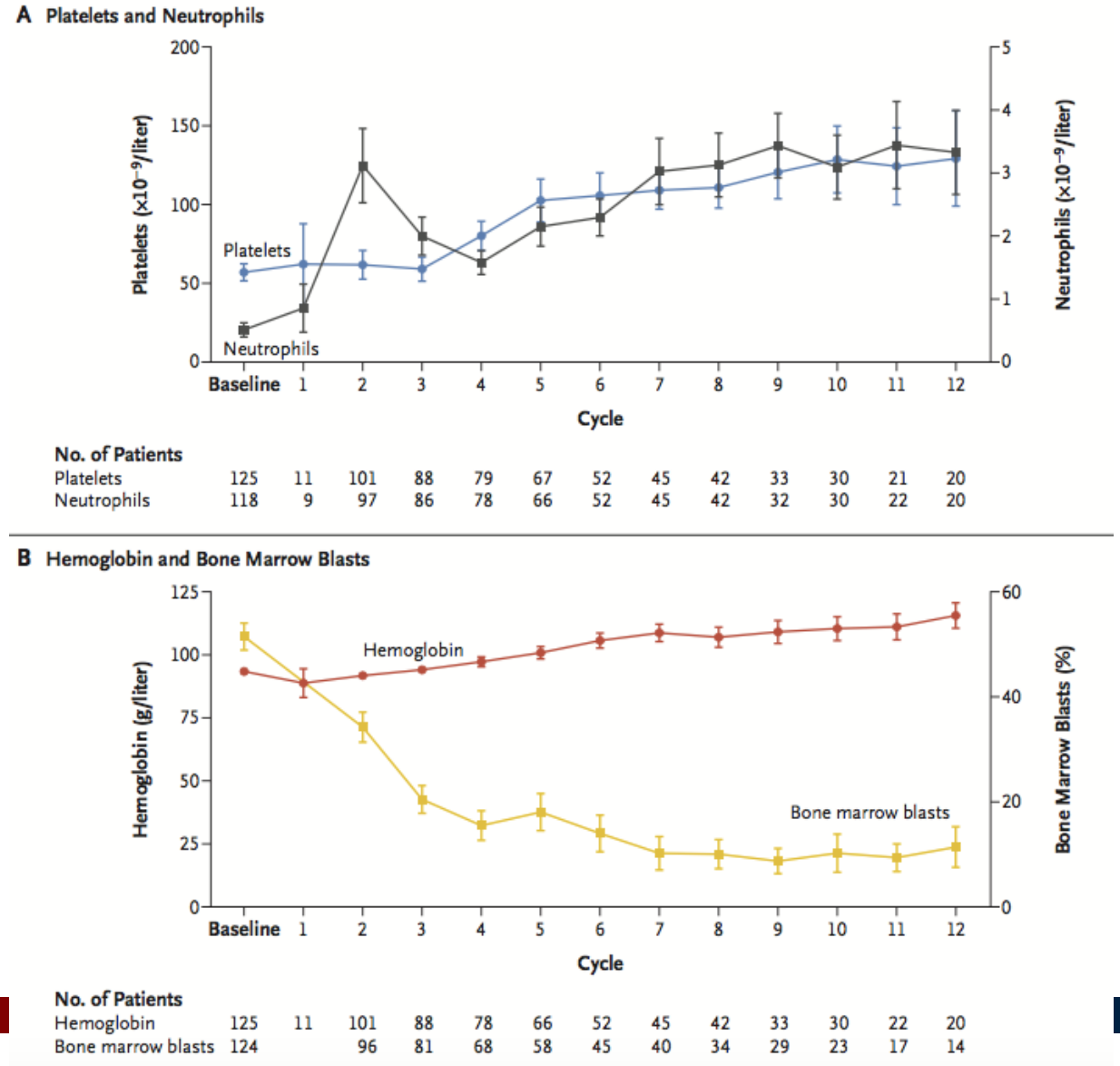
De Botton et al. Blood Advances 2023

Ivosidenib is first IDH1 inhibitor approved in AML

Response	Primary Efficacy Population (N=125)	Relapsed or Refractory AML (N=179)	Untreated AML (N=34)†	MDS (N=12)‡
CR or CRh				NA
No. of patients	38	54	12	NA
% (95% CI)	30.4 (22.5–39.3)	30.2 (23.5–37.5)	35.3 (19.7–53.5)	NA
Median time to CR or CRh (range) — mo	2.7 (0.9–5.6)	2.0 (0.9–5.6)	2.8 (1.9–2.9)	NA
Median duration of CR or CRh (95% CI) — mo	8.2 (5.5–12.0)	6.5 (5.5–11.1)	NE (1.0–NE)	NA
CR				
No. of patients	27	39	7	5
% (95% CI)	21.6 (14.7–29.8)	21.8 (16.0–28.6)	20.6 (8.7–37.9)	41.7 (15.2–72.3)
Median time to CR (range) — mo	2.8 (0.9–8.3)	2.8 (0.9–8.3)	2.8 (1.9–3.7)	1.9 (1.0–5.6)
Median duration of CR (95% CI) — mo	9.3 (5.6–18.3)	9.3 (5.6–12.5)	NE (5.6–NE)	NE (2.8–NE)
Overall response				
No. of patients	52	70	19	11
% (95% CI)	41.6 (32.9–50.8)	39.1 (31.9–46.7)	55.9 (37.9–72.8)	91.7 (61.5–99.8)
Median time to first response (range) — mo§	1.9 (0.8–4.7)	1.9 (0.8–4.7)	1.9 (0.9–2.9)	1.6 (1.0–2.8)
Median duration of response (95% CI) — mo	6.5 (4.6–9.3)	6.5 (4.6–9.3)	9.2 (1.9–NE)	NE (2.3–NE)

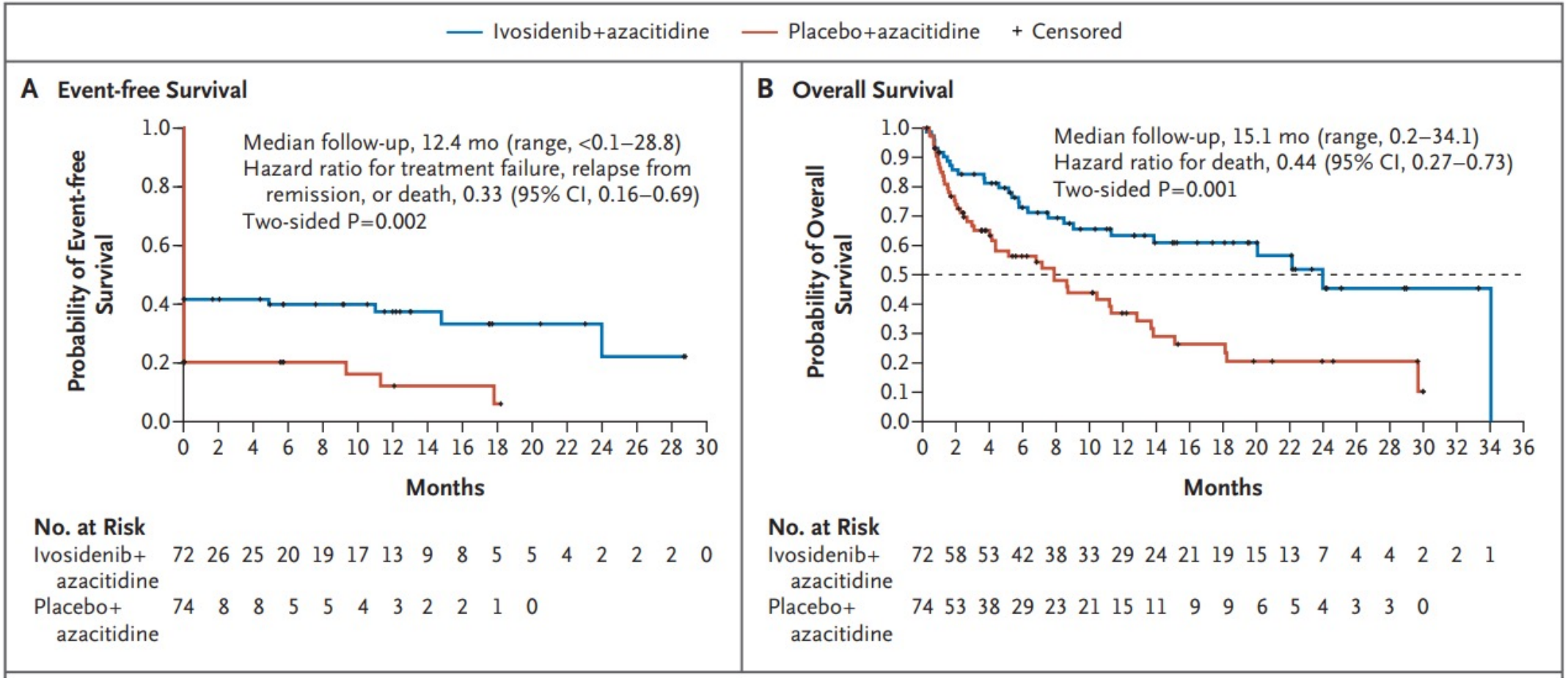
DiNardo et al. NEJM 2018

Ivosidenib Improves Counts Over Time



DiNardo et al. NEJM 2018

Ivosidenib + Azacitidine Improves EFS and OS Compared to Azacitidine Alone



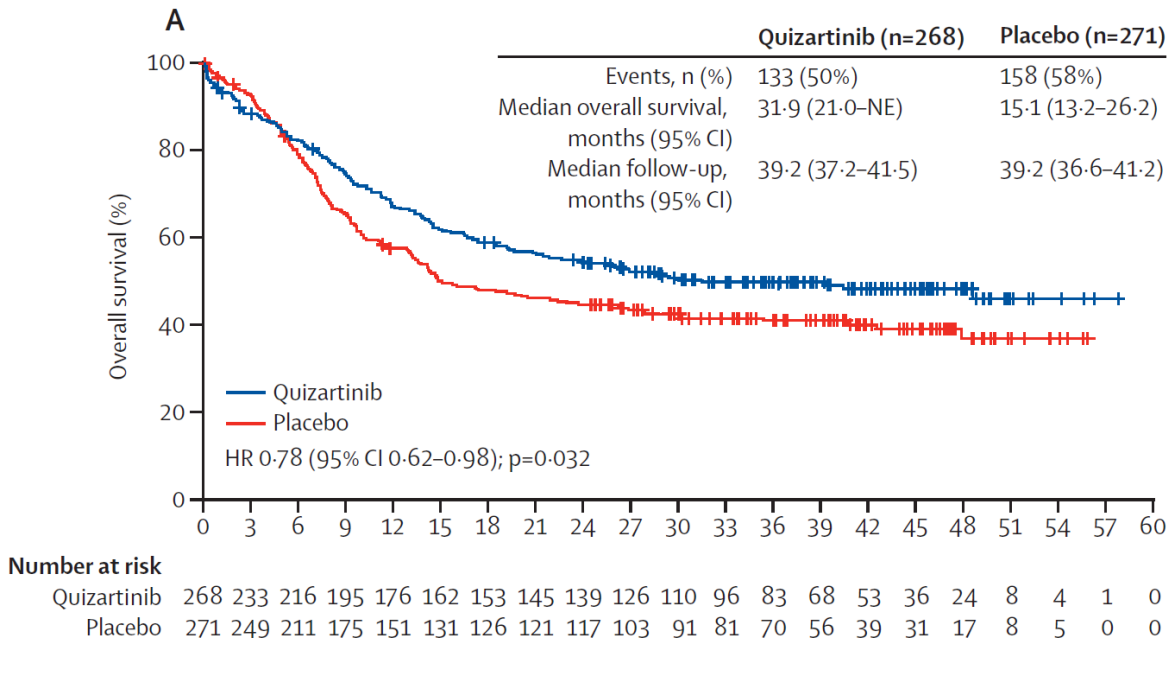
Montesinos et al. NEJM 2022

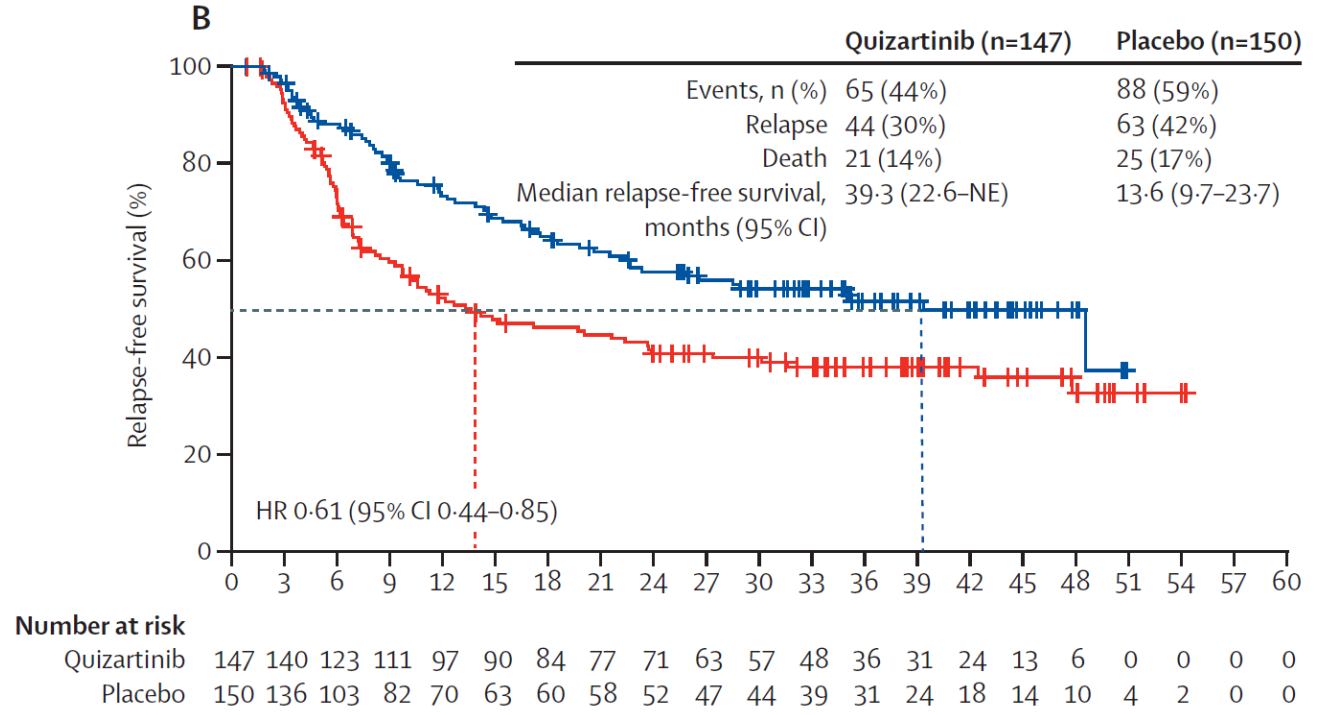
Quizartinib plus chemotherapy in newly diagnosed patients with *FLT3*-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial

Parameter	Quizartinib (N=167)	Placebo (N=90)	*P*
Response after 1 induction cycle, n (%)			
CRc (CR + CRi)	122 (73)	64 (71)	0.74
CR	89 (53)	47 (52)	
CRi	33 (20)	17 (19)	
CR/CRi with MRD negativity	69 (42)	36 (40)	0.80
PR	18 (11)	8 (9)	
MLFS	3 (2)	0 (0)	
Resistance	20 (12)	11 (12)	
Death	4 (2)	7 (8)	
Response after 1 or 2 induction cycles, n (%)			
CRc (CR + CRi)	131 (78)	70 (78)	0.97
CR/CRi with MRD negativity	74 (44)	39 (43)	0.88

Erba et al. Lancet 2023

Quizartinib Improves RFS and OS





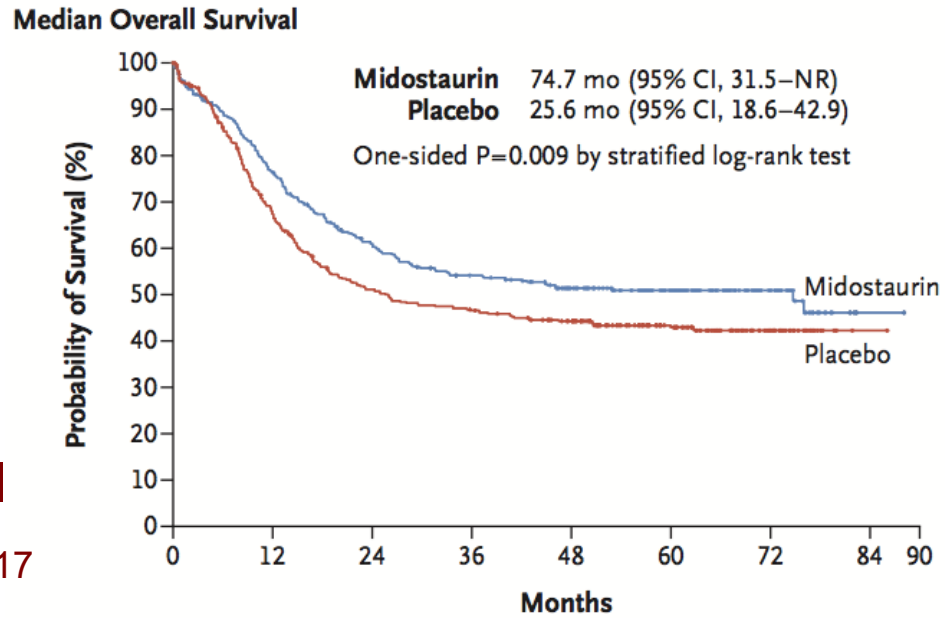
Erba et al. Lancet 2023

ORIGINAL ARTICLE

Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a *FLT3* Mutation

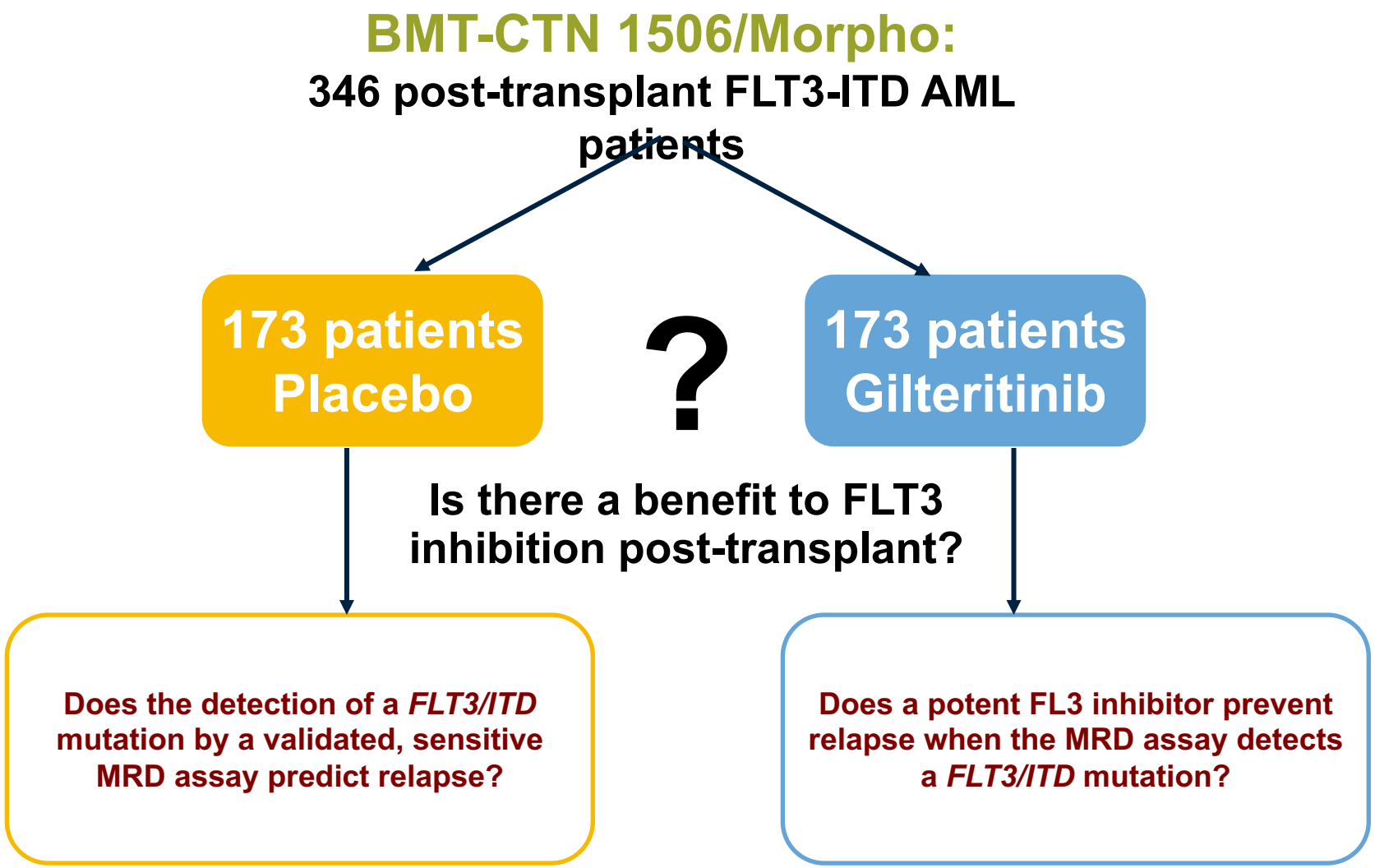
Table 3. Summary of Complete Remission.*

Variable	Midostaurin Group (N=360)	Placebo Group (N=357)	P Value†
Protocol-specified complete remission — no. (%)	212 (59)	191 (54)	0.15
Kaplan–Meier estimate of time to complete remission — days			
Median	35	35	
Range	20–60	20–60	



Stone et al. NEJM 2017

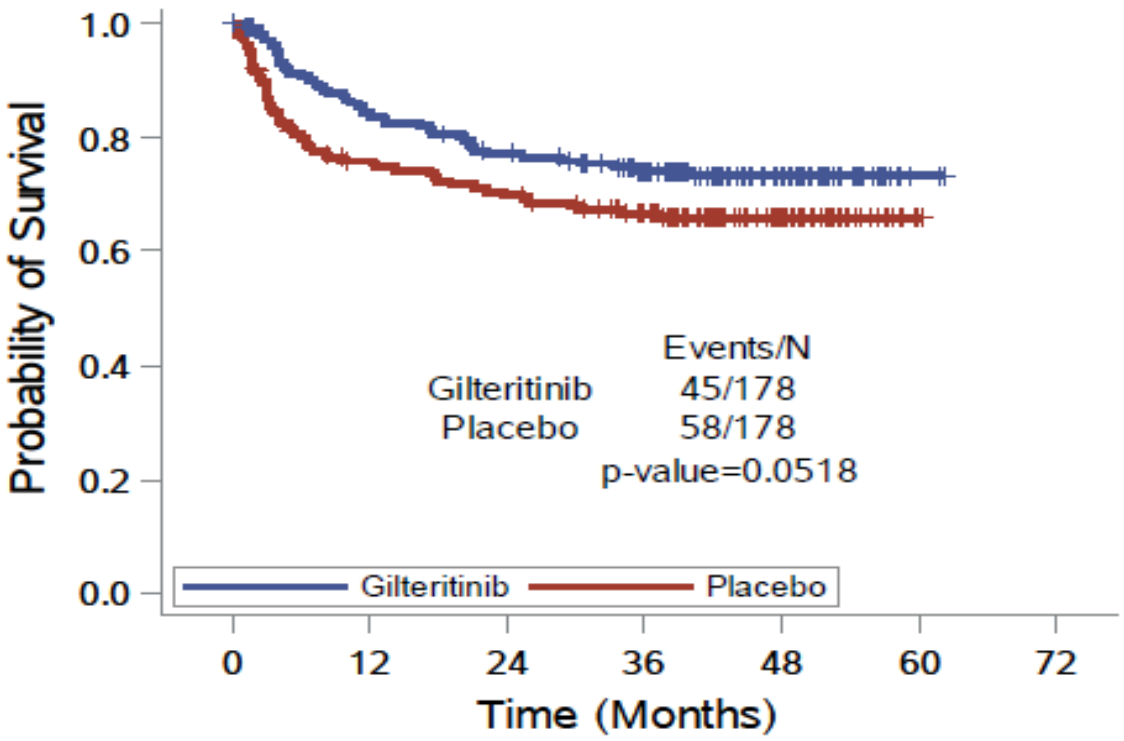
BMT CTN 1506: Efficacy of Gilteritinib in Post-Transplant AML



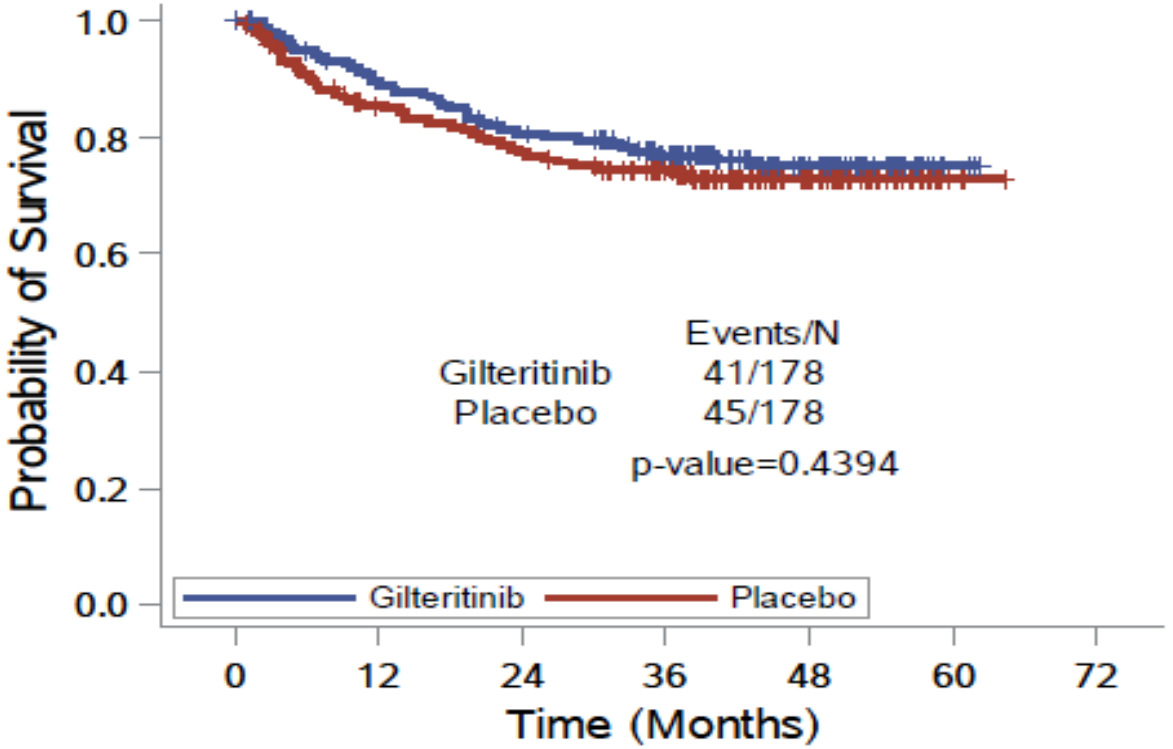
Levis M, et al. *Blood*. 2019;134:4602.

BMT-CTN 1506 (MORPHO): Efficacy Outcome

Primary objective:
Relapse-free survival
HR = 0.679 (0.459-1.005)
P = 0.0518



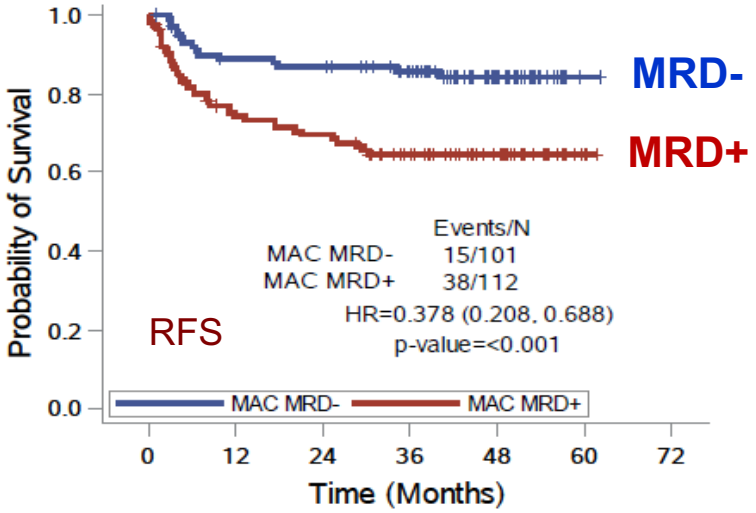
Key secondary objective:
Overall survival
HR = 0.846 (0.554-1.293)
P = 0.4394



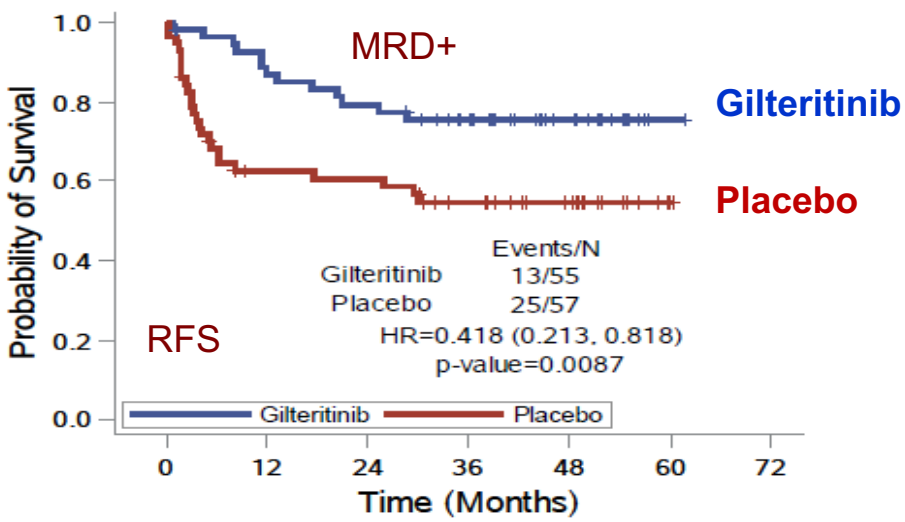
Myeloablative conditioning, MRD6, and Gilteritinib

MRD influences survival with myeloablative conditioning

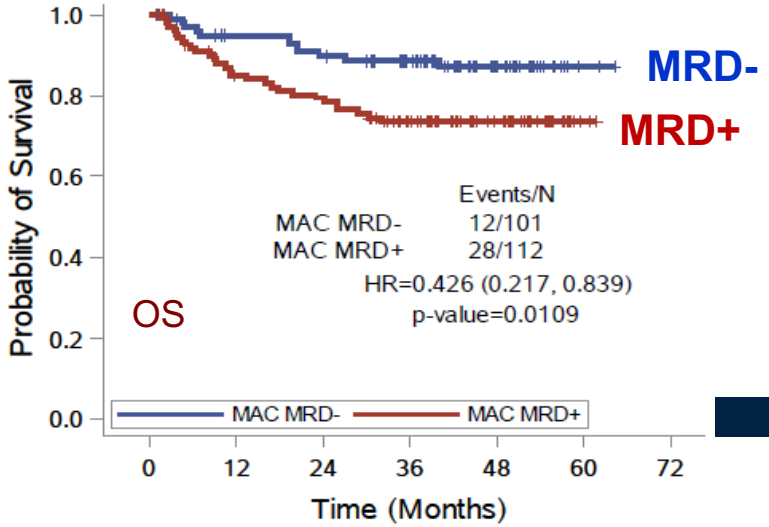
Myeloablative conditioning



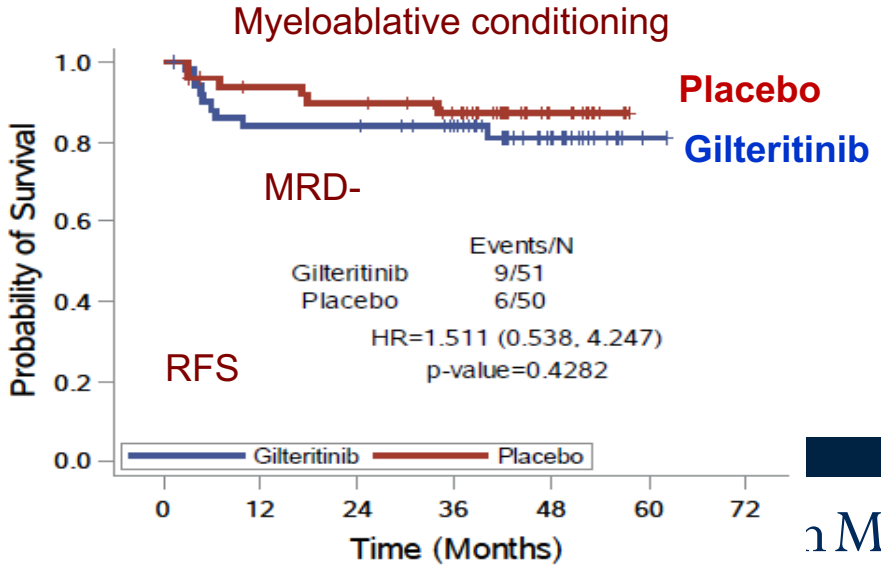
Myeloablative conditioning



Myeloablative conditioning



Myeloablative conditioning



Where will 2024 take us?

- Menin inhibitors
- Progress in *TP53* mutated AML?

KMT2Ar Acute Leukemia

- Many patients relapse after chemotherapy and/or HSCT[1]
- In adults, remission rates after relapse (CR, 5%) and median OS (2.4 months) after ≥2 salvage therapies remain low[1]
- Outcomes in infants/children after relapse remain poor

No approved targeted therapies for *KMT2Ar* disease

OS in Adult Patients With R/R *KMT2Ar* AML After ≥3rd-Line Therapy

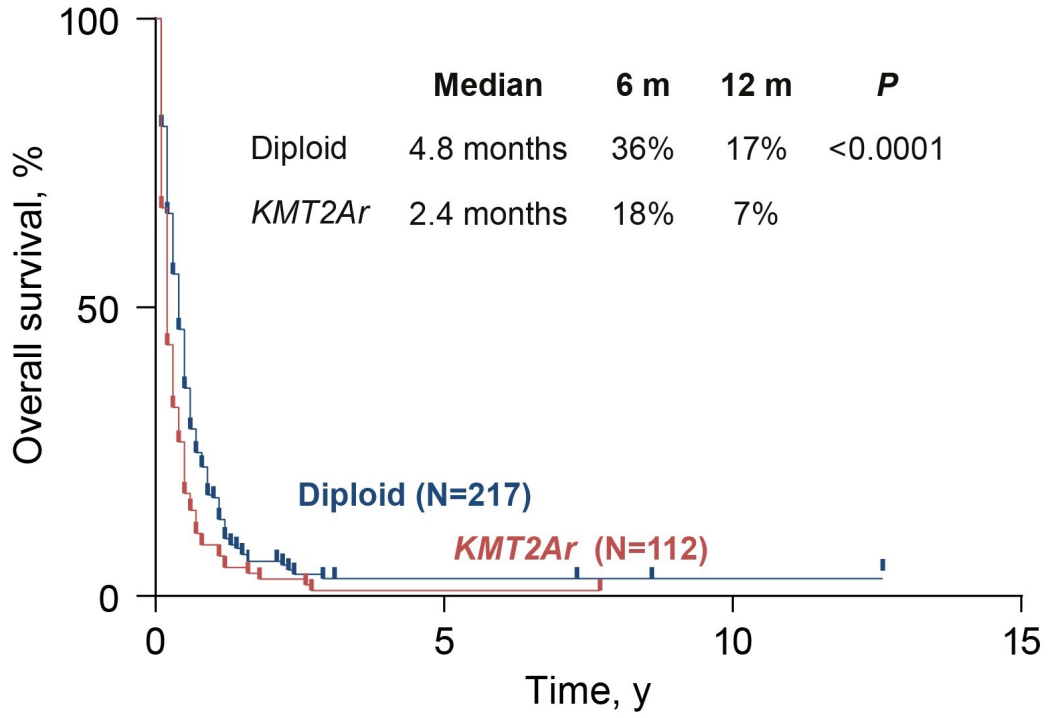


Figure reproduced from Issa GC, Zarka J, Sasaki K, et al. *Blood Cancer J*. 2021;11:162
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AML, acute myeloid leukemia; CR, complete remission; HSCT, hematopoietic stem cell transplant; *KMT2Ar*, histone-lysine N-methyltransferase 2A rearrangements; OS, overall survival; R/R, relapsed/refractory.

1. Issa GC, Zarka J, Sasaki K, et al. *Blood Cancer J*. 2021;11:162.

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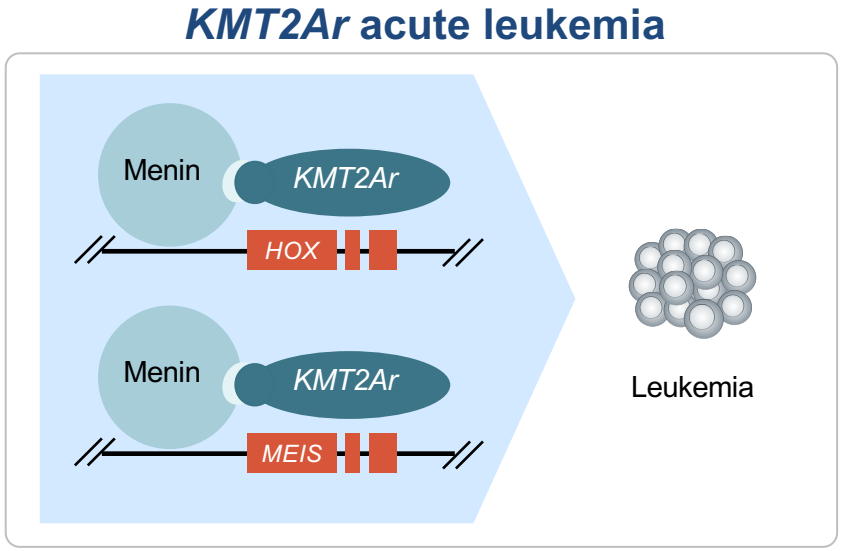
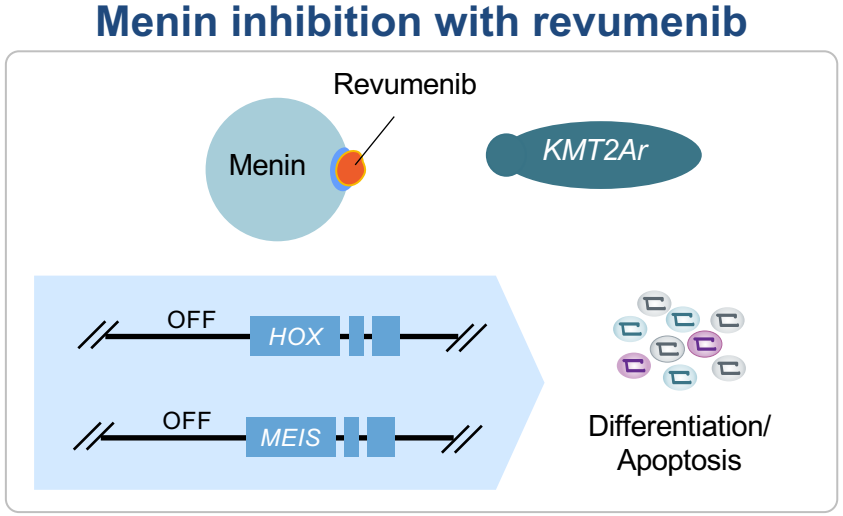
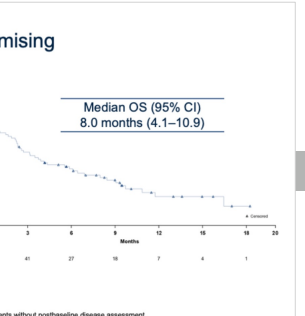
Revumenib

- The menin-KMT2A interaction is a key driver of leukemogenesis[1]
- In a phase 1 study of R/R *KMT2Ar* and *NPM1m* acute leukemias, revumenib demonstrated
  - Clinically meaningful responses that were consistent across subgroups[2]
  - High percentage (67%) of responders proceeding to transplant[2]
  - Manageable safety profile[2]







Aldoss et al. ASH 2023

HOX, homeobox; KMT2A, histone-lysine N-methyltransferase 2A; *KMT2Ar*, KMT2A rearrangements; *MEIS*, Meis homeobox; *NPM1m*, nucleophosmin 1–mutated; R/R, relapsed/refractory.

1. Issa GC, Zarka J, Sasaki K, et al. *Blood Cancer J*. 2021;11:162. **2.** Issa GC, Aldoss I, DiPersio J, et al. *Nature*. 2023;615:920-924.

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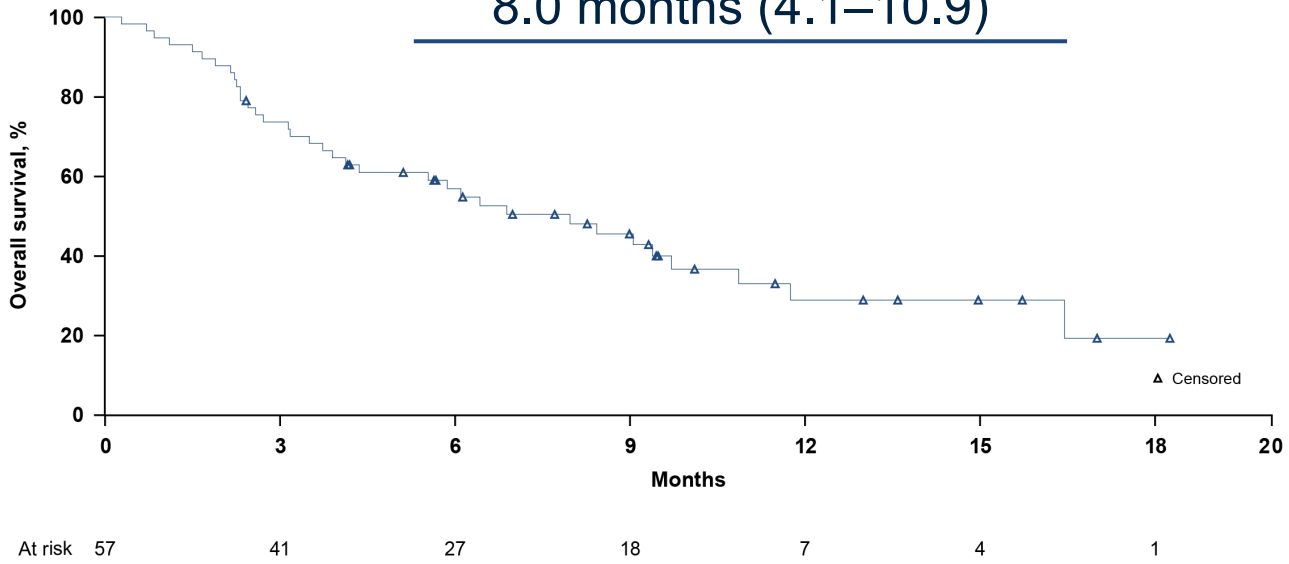
Response and Overall Survival Promising

Parameter	Efficacy population (n=57)
ORR, n (%)	**36 (63)**
CR+CRh rate, n (%)	13 (23)
95% CI	12.7–35.8
P value, 1-sided	0.0036
CRc	25 (44)
95% CI	30.7–57.6
Negative MRD status[a]	
CR+CRh	7/10 (70)
CRc	15/22 (68)

Median OS (95% CI)
8.0 months (4.1–10.9)

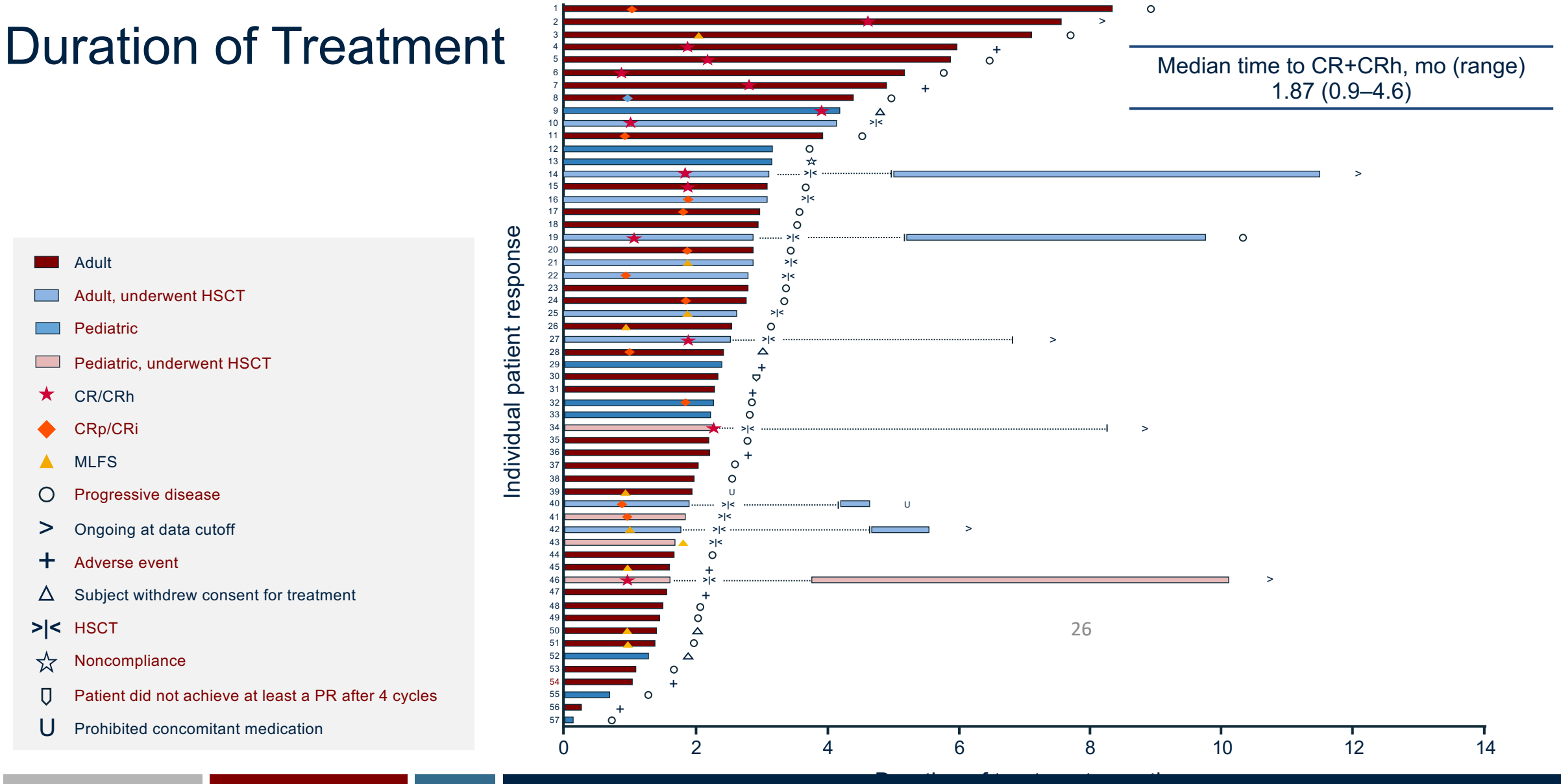


Data cutoff: July 24, 2023. [a]MRD done locally; not all patients had MRD status reported. [b]Includes patients without postbaseline disease assessment.

Aldoss et al. ASH 2023

CR, complete remission; CRc, composite CR (CR+CRh+CRp+CRi); CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphological leukemia-free state; MRD, minimal residual disease; ORR, overall response rate (CRc+MLFS+PR); PD, progressive disease; PR, partial remission.

Duration of Treatment



Aldoss et al. ASH 2023

CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphologic leukemia-free state; PR, partial remission.

Duration of Response

Parameter	Patients achieving CR+CRh (n=13)
Median duration of CR+CRh, months (95% CI)	6.4 (3.4–NR)
Proceeded to HSCT, n (%)	14/36 (39)
Proceeded to HSCT in CR or CRh	6/14 (43)
Proceeded to HSCT in MLFS or CRp	8/14 (57)
Restarted revumenib post HSCT, n (%)	7/14 (50)*

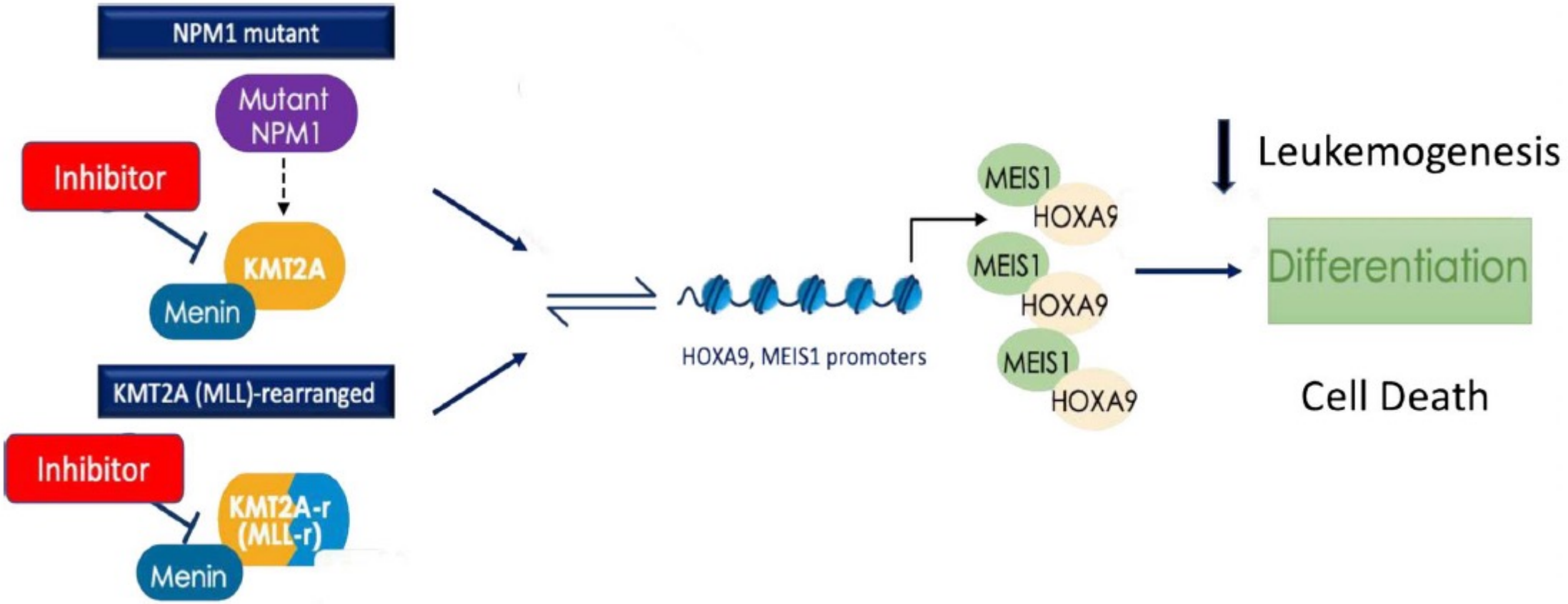
Data cutoff: July 24, 2023

*3 additional patients remained eligible to initiate revumenib after HSCT at the time of data cutoff.

Aldoss et al. ASH 2023

CR, complete remission; CRh, CR with partial hematologic recovery; CRp, CR with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; MLFS, morphological leukemia-free state; NR, not reached.

Menin Inhibitors also used in NPM1 mutated AML

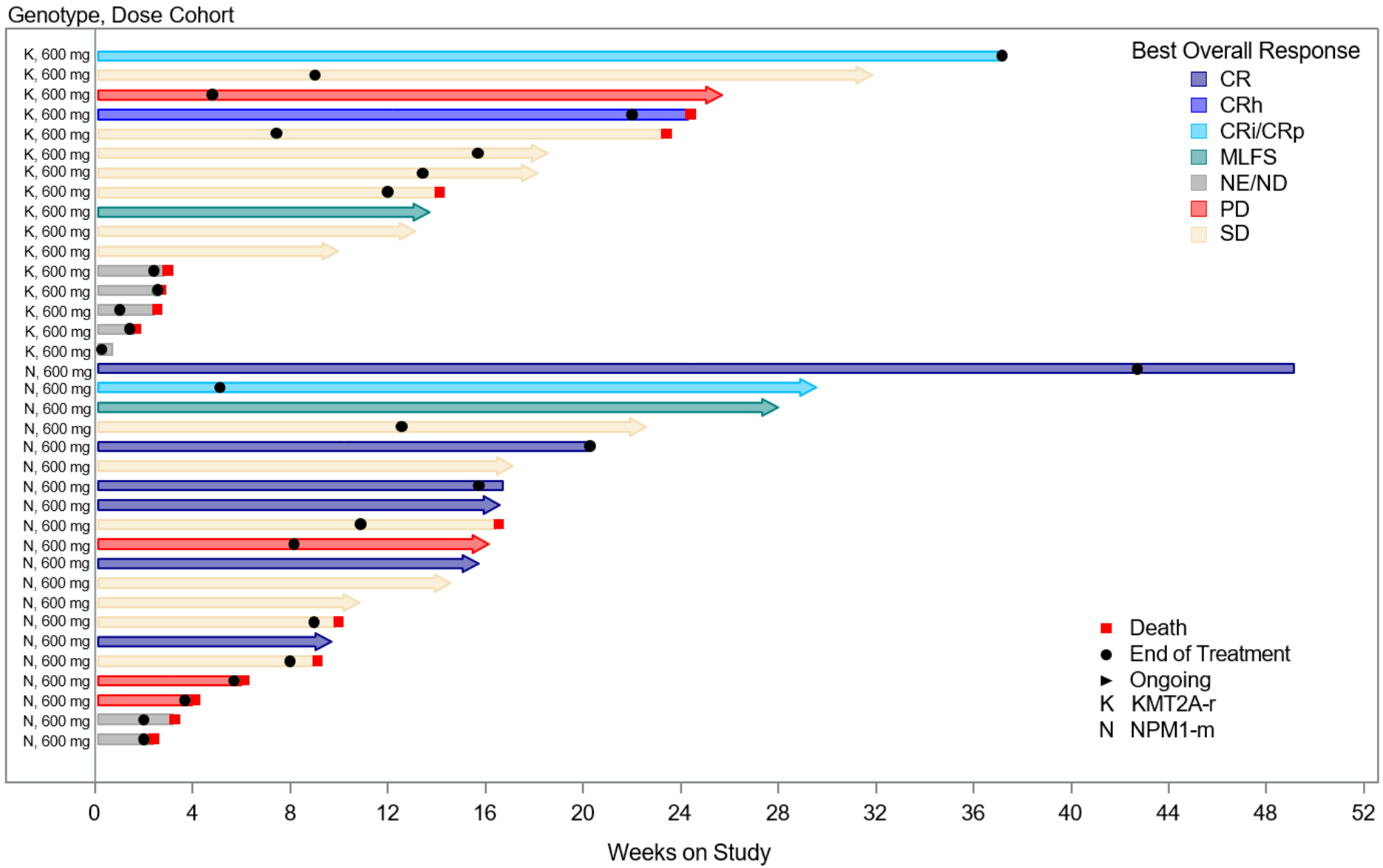


Swaminathan et al. The Cancer Journal 2022

Ziftomenib (KO-539) in Patients with R/R AML

KMT2A-r

NPM1-m



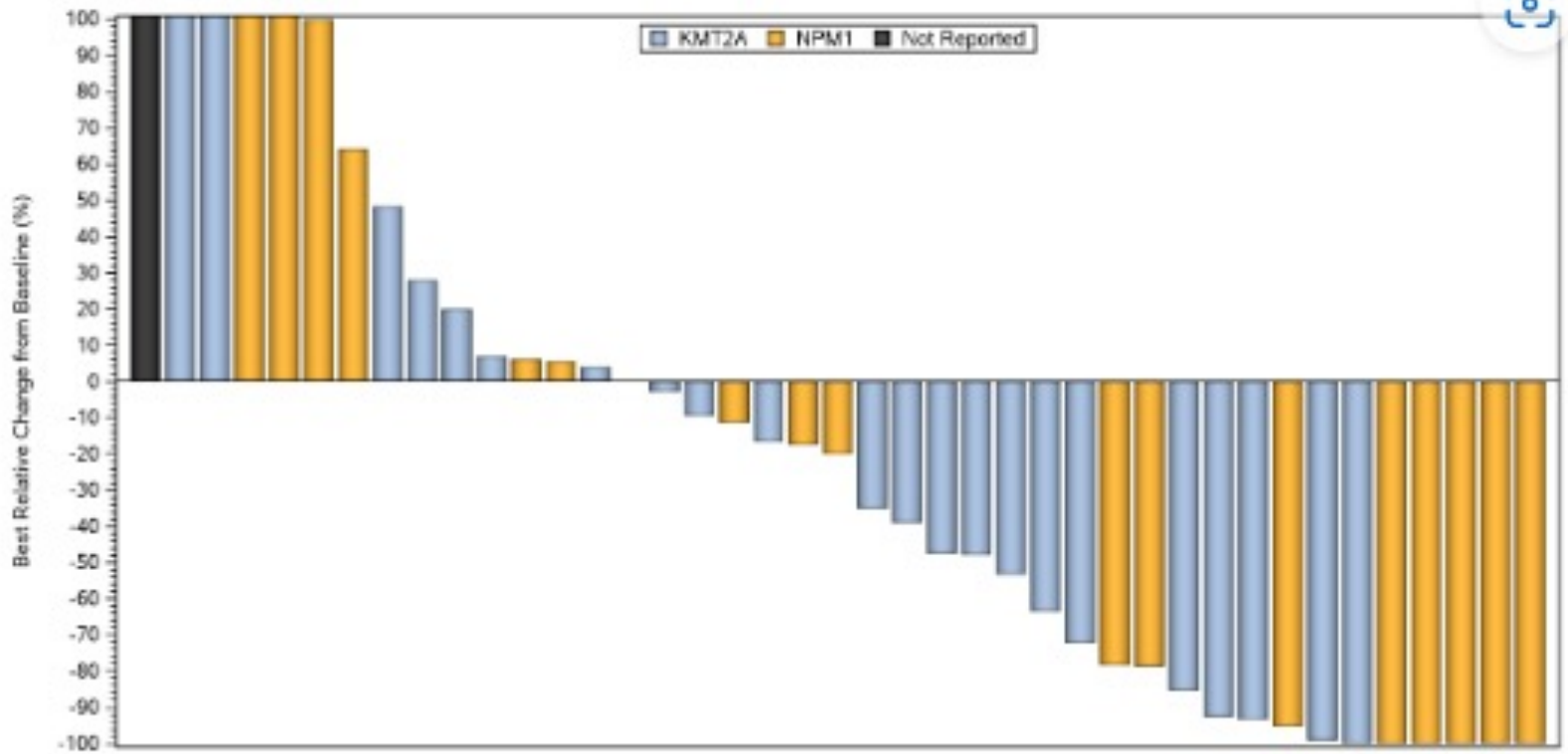
Erba et al. ASH 2022

24-Oct-2022 Data Cut

Penn Medicine

JNJ-75276617 in Adult Patients with Relapsed/Refractory Acute Leukemia Harboring *KMT2A* or *NPM1* Alterations

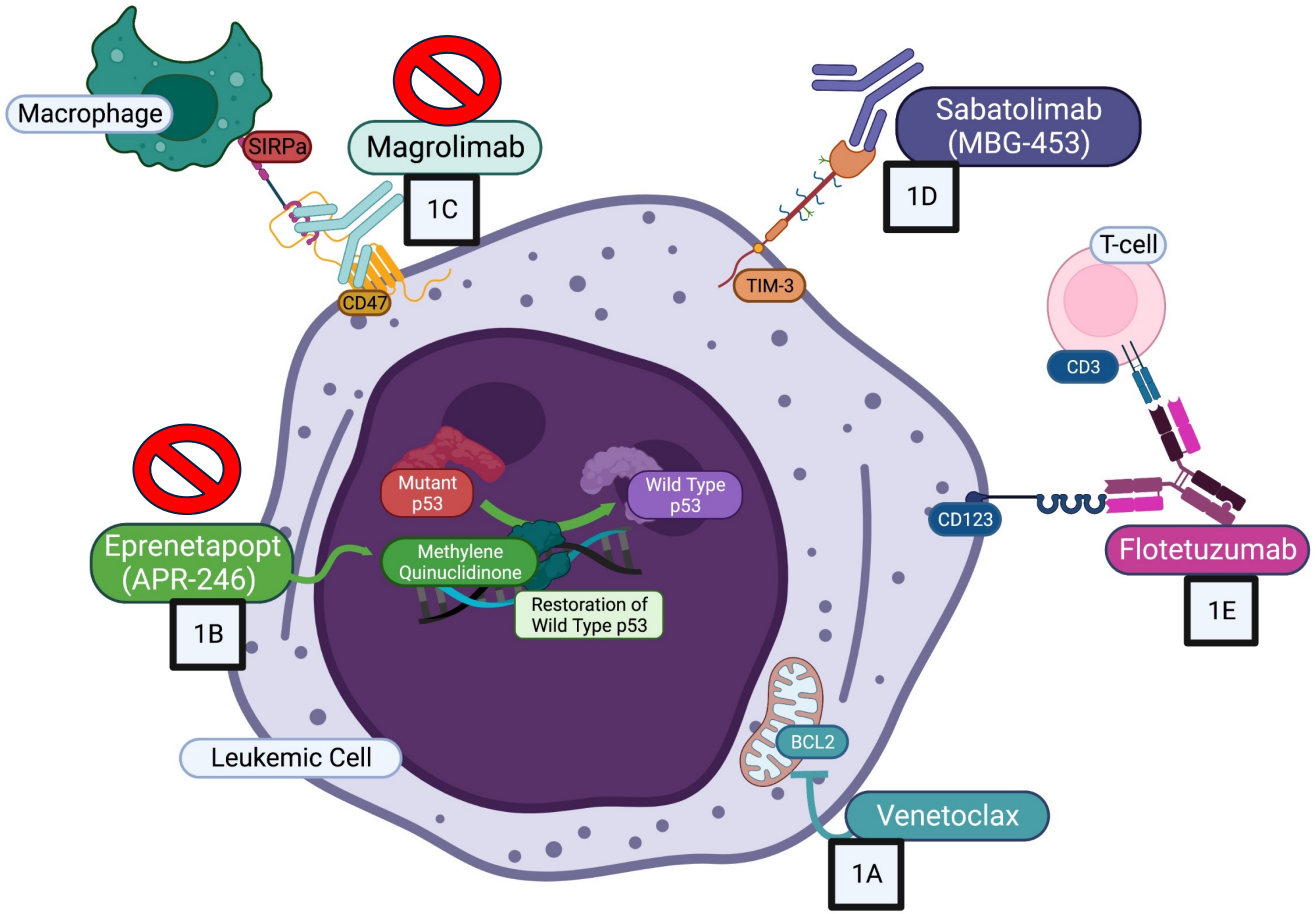
Figure 1. Best Percent Change from Baseline in Bone Marrow Blasts With JNJ-75276617 Monotherapy in R/R Acute Leukemia



Note: Bars are only presented for participants where a measurable change from baseline is found in the data (n=41; 23 *KMT2A*-altered, 17 *NPM1*-altered, 1 Not Reported).
Note: Each bar represents a unique study participant.
Note: One participant did not have *NPM1* or *KMT2A* mutation reported as of data-cut.
Note: Five participants had best relative change from baseline of >100%.

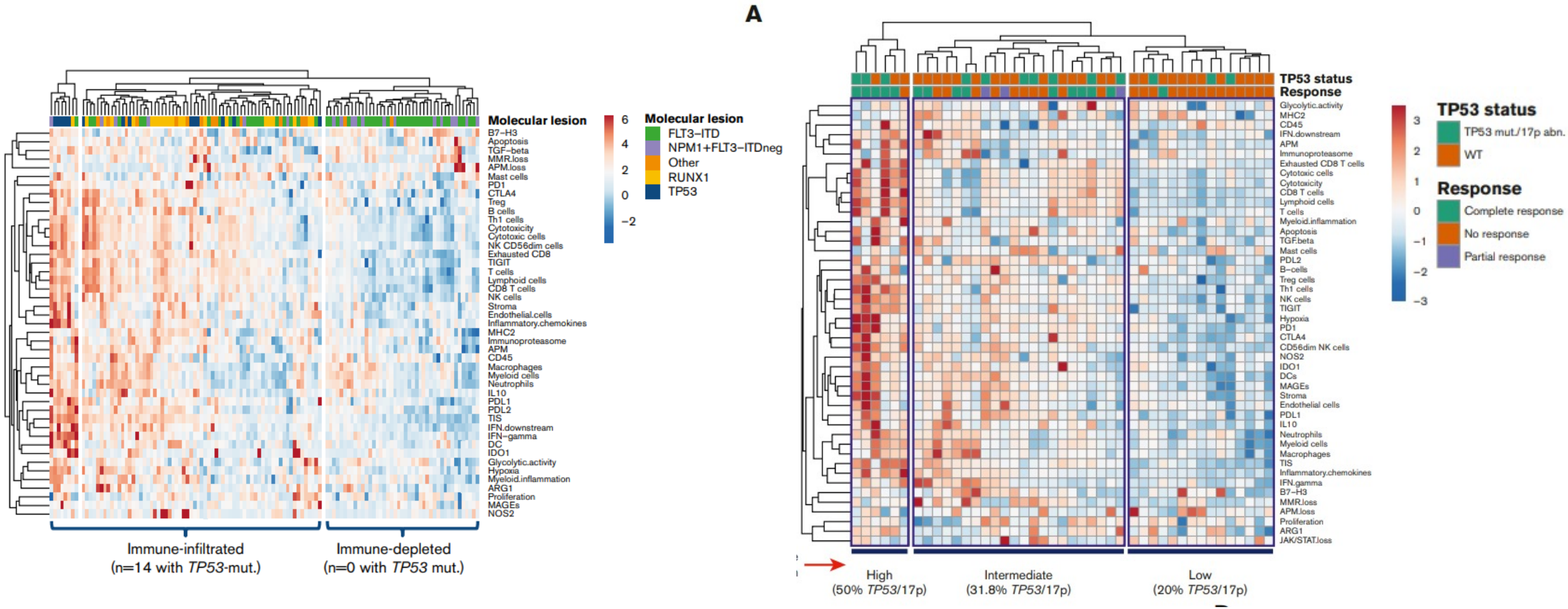
Jabbour et al. ASH 2023

TP53 Remains the Most Challenging to Treat



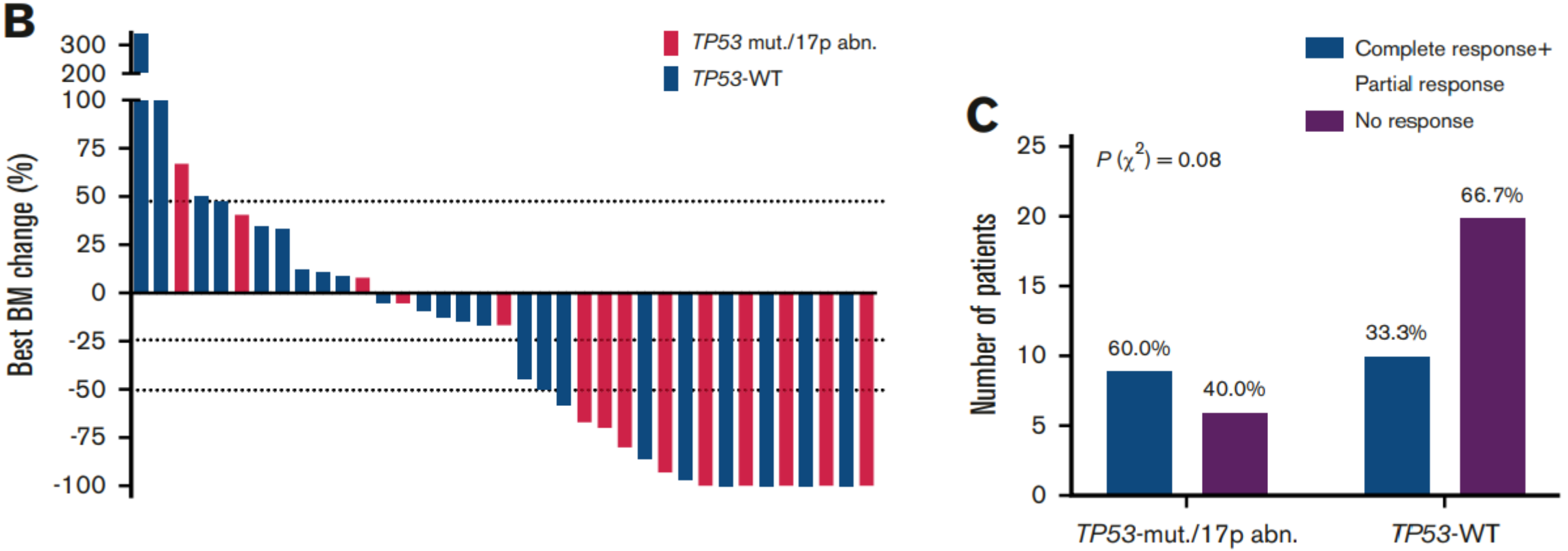
Marks, Lai et al. unpublished

TP53 Mutations Correlate with an Immune-infiltrated Tumor Microenvironment and Response to Flotetuzumab



Vadakekolathu J, Lai C et al. Blood Adv, 2020

Response to Flotetuzumab in Patients with *TP53* Mutations and/or 17p deletion



Vadakekolathu J, Lai C et al. Blood Adv, 2020

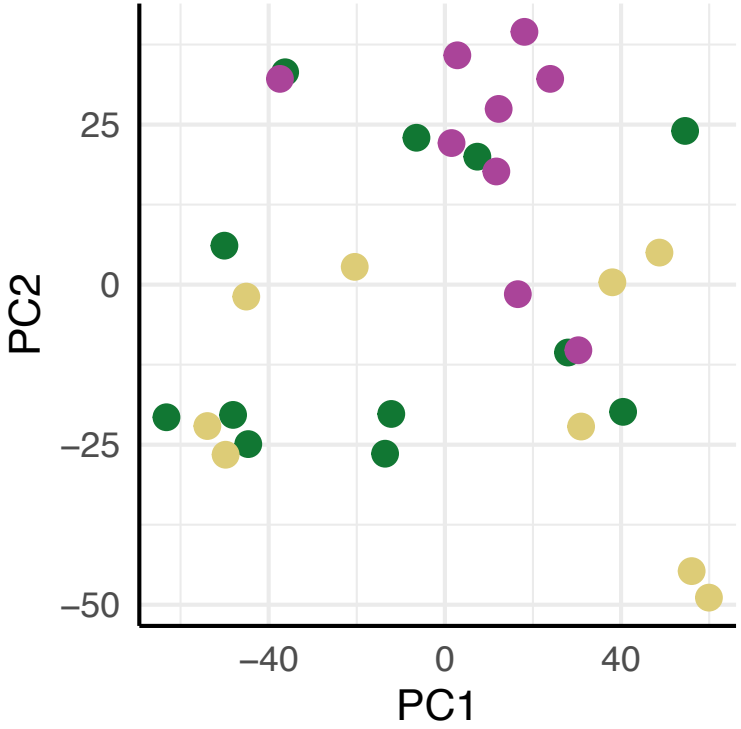
Magrolimab (Anti CD-47) + Azacitidine Initially Promising

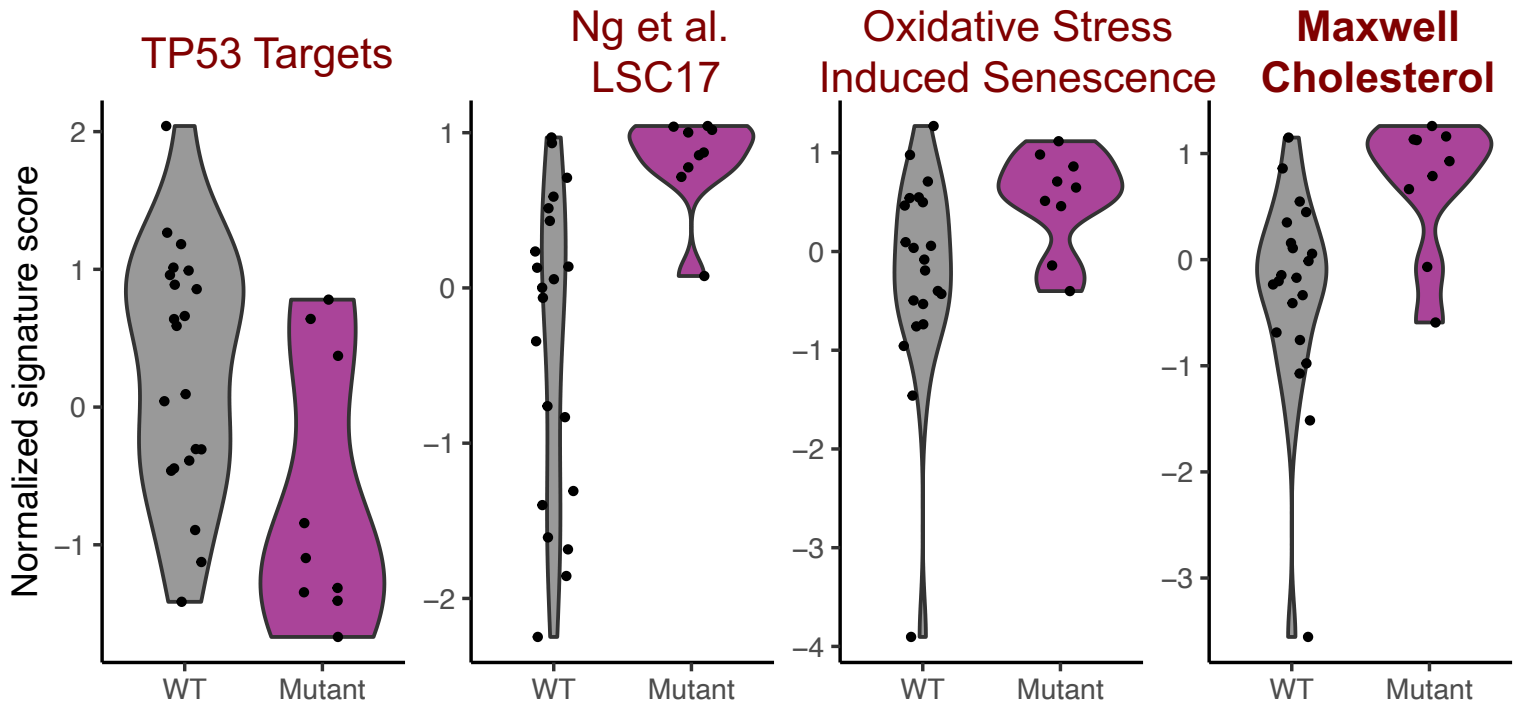
Outcome	All (N = 95[a])	*TP53*-wt MDS (N = 61)	*TP53*-mut MDS (N = 25)
OR rate, %[b]	74.7	78.7	68.0
CR, % (95% CI)	32.6 (23.4 to 43.0)	31.1 (19.9 to 44.3)	40.0 (21.1 to 61.3)
mCR, %	31.6	37.7	20.0
PR, %	0	0	0
SD with HI, %	10.5	9.8	8.0
Duration of CR, months, median (95% CI)	11.1 (7.6 to 13.4)	12.9 (8.0 to NR)	7.6 (3.1 to 13.4)
Time to CR, months, median (range)	3.7 (1.7-7.2)	4.6 (1.7-7.2)	3.1 (1.9-4.0)
Duration of OR, months, median (95% CI)	9.8 (8.8 to 12.9)	9.8 (8.5 to 18.5)	9.2 (5.0 to 12.2)
Time to OR, months, median (range)	1.9 (0.7-10.9)	1.9 (0.7-5.5)	1.9 (1.8-10.3)
mCR with HI/Any HI, %	16.8/58.9	19.7/60.7	12.0/56.0
Converted to RBC transfusion independence, %[c]	35.1	26.1	46.2
PFS, months, median (95% CI)	11.6 (9.0 to 14.0)	11.8 (8.8 to 16.6)	11.0 (6.3 to 12.8)
OS, months, median (95% CI)	NR (16.3 to NR)	NR (21.3 to NR)	16.3 (10.8 to NR)

Abbreviations: CR, complete remission; HI, hematologic improvement; mCR, marrow CR; MDS, myelodysplastic syndrome; mut, mutation; NR, not reached; OR, objective response; OS, overall survival; PFS, progression-free survival; PR, partial remission; SD, stable disease; wt, wild-type.

What other pathways can be explored?

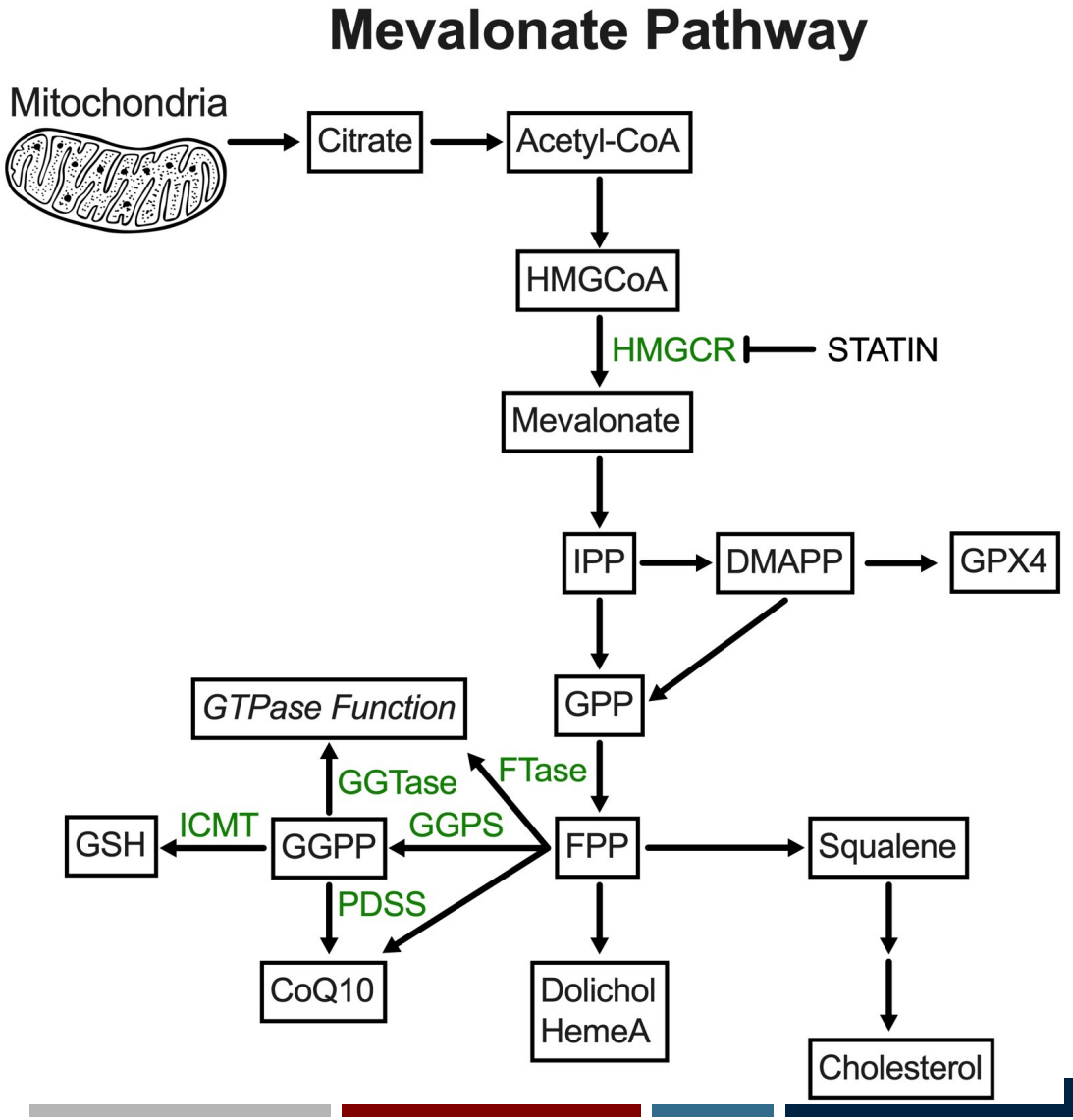
Primary *TP53* mutant AML RNA sequencing





- Primary *TP53* mutant AML has upregulation of cholesterol biosynthesis genes.
- Validated in a Beat AML cohort (Tyner et al. *Nature* 2018) of newly diagnosed *TP53* mutant vs wildtype AML patients.

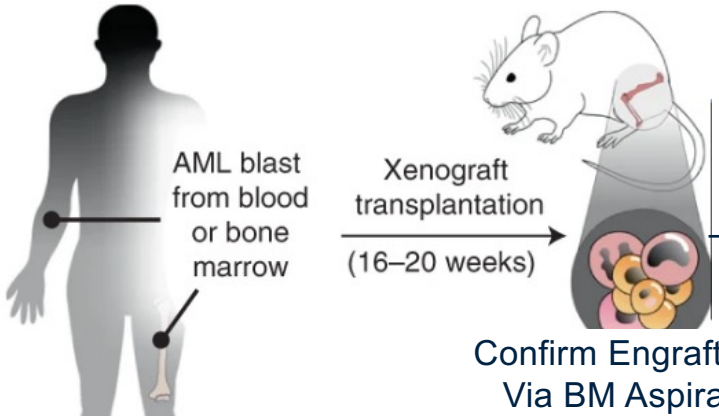
Mevalonate pathway: a specific target in *TP53* mutant AML



- *TP53* mutations in solid tumor models lead to upregulation AND dependency on the mevalonate pathway
  - *Freed-Paster et al. Cell 2023, Moon et al. Cell 2019, Oni et al. JEM 2020, Kaymak et al. Cancer Research 2020*
- Multiple byproducts are required for mitochondrial metabolism, which plays a crucial role in AML chemoresistance.
  - *Farge et al. Cancer Discovery 2017, Jones et al. Cancer Cell 2018, Liyanage et al. Blood 2017*

We hypothesized that the mevalonate pathway controls mitochondrial-mediated chemoresistance in *TP53* mutant AML.

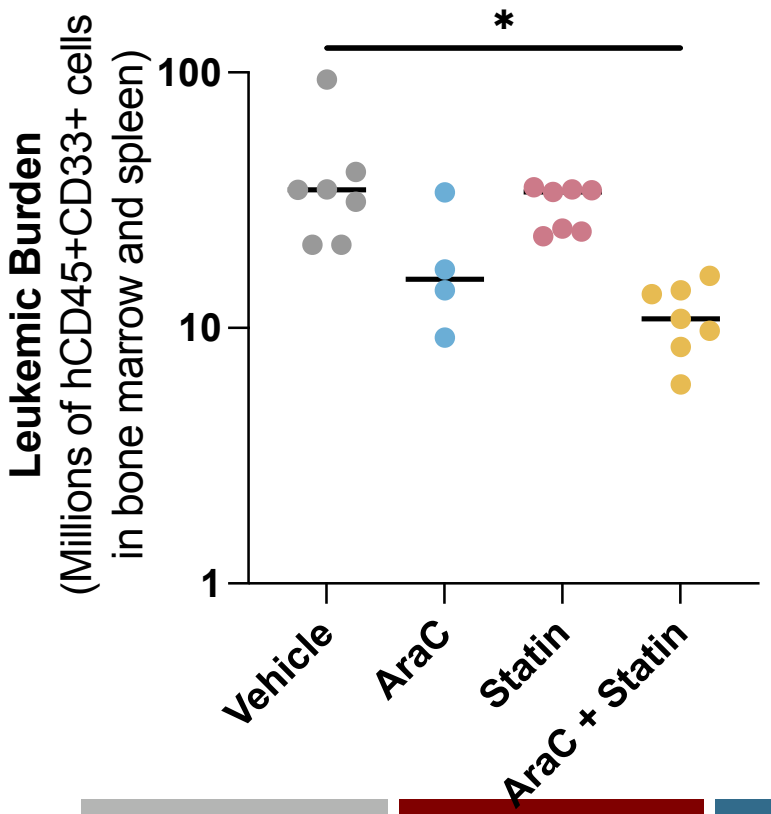
Statins sensitize a PDX Model of *TP53* mutant AML to AraC

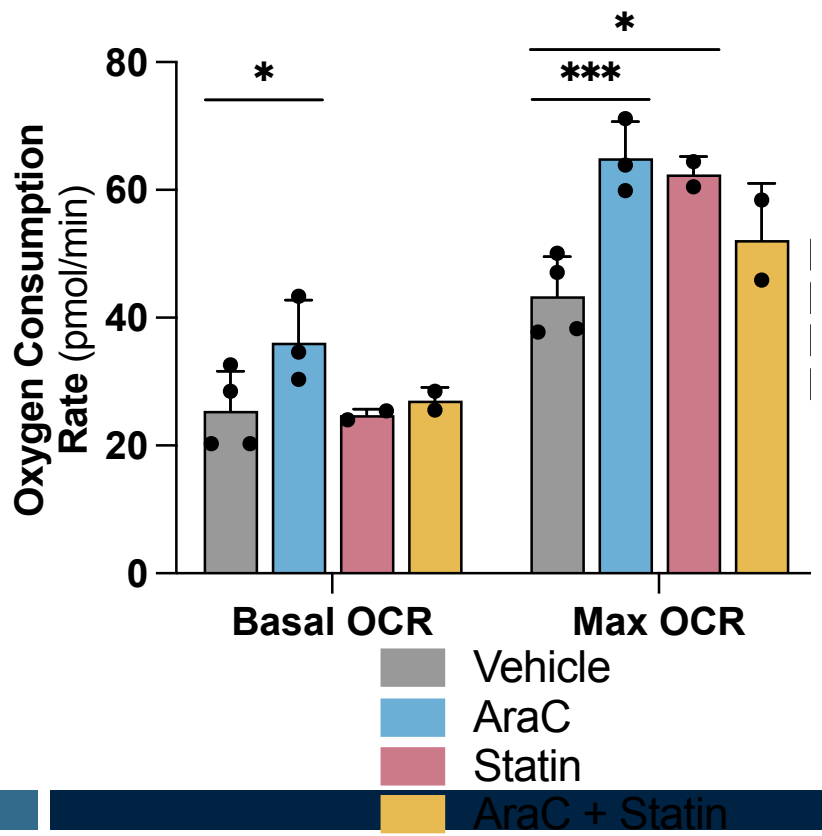


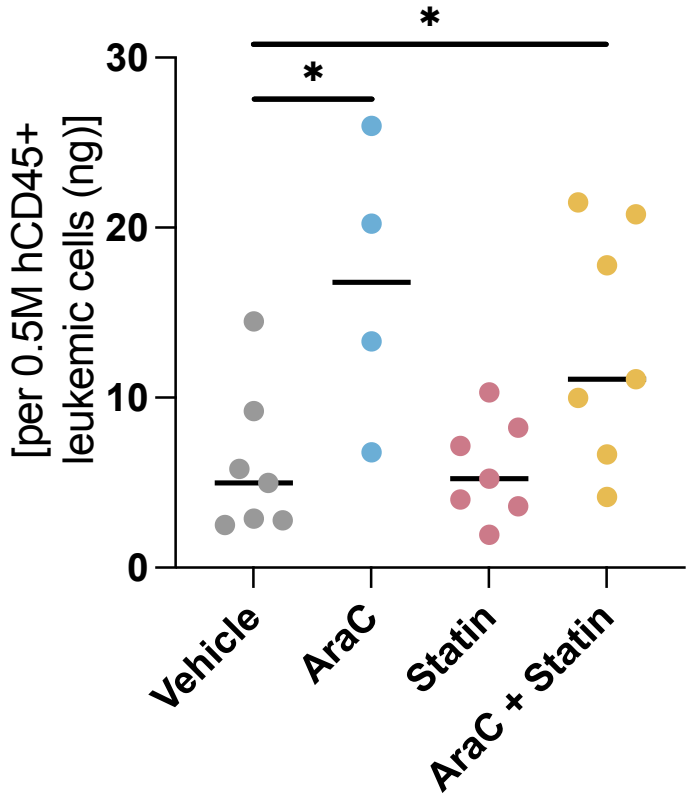
4 Treatment Groups:

- Vehicle
- AraC (50mg/kg/d) I.P.
- Rosuvastatin (1mg/kg/d) P.O.
- AraC + Rosuvastatin

D1 D5 D7 D8



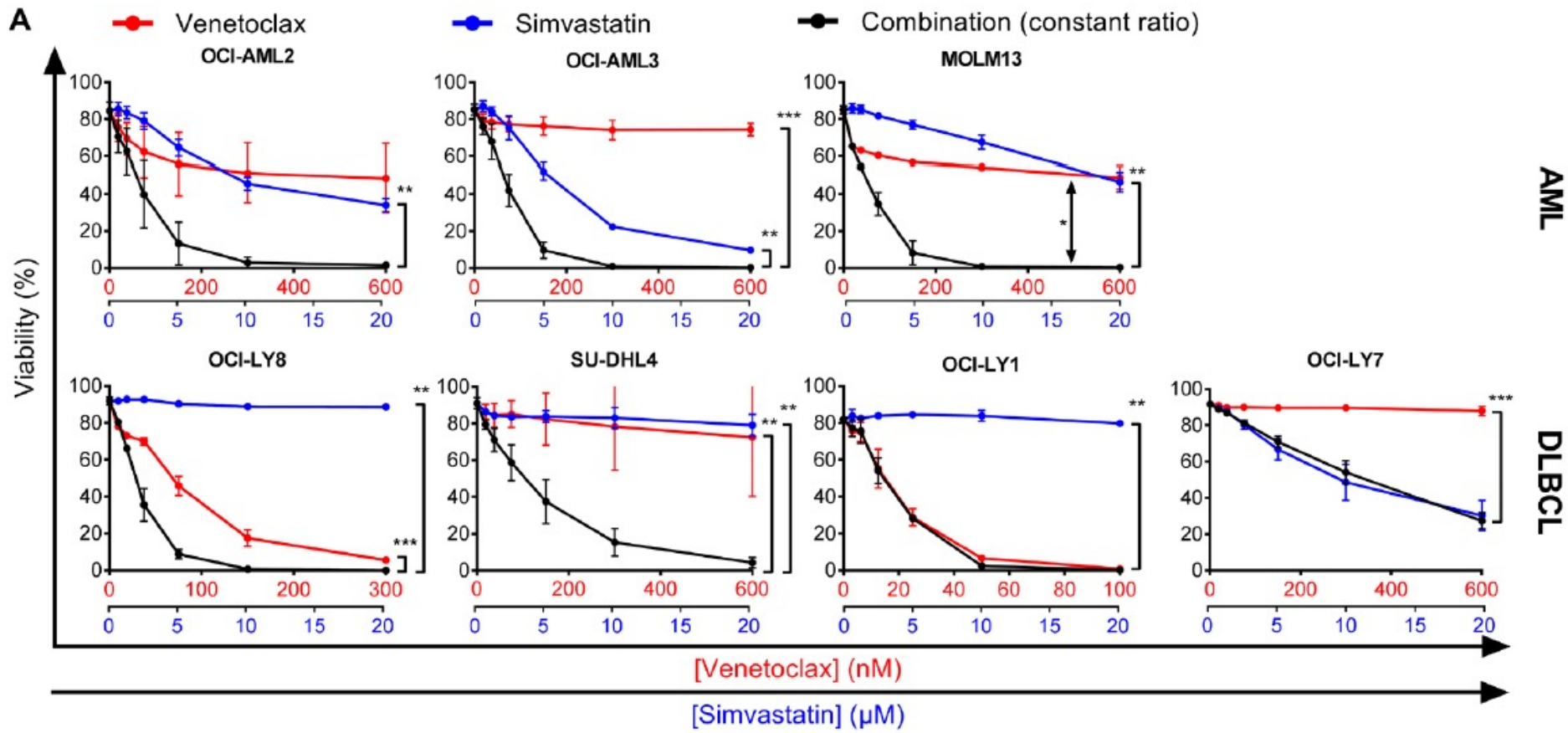




UPenn SCXC, Clementina Mesaros; Figure adapted from Bosc et al. *Nature Cancer* 2021

Penn Medicine

Statins Selectively Enhance Efficacy of Venetoclax Against Blood Cancers



Lee et al. Science Translational Medicine 2018

Up and coming…

- Multi-center Investigator Initiated Study
  - University of California Hospitals
  - University of Pennsylvania
- Newly diagnosed *TP53* mutated high risk MDS and AML
- Treatment:
  - Azacitidine + venetoclax + pitavastatin

Conclusions

- AML treatment landscape has improved and has become more complicated
- New FDA approved drugs in the last year are olutasidenib for IDH1 mutated AML and quizartinib for FLT3 mutated AML
- Menin inhibitors are effective in NPM1 mutated and KMT2Ar AML and may have an FDA approval later this year
- *TP53* mutated patients have poor outcomes and better therapies are needed

Take home message

Normal bone marrow

Bone marrow with AML

- Know the types of flowers in your garden = What molecular abnormalities are present? What mutations are driving the disease burden?
- Understand the optimal conditions for growth = Modify how we approach standard therapy in older AML
- Use the appropriate weed killer = Tailor treatment to individual genetic profiles and physiologic function to change survival outcomes

Questions?

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Thank you!