An Update for Acute Myeloid Leukemia in 2021

David A. Sallman, MD
Department of Malignant Hematology
Myeloid Section Lead
Moffitt Cancer Center
david.sallman@moffitt.org

MOFFITT CANCER CENTER

7+3 is No Longer Standard

Table 5. 2017 ELN risk stratification by genetics

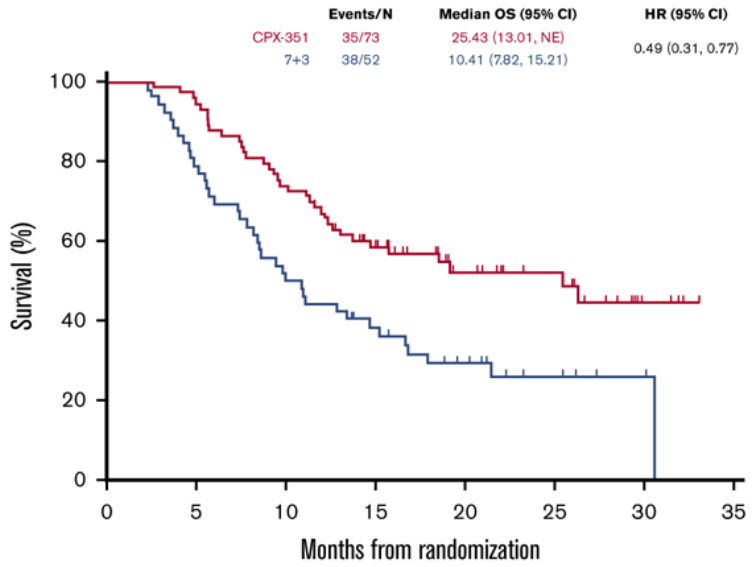
Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Maybe? →

Long Term Outcomes of CPX-351 vs 7+3

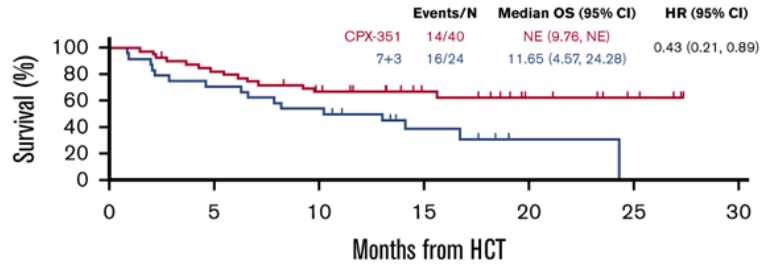
Older adults with newly diagnosed high-risk/secondary AML who achieved remission with CPX-351 versus 7+3: *post hoc* analyses of outcomes from a phase 3 study

Overall survival benefit in patients who achieved CR or CRi with CPX-351 versus 7+3 regimen



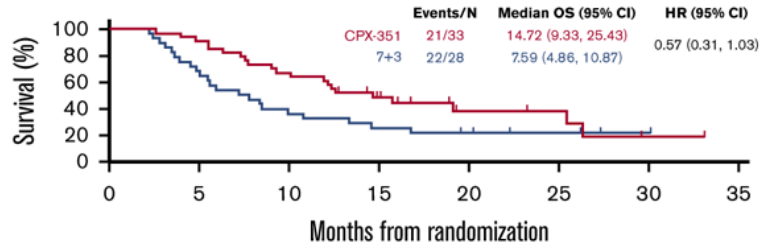
Proceeded to transplant

Landmarked survival benefit in patients who achieved CR or CRi with CPX-351 versus 7+3 regimen



Did not proceed to transplant

Overall survival benefit in patients who achieved CR or CRi with CPX-351 versus 7+3 regimen



Conclusion:

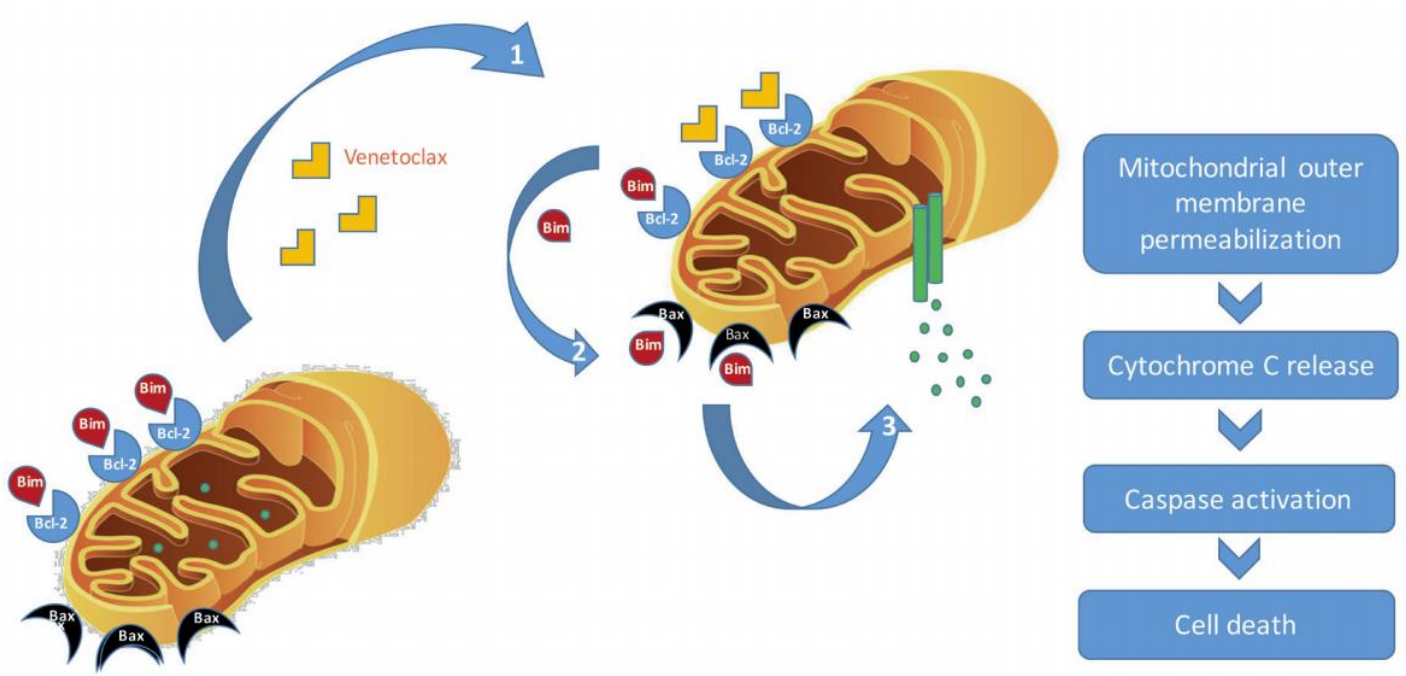
Survival was longer for patients who achieved remission (CR or CRi) with CPX-351 versus conventional 7+3 chemotherapy

7+3 CR+CRi ≠ CPX-351 CR+CRi

Lancet J et al., *Blood Advances* 2021

MOFFITT CANCER CENTER

BCL-2 Inhibitor: Venetoclax

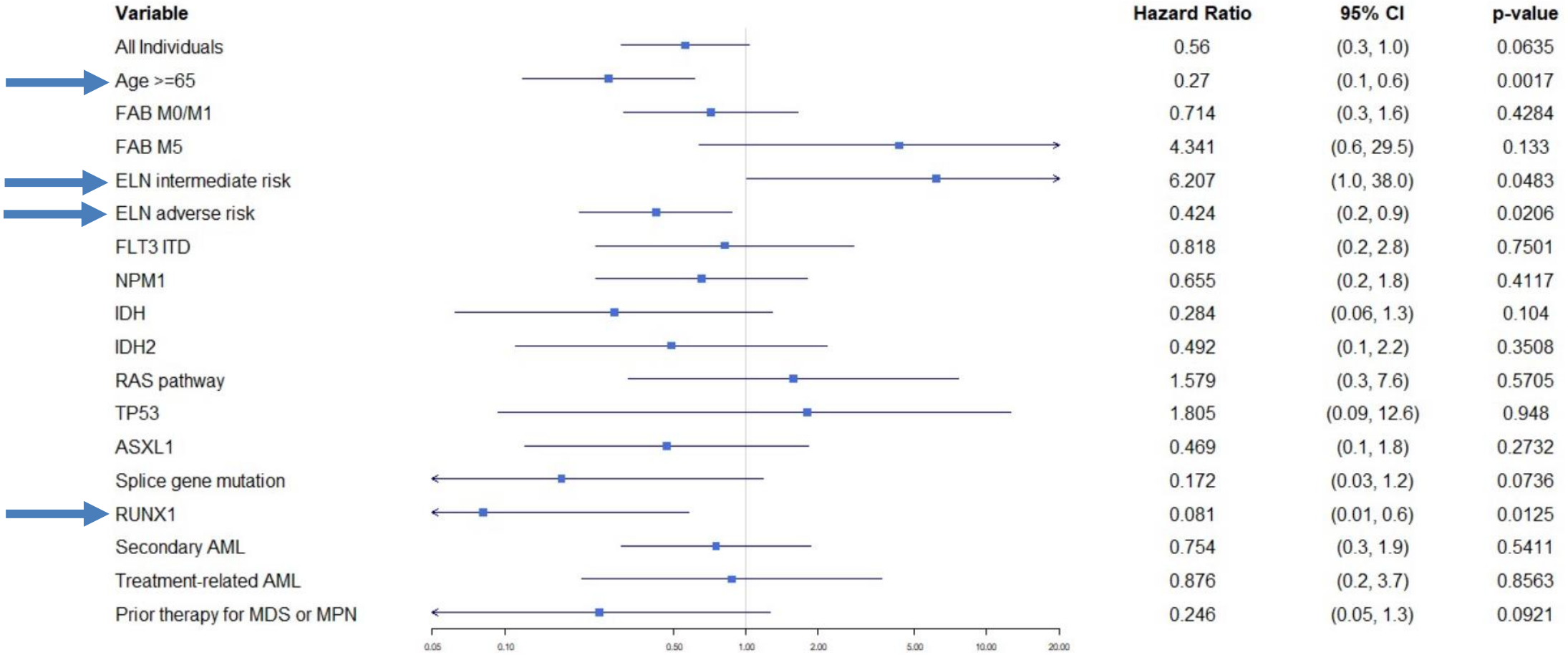


- BCL-2 stabilizes mitochondria, preventing activation of proapoptotic proteins[1]
- Inhibition of BCL-2 enables apoptosis
- BCL-2 expression is elevated in high-risk MDS and AML (~80%) and balance tips for pro-survival in AML

Sharma P, Pollyea DA. *Curr Hematol Malig Rep*. 2018;13:256-264. 2. Janssens A. *Belg J Hematol*. 2017;8:265-271.

MOFFITT CANCER CENTER

Venetoclax + Azacitidine Versus 7+3: Factors that Predict Survival



Variable	Hazard Ratio	95% CI	p-value
All Individuals	0.56	(0.3, 1.0)	0.0635
Age >=65	0.27	(0.1, 0.6)	0.0017
FAB M0/M1	0.714	(0.3, 1.6)	0.4284
FAB M5	4.341	(0.6, 29.5)	0.133
ELN intermediate risk	6.207	(1.0, 38.0)	0.0483
ELN adverse risk	0.424	(0.2, 0.9)	0.0206
FLT3 ITD	0.818	(0.2, 2.8)	0.7501
NPM1	0.655	(0.2, 1.8)	0.4117
IDH	0.284	(0.06, 1.3)	0.104
IDH2	0.492	(0.1, 2.2)	0.3508
RAS pathway	1.579	(0.3, 7.6)	0.5705
TP53	1.805	(0.09, 12.6)	0.948
ASXL1	0.469	(0.1, 1.8)	0.2732
Splice gene mutation	0.172	(0.03, 1.2)	0.0736
RUNX1	0.081	(0.01, 0.6)	0.0125
Secondary AML	0.754	(0.3, 1.9)	0.5411
Treatment-related AML	0.876	(0.2, 3.7)	0.8563
Prior therapy for MDS or MPN	0.246	(0.05, 1.3)	0.0921

Cherry et al., Blood Advances; Courtesy of Pollyea D

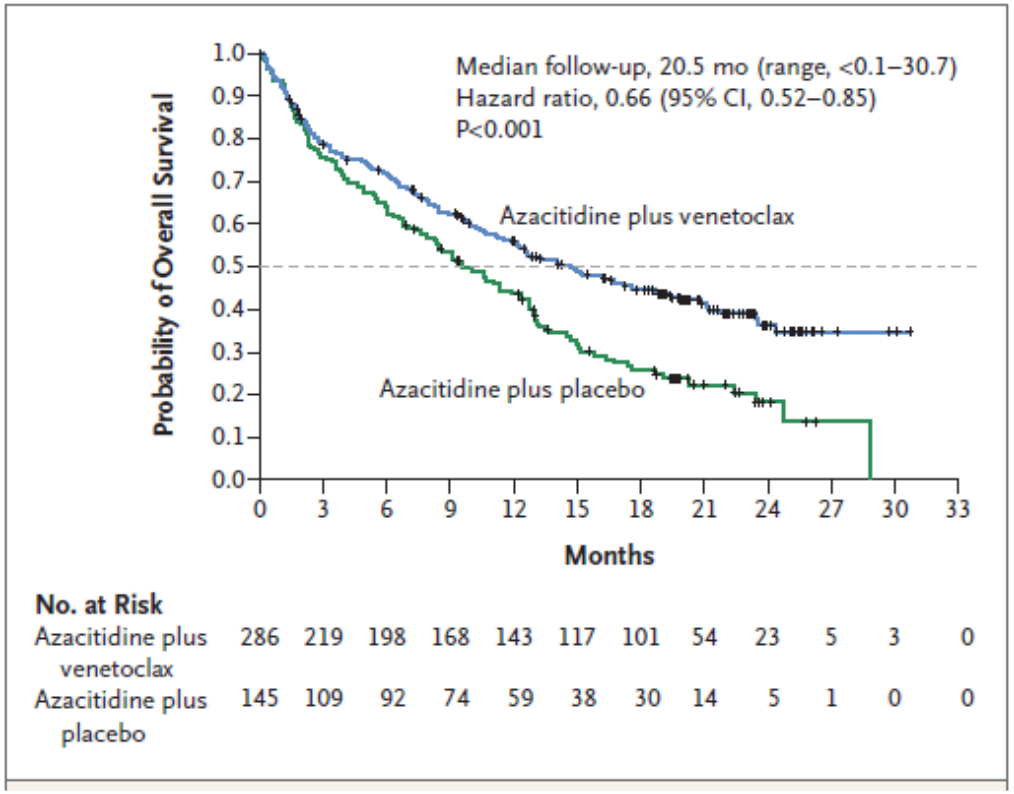
Intensive Chemotherapy + Venetoclax

	Venetoclax and Cladribine+Idarubicin+ Cytarabine	Venetoclax and Fludarabine+Cytarabine+ Idarubicin
N	41	29
Overall Response Rate	95%	97%
Complete Response Rate	85%	69%

Kadia et al., Lancet Hematology 2021; Dinardo et al., JCO 2021

MOFFITT CANCER CENTER

Phase 3 azacitidine + venetoclax

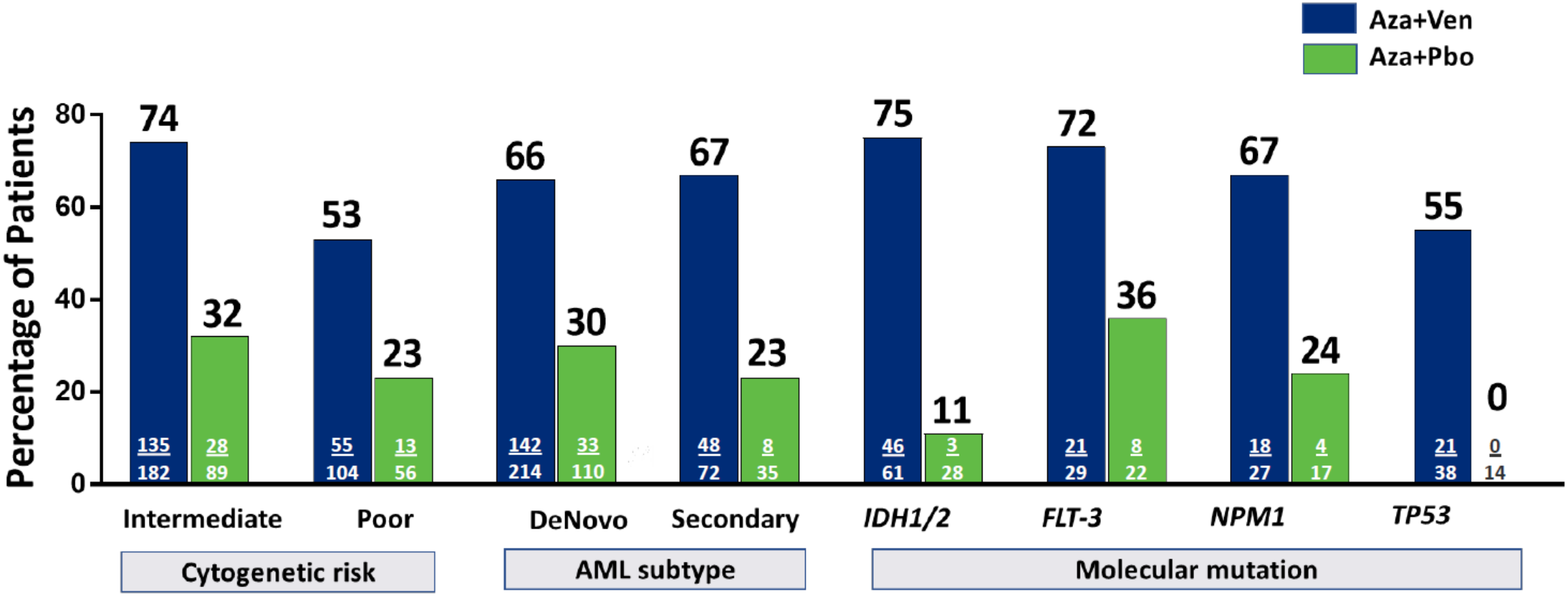


Molecular marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)	0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16–0.71)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)	0.34 (0.20–0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36–1.51)

Dinardo C et al., NEJM 2020

FITT CANCER CENTER

VIALE-A Study of Venetoclax + Azacitidine vs Azacitidine by Subset



Dinardo C et al., EHA 2020

MOFFITT CANCER CENTER

Toxicity Concerns of HMA + Ven

- Nearly all pts with G4 cytopenias
- Mitigation Strategies
  - D21 Bm
  - Holding therapy post BM blast clearance
  - ? GCSF Support
  - Schedule decrease with venetoclax (and consideration of HMA dose reduction)

Dinardo C et al., NEJM 2020

MOFFITT CANCER CENTER

Potential Predictors of Poor Response

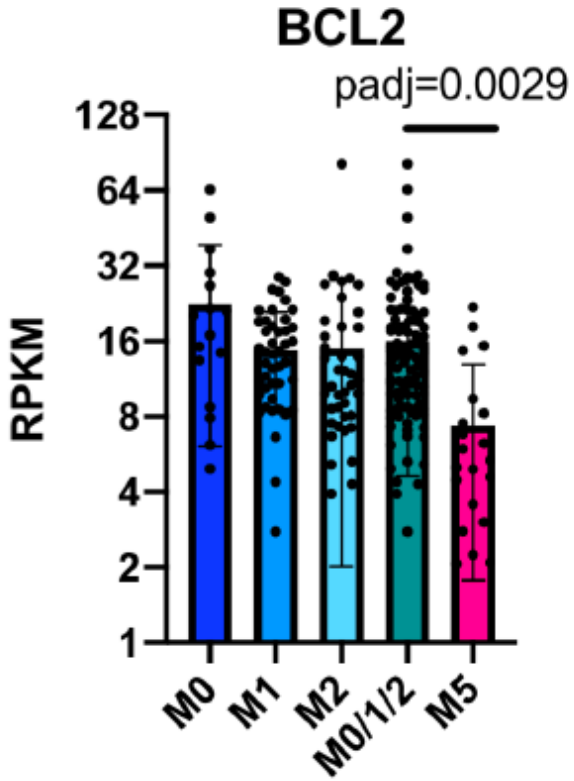
Baseline Variables	Univariate OR	P-value	Multivariate OR	P-value
Age	0.98 (0.95-1.02)	0.40		
Antecedent Hematologic Dz	0.57 (0.12-2.77)	0.48		
Complex Cytogenetics	2.67 (0.86-8.24)	0.09		
ELN Risk Group	4.08 (0.50-33.64)	0.07		
RAS Pathway	6.42 (1.81-22.71)	0.004	2.27 (0.20-25.52)	0.51
TP53	1.48 (0.28-7.77)	0.64		
NPM1	0.162 (0.02-1.30)	0.09	0.49 (0.034-7.0)	0.60
FLT3	0.66 (0.14-3.27)	0.61		
FAB M0/M1	0.13 (0.04-0.43)	0.0008		
FAB M5	18.30 (4.70-71.13)	<0.0001	33.48 (2.66-421.9)	0.0066

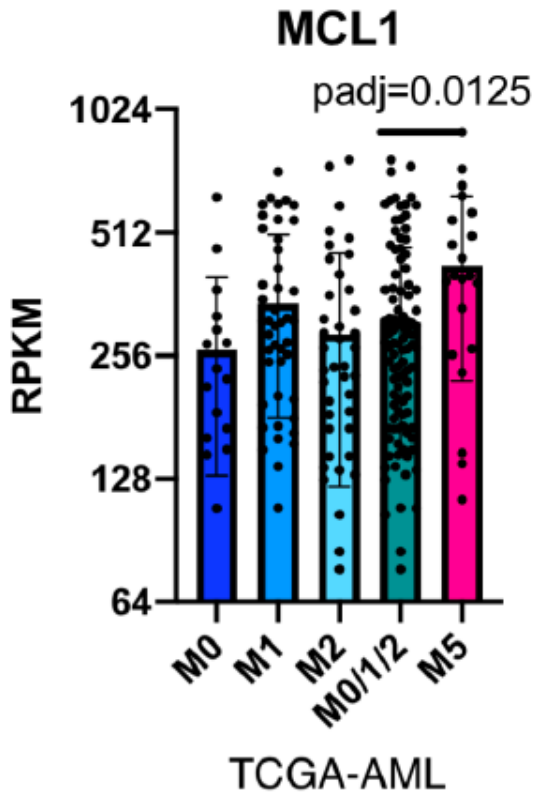
FAB M5 62% Refractory

Pei et al, Cancer Discovery 2020

MOFFITT CANCER CENTER

FAB M5 Venetoclax Resistance May Be Driven By MCL-1 Dependence

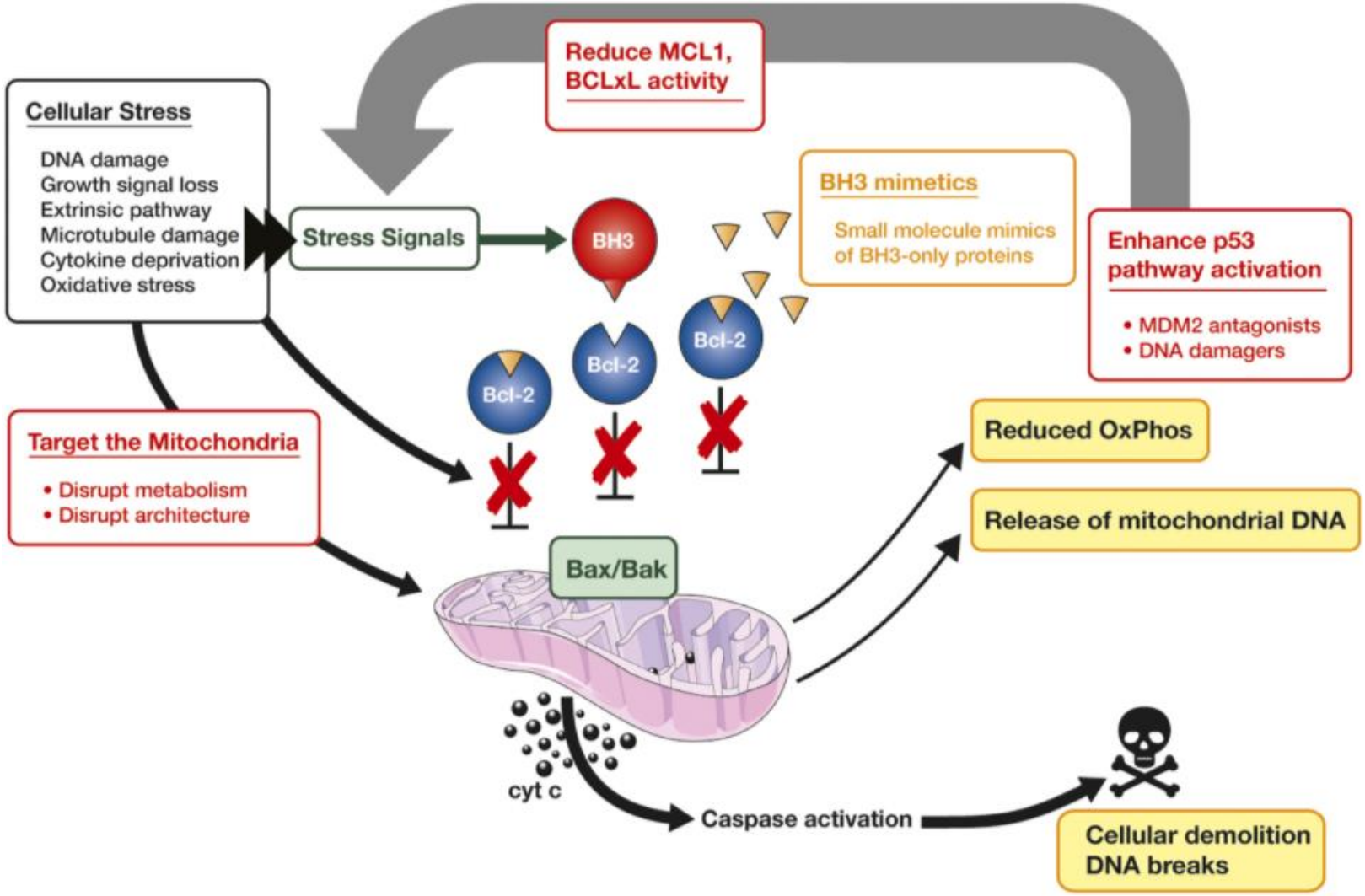




Pei et al, Cancer Discovery 2020

MOFFITT CANCER CENTER

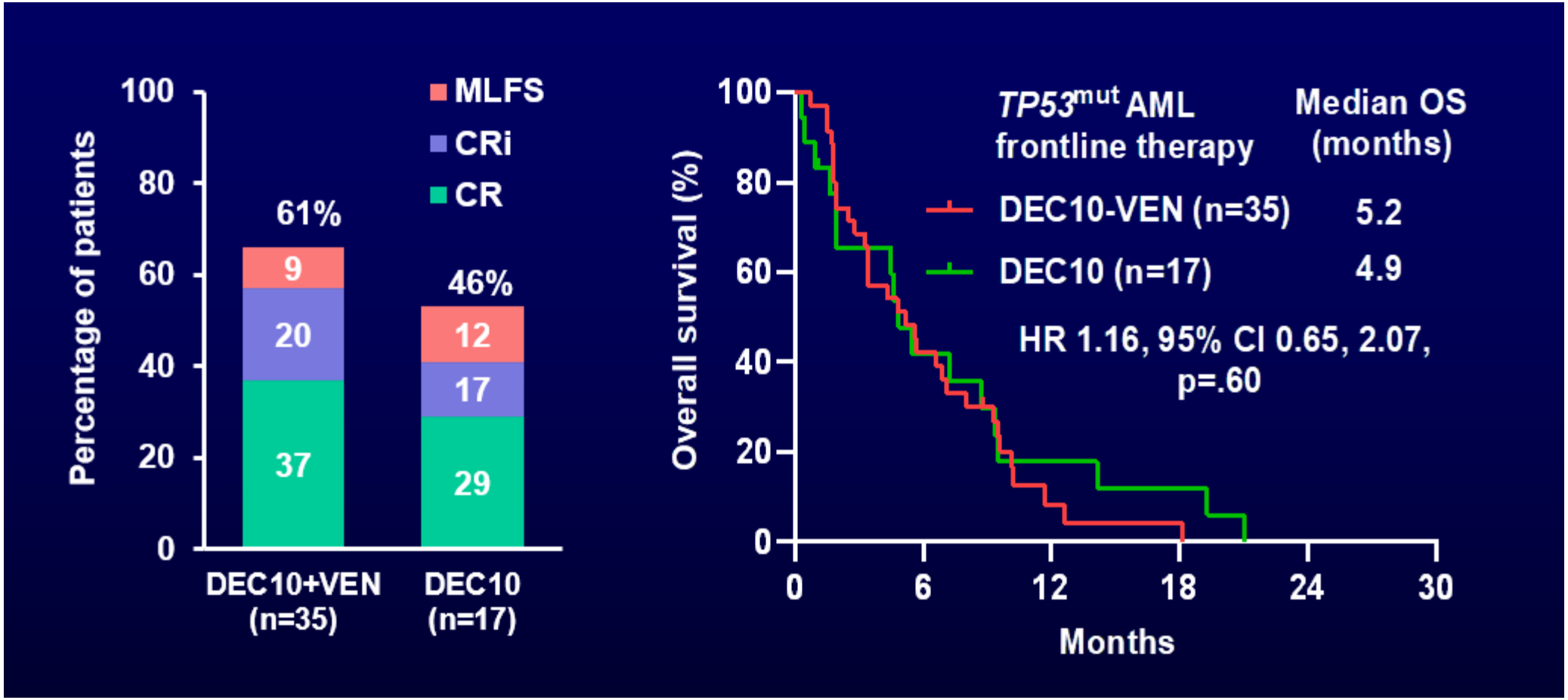
How to Enhance venetoclax activity?



Roberts A. Hematology Am Soc Hematol Educ Program (2020) 2020 (1): 1–9.

Outcomes of *TP53*-mutant AML with DEC10-VEN

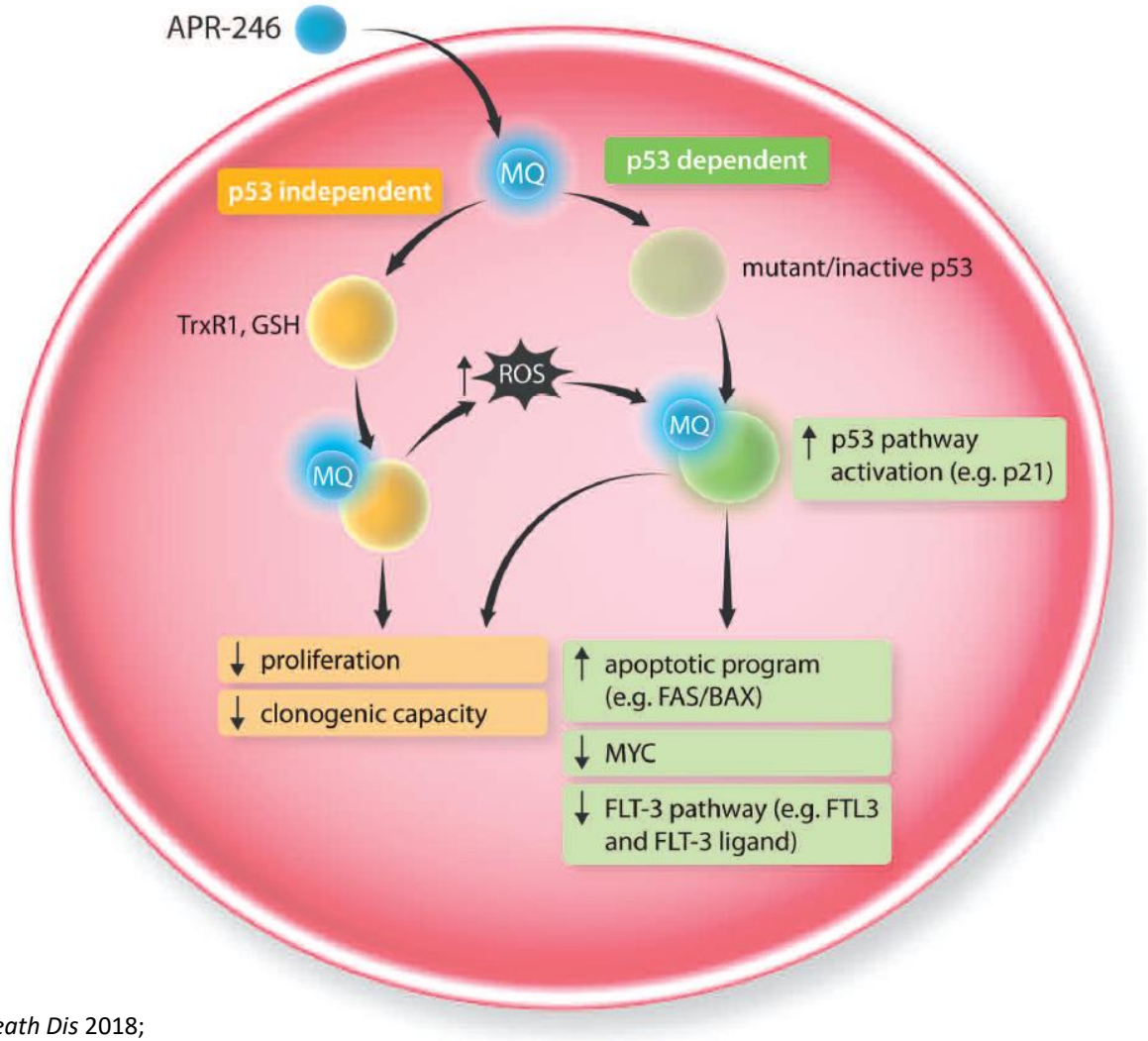
Results: DEC10-VEN vs DEC10 in *TP53*^{mut} AML



Kim K et al., ASH 2020

MOFFITT CANCER CENTER

APR-246 Mechanism of Action

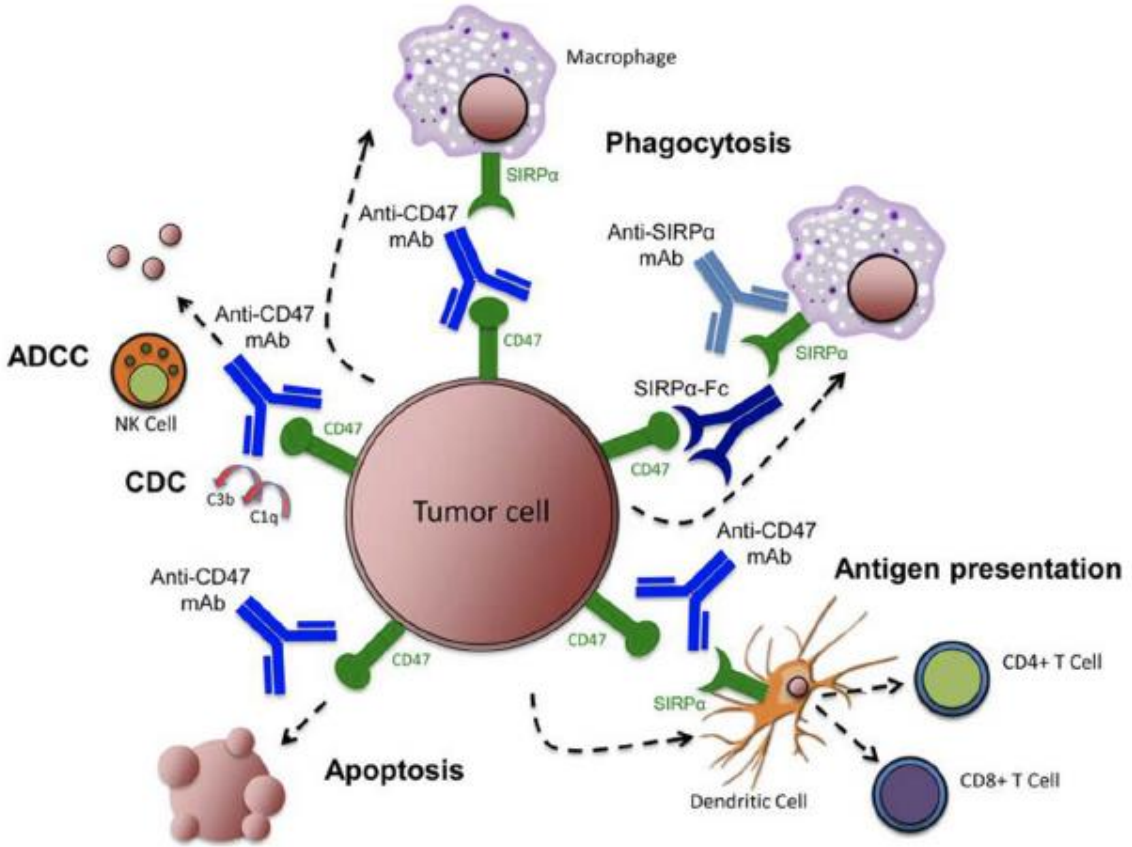


Maslah N et al., *Haematologica* 2019; Zhang Q et al., *Cell Death Dis* 2018;
Lambert JM et al., *Cancer Cell* 2009; Lehmann S et al., *J Clin Oncol* 2012; Sallman D et al., *Haematologica* 2020

MOFFITT CANCER CENTER

Therapeutic Impact of CD47/SIRPα Blockade in Cancer

- CD47 is a “do not eat me” signal on cancers that enables macrophage immune evasion
- CD47 is the dominant macrophage checkpoint overexpressed on most cancers
- In AML, CD47 expression is overexpressed on LSC/bulk AML vs normal HSC/MPP
- CD47 leads to a strong fitness advantage in AML LSCs
- Increased CD47 expression predicts worse prognosis in AML patients

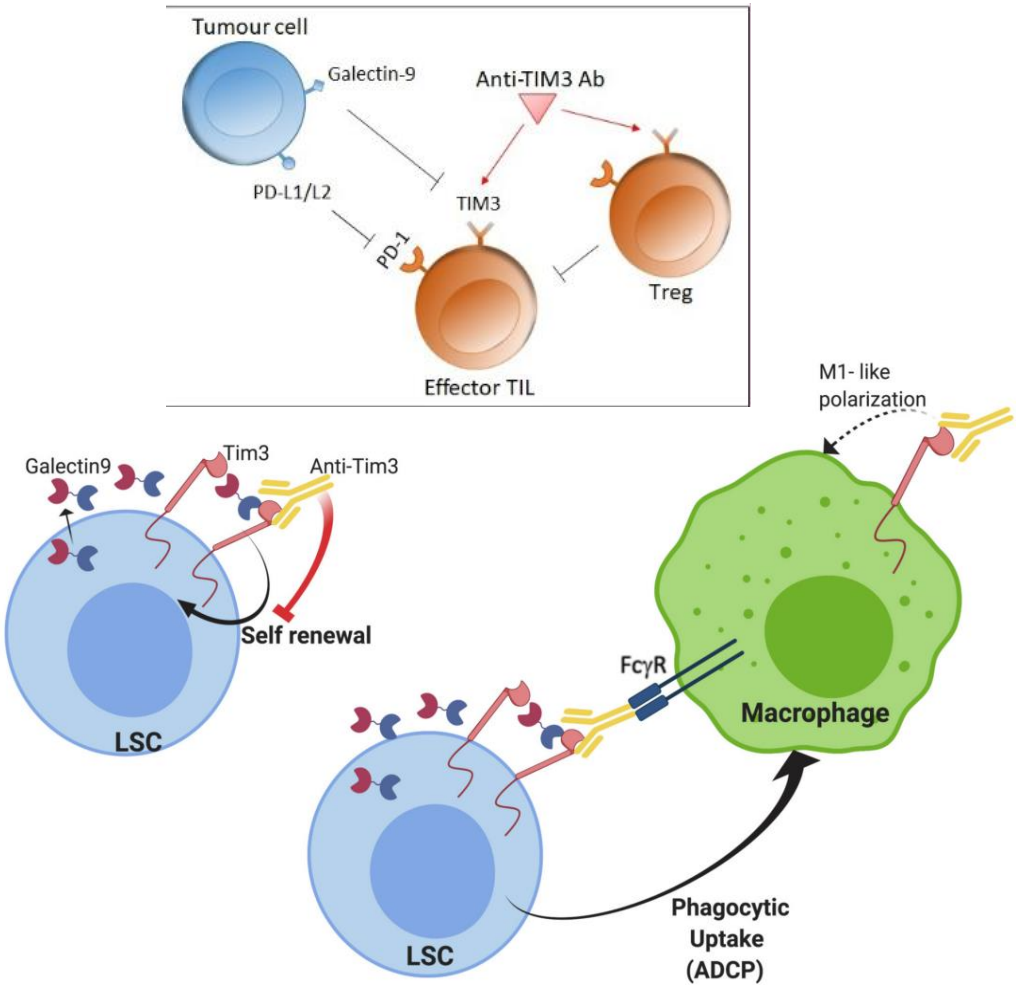


Zhang W et al., *Frontiers in Immunology* 2020; Chao M et al., *Curr Opin Immunol* 2012
Majeti, Chao et al., *Cell* 2009; Jaiswal et al., *Cell* 2009

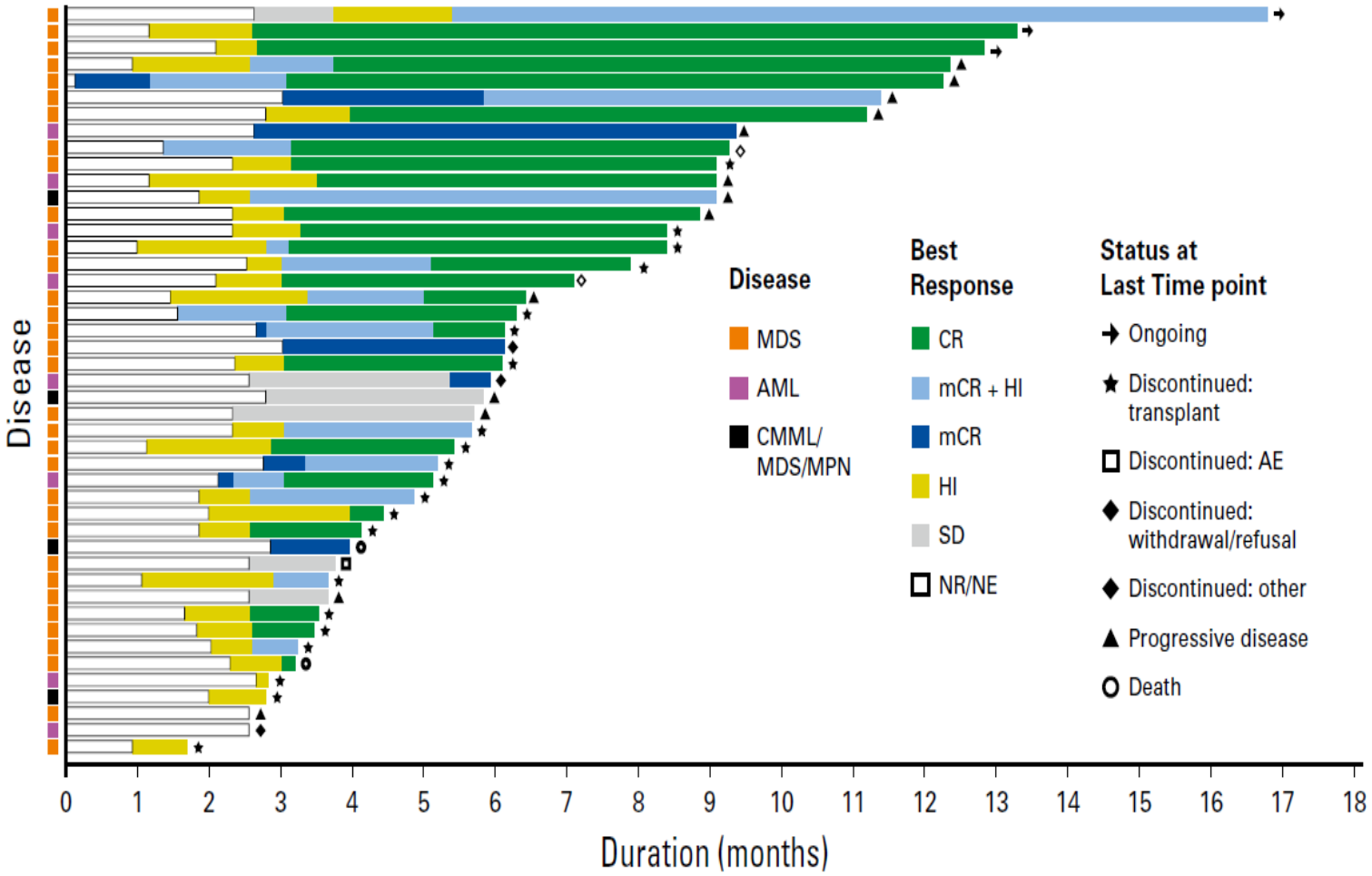
MOFFITT CANCER CENTER

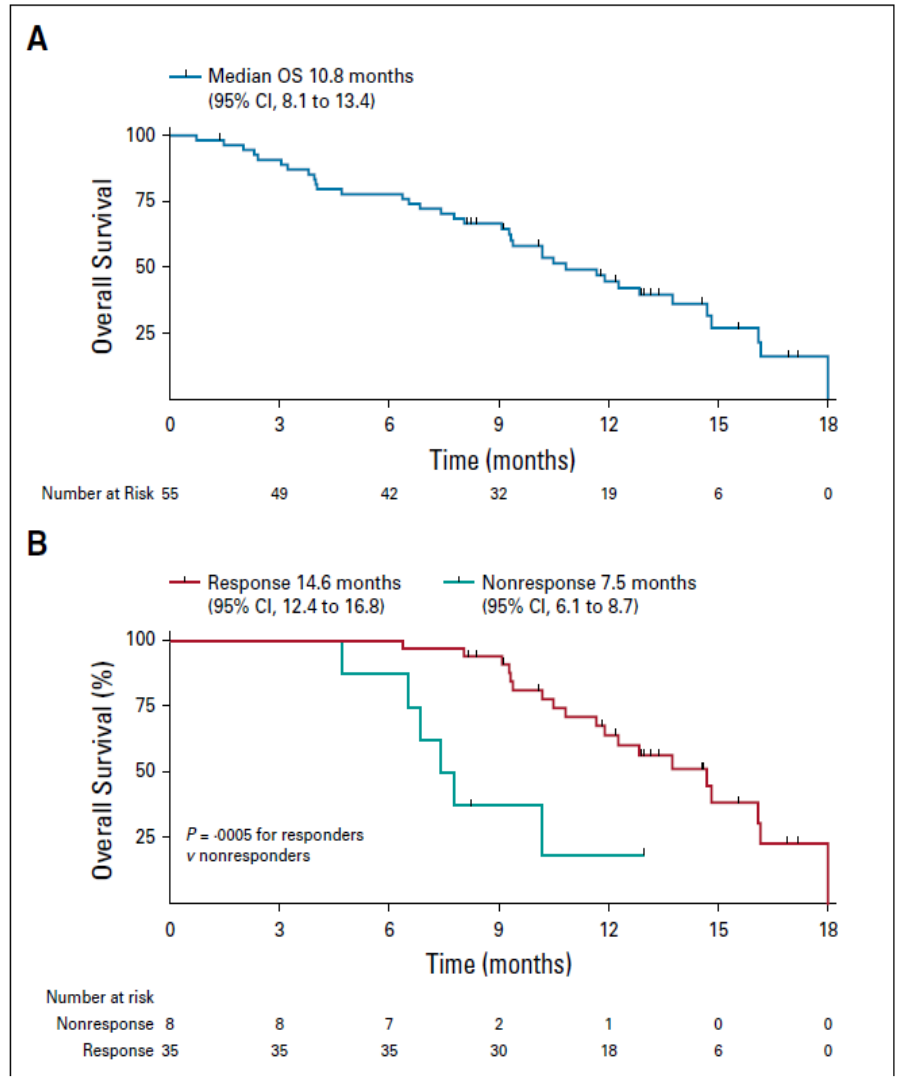
Targeting TIM3 and Sabatolimab

- TIM-3 promotes autocrine LSC self-renewal
- Blocking TIM-3 inhibits downstream signaling that promotes self-renewal
- TIM-3 ligation on T-Cells leads to apoptosis of the effector cell
- May also promote phagocytosis by myeloid cells, macrophages



Response and Outcomes to Eprenetapopt and Azacitidine





MDS ITT ORR was 73% and 50% CR; P2 GFM ORR 62% and 47% CR

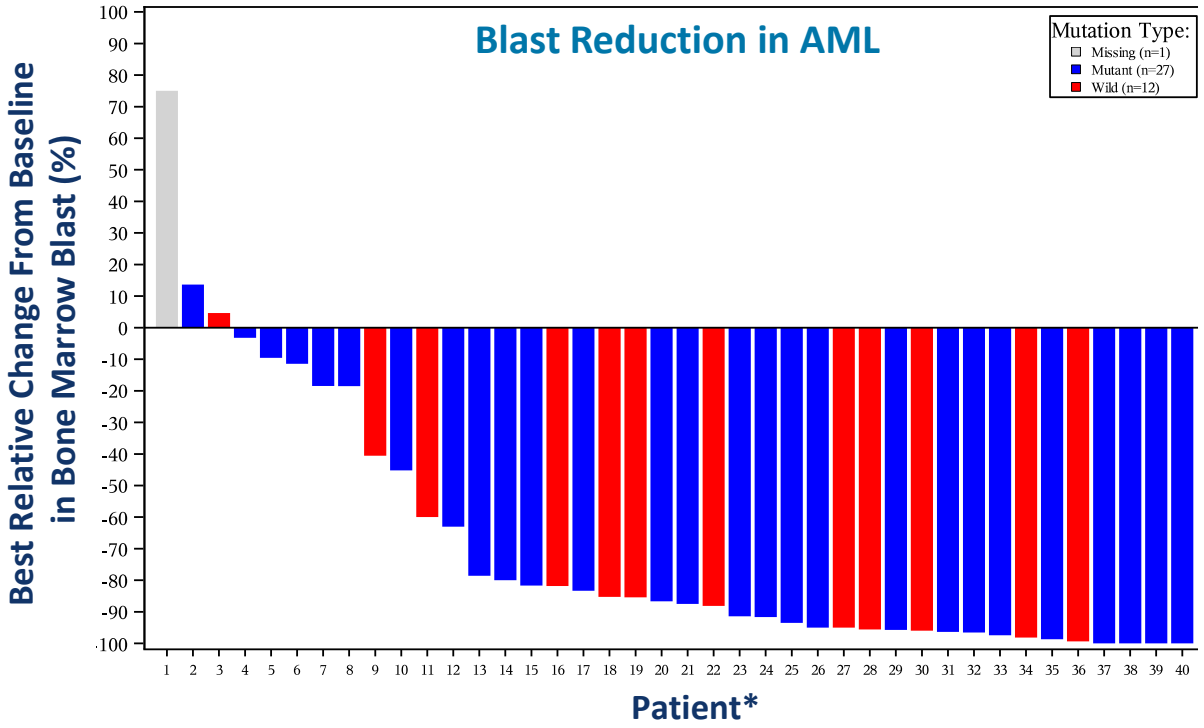
Ongoing Triplet with Venetoclax in AML is Ongoing

Sallman D et al., *JCO* 2021; Cluzeau T et al., *JCO* 2021

MOFFITT CANCER CENTER

Magrolimab + AZA Induces High Response Rates in AML

Best Overall Response	All AML (N=43)	*TP53*-mutant AML (29)
ORR	27 (63%)	20 (69%)
CR	18 (42%)	13 (45%)
CRi	5 (12%)	4 (14%)
PR	1 (2%)	1 (3%)
MLFS	3 (7%)	2 (7%)
SD	14 (33%)	8 (28%)
PD	2 (5%)	1 (3%)

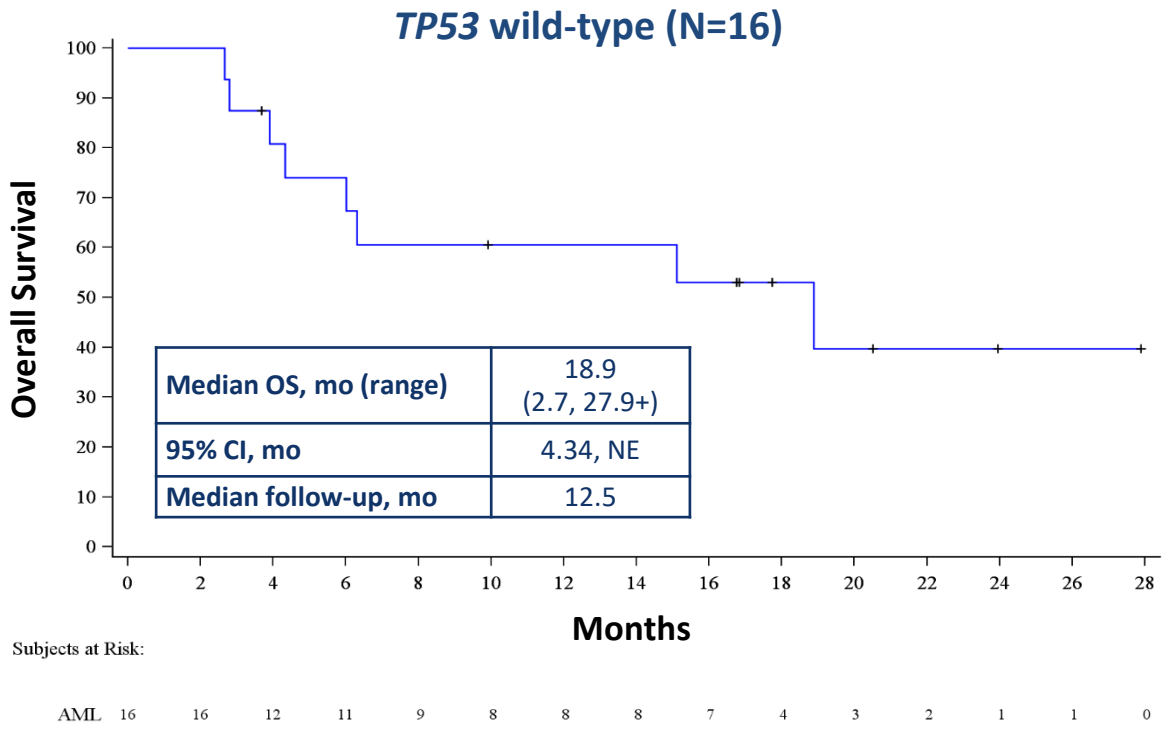


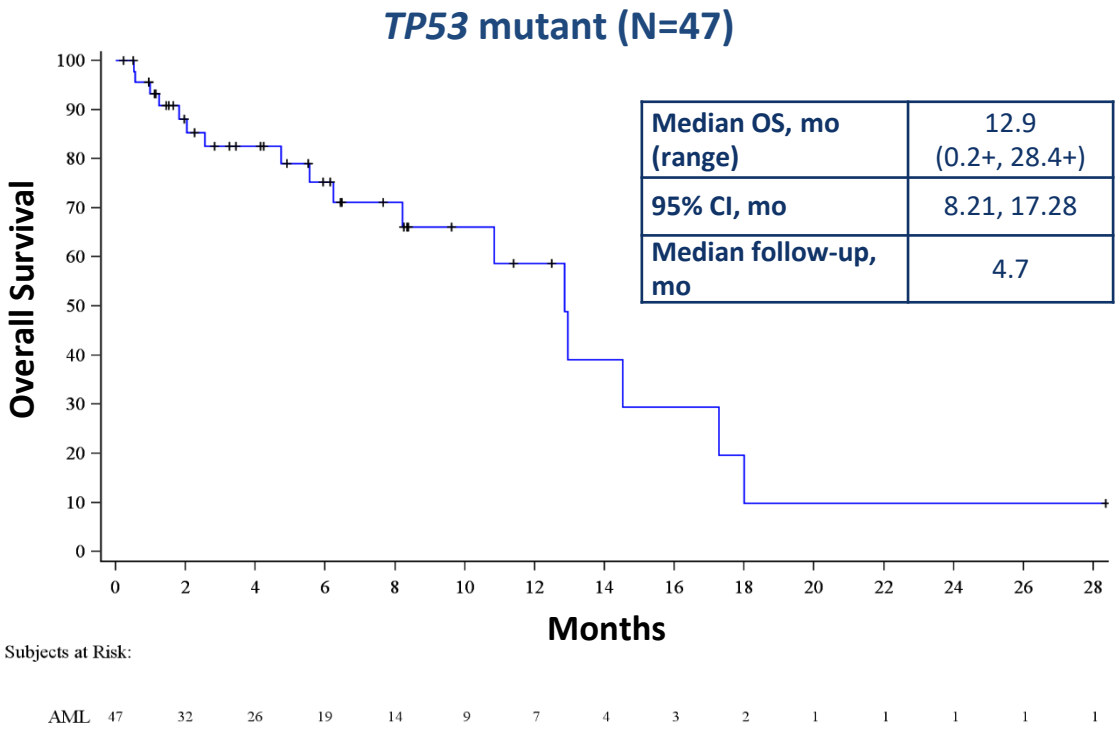
- Magrolimab + AZA induces a 63% ORR and 42% CR rate in AML, including similar responses in *TP53*-mutant patients
- Median time to response is 1.95 months (range 0.95 to 5.6 mo), more rapid than AZA monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 18%–20%)[1,2]

Response assessments per 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown. *Three patients not shown due to missing values; <5% blasts imputed as 2.5%.

1. Fenaux P, et al. *J Clin Oncol*. 2010;28(4):562-569. 2. Dombret H, et al. *Blood*. 2015;126(3):291-299.

Preliminary Median Overall Survival Is Encouraging in Both *TP53* Wild-Type and Mutant Patients



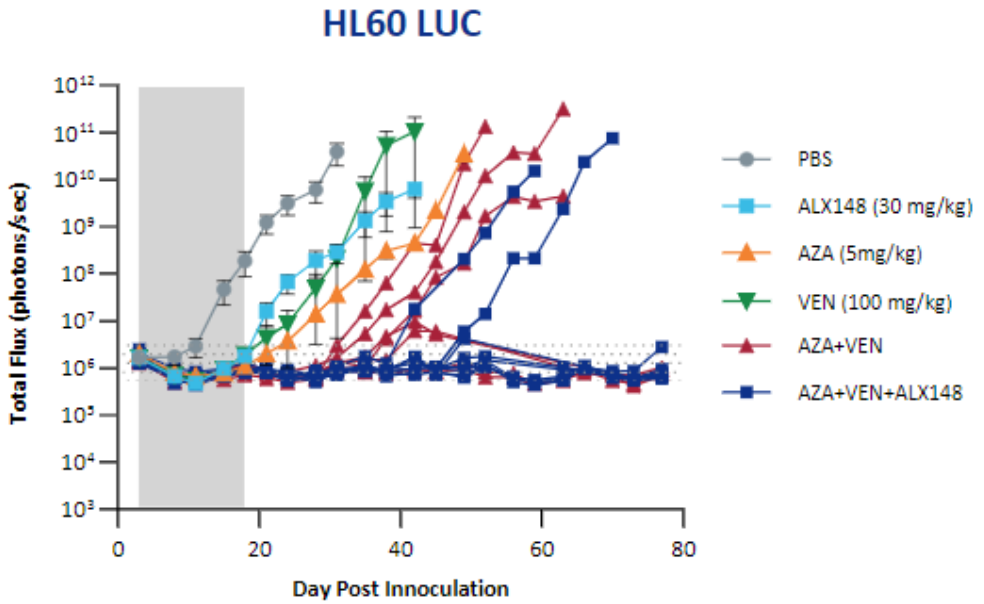


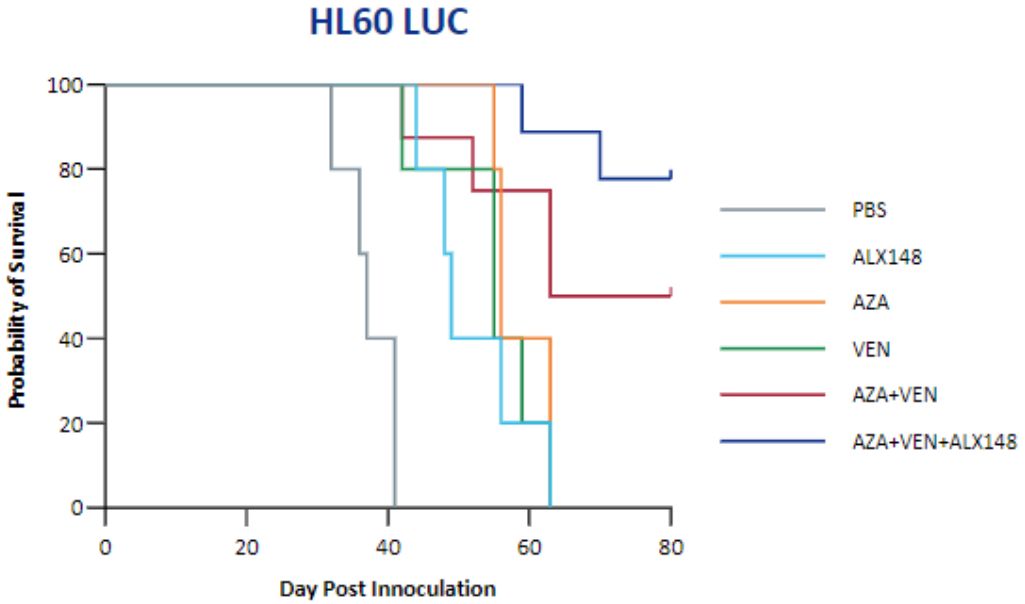
- The median OS is 18.9 months in *TP53* wild-type patients and 12.9 months in *TP53*-mutant patients
- This initial median OS data may compare favorably to venetoclax + hypomethylating agent combinations (14.7-17.5 mo in all-comers,[1,3] 5.2–7.2 mo in patients who are *TP53* mutant[2,3])
- Additional patients and longer follow-up are needed to further characterize the survival benefit

NE, not evaluable.

1. DiNardo CD, et al. *N Eng J Med*. 2020;383(7):617-629. 2. Kim K, et al. Poster presented at: 62nd ASH Annual Meeting; December 5-8, 2020 (virtual). 3. DiNardo CD, et al. *Blood*. 2019;133(1):7-17.

ALX148 + Venetoclax and Azacitidine





- AZA, VEN and ALX148 therapies were initiated day 4 post engraftment with AZA and ALX148 given intraperitoneally every 3 days for a total of 5 doses and for 14 consecutive days by oral gavage for VEN.
- AZA and VEN combination therapies yielded 4 out of 8 mice with progressive disease.
- In contrast, the combination of AZA+VEN+ALX148 completely eliminated tumor growth for 7 out of 9 mice within an 80 day evaluation period. Study is ongoing.

Chen A et al., *ASH 2020*

MOFFITT CANCER CENTER

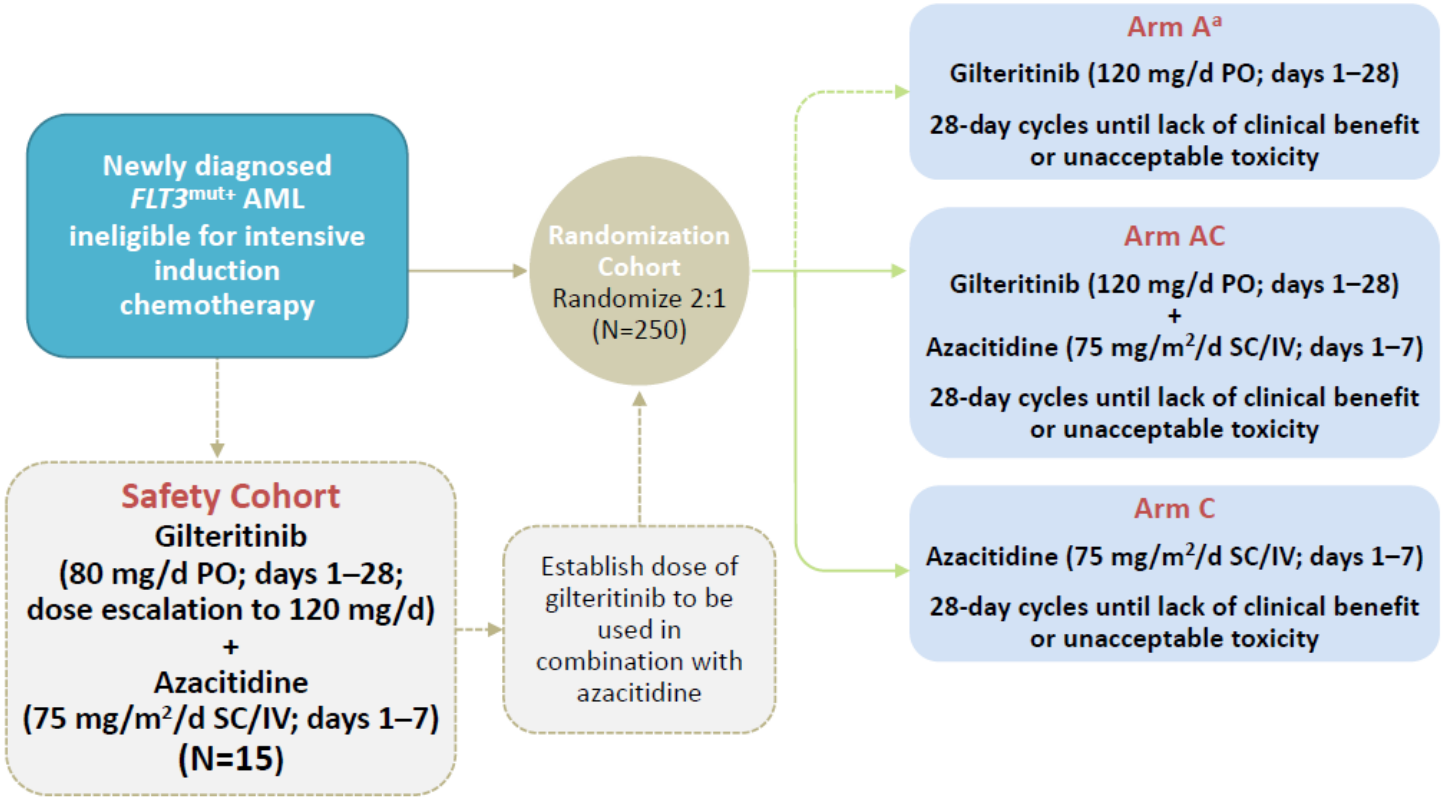
Critical Importance in Evaluating AML Patients for Clinical Trial with *TP53* Mutations

- P3 ENHANCE-2 Study of Azacitidine (Aza) + Magrolimab vs Aza+Venetoclax or Intensive chemotherapy based on investigator assessment of fitness.
- Triplet studies of Aza+magrolimab+venetoclax and Aza+sabatolimab+venetoclax
- Triplet study of Aza+eprenetapopt (APR-246) + venetoclax

- Additional Triplet Combinations on Top of Aza Backbone are Planned

MOFFITT CANCER CENTER

LACEWING 2020: Study Design and Update



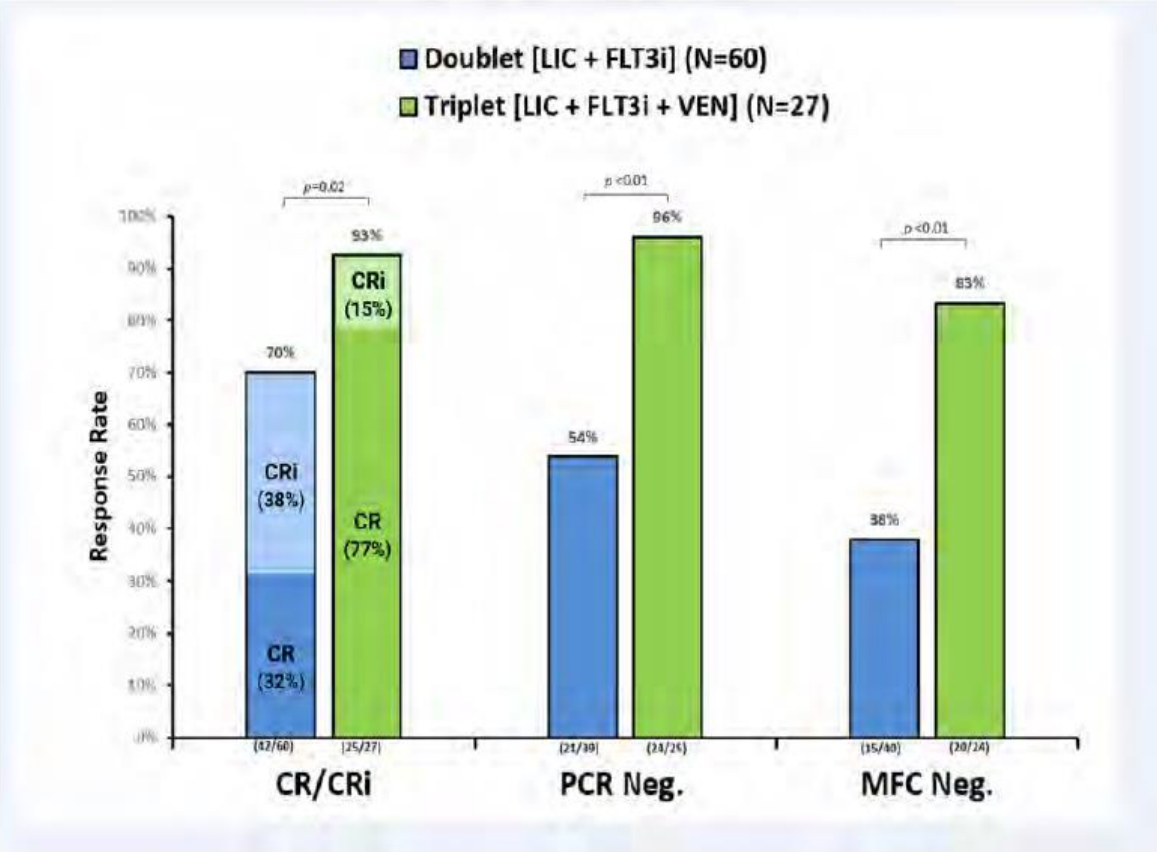
Characteristic	Safety Cohort (N=15)
Age, y	
Median (range)	75 (65–86)
≥75, n (%)	9 (60)
FLT3 status, n (%)	
ITD alone	10 (67)
TKD alone	3 (20)
ITD/TKD	1 (7)
Wild type	1 (7)
ECOG PS ≤1, n (%)	6 (40)
CR	**5/15 (33)**
CRc	**10/15 (67)**
DOR (n=10)	**10.4 mo**

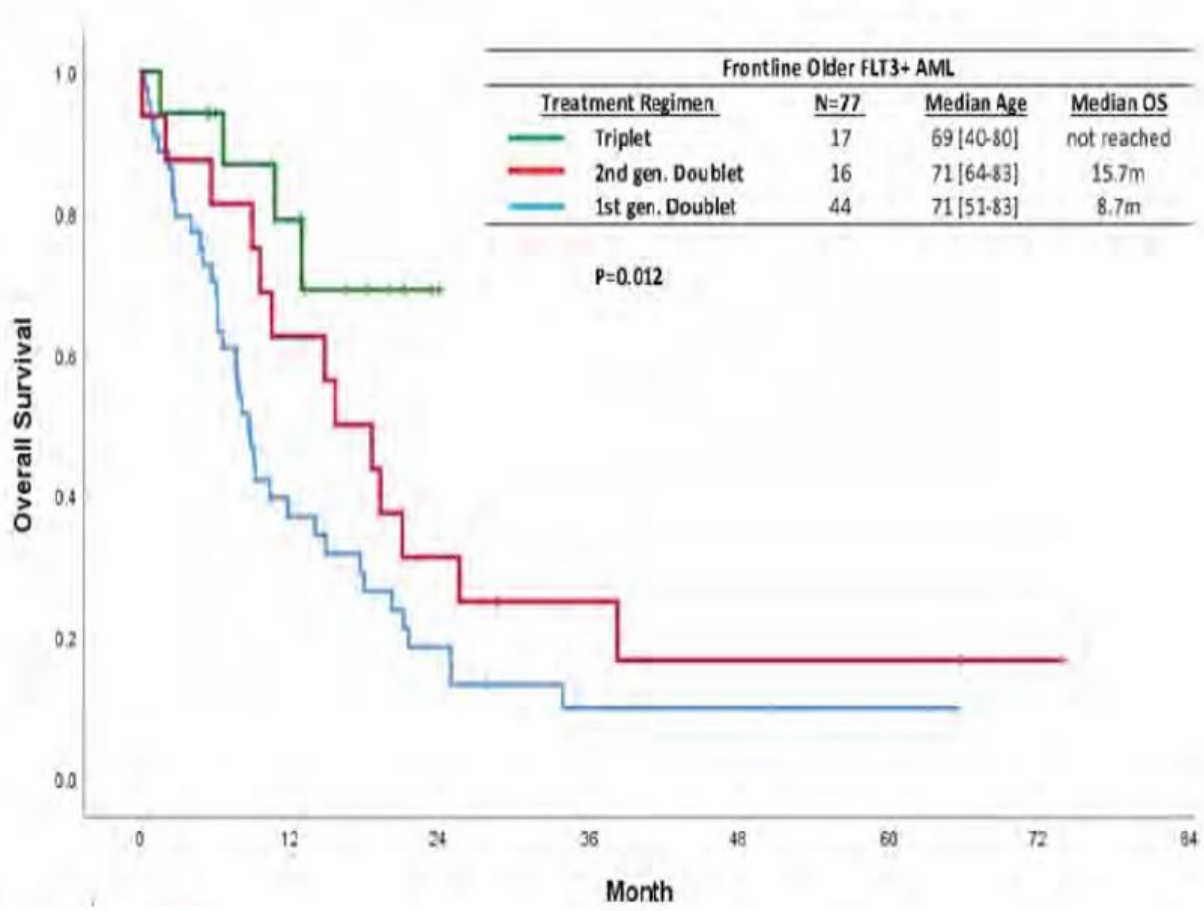
Post-ASH press release reported that trial failed to meet primary endpoint

Wang E et al., ASH 2020

MOFFITT CANCER CENTER

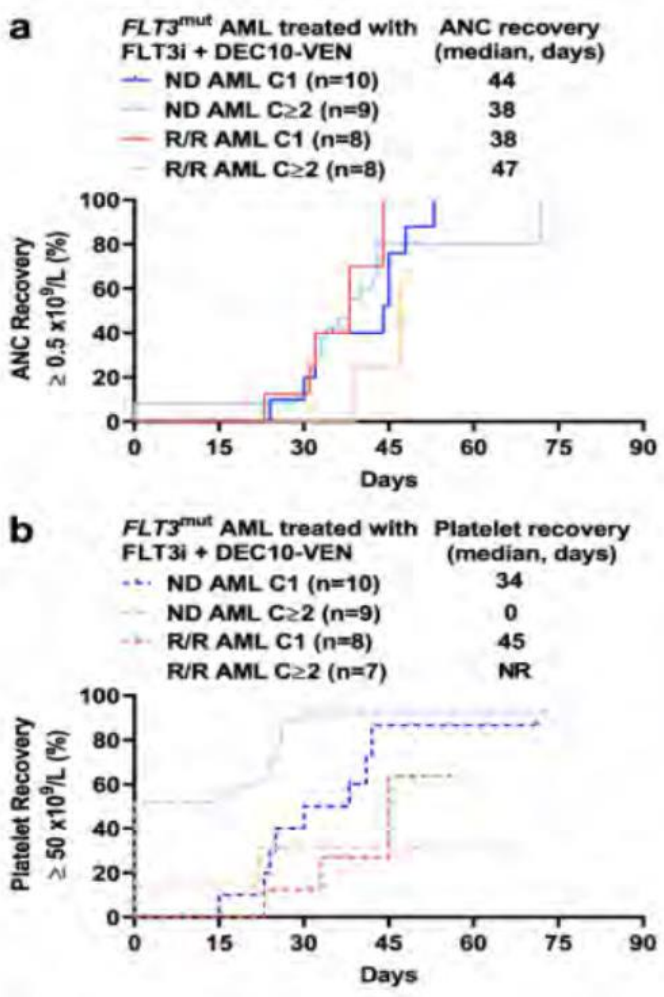
Doublet vs Triplet with Venetoclax

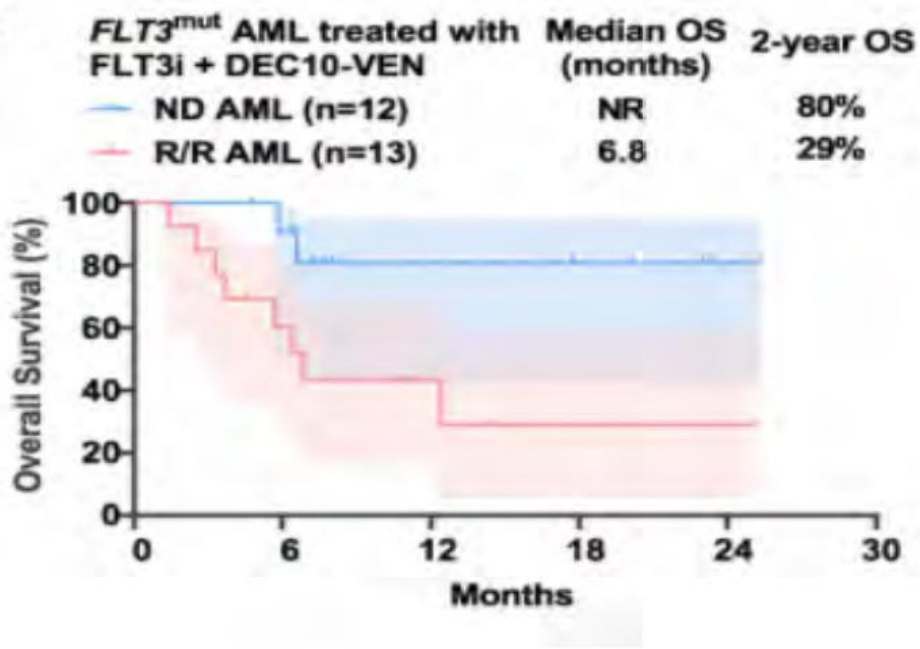




Yilmaz M et al., ASH 2020

FLT3i Triplet with 10 day decitabine

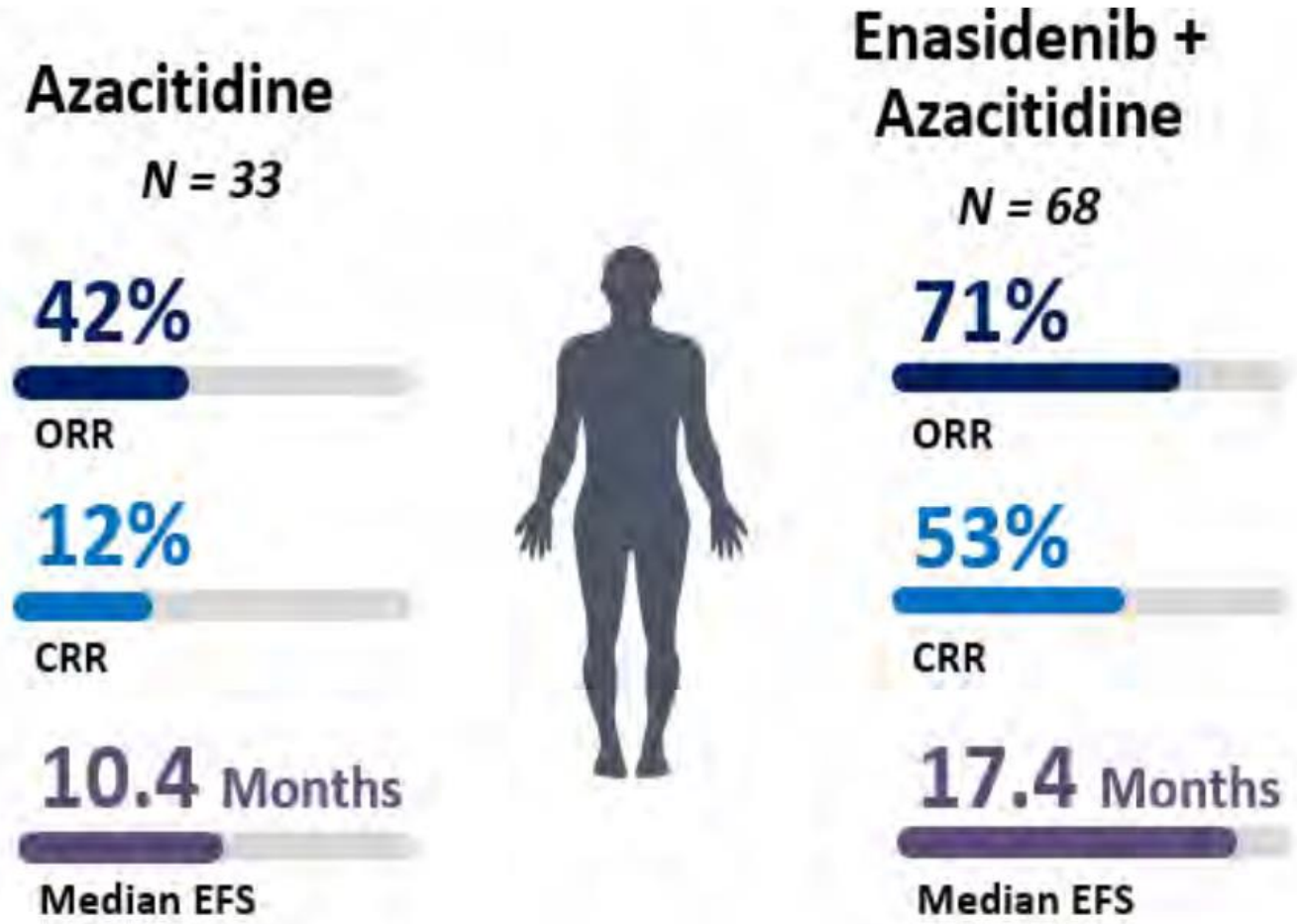


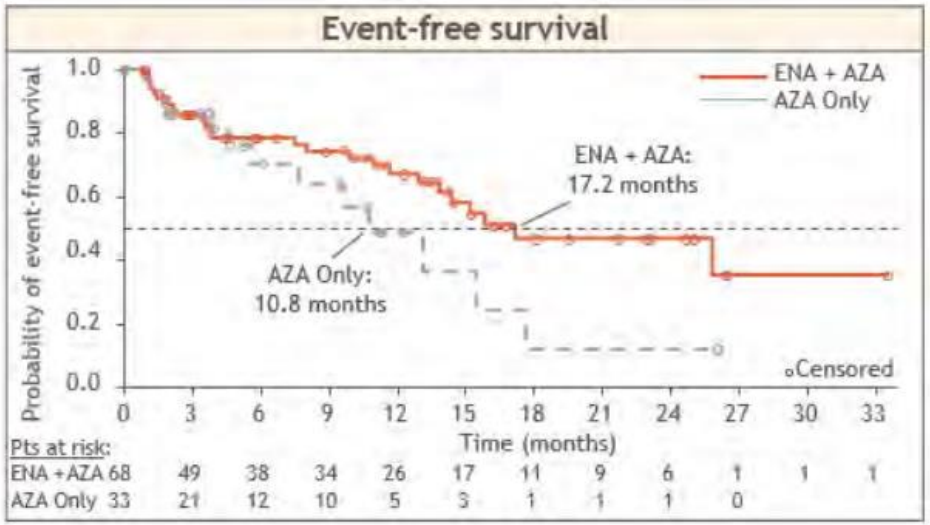


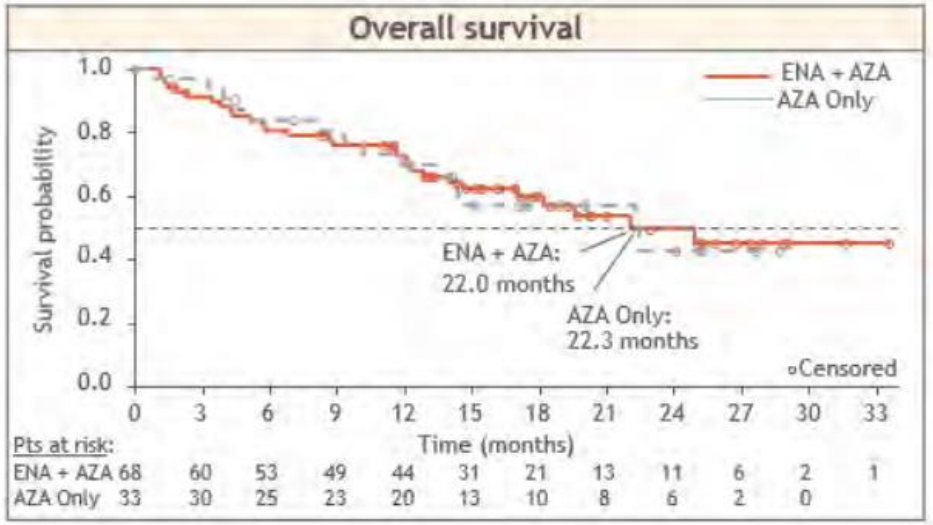
Additional Outcomes	
60-d mortality	0% ND 7% R/R (n=1)
Median course duration	**Cycle 1: 46 days** Cycle 2+: 40 days

Maiti et al., Blood cancer J 2021

Aza +/- Ena for Newly Diagnosed IC-Ineligible IDH2





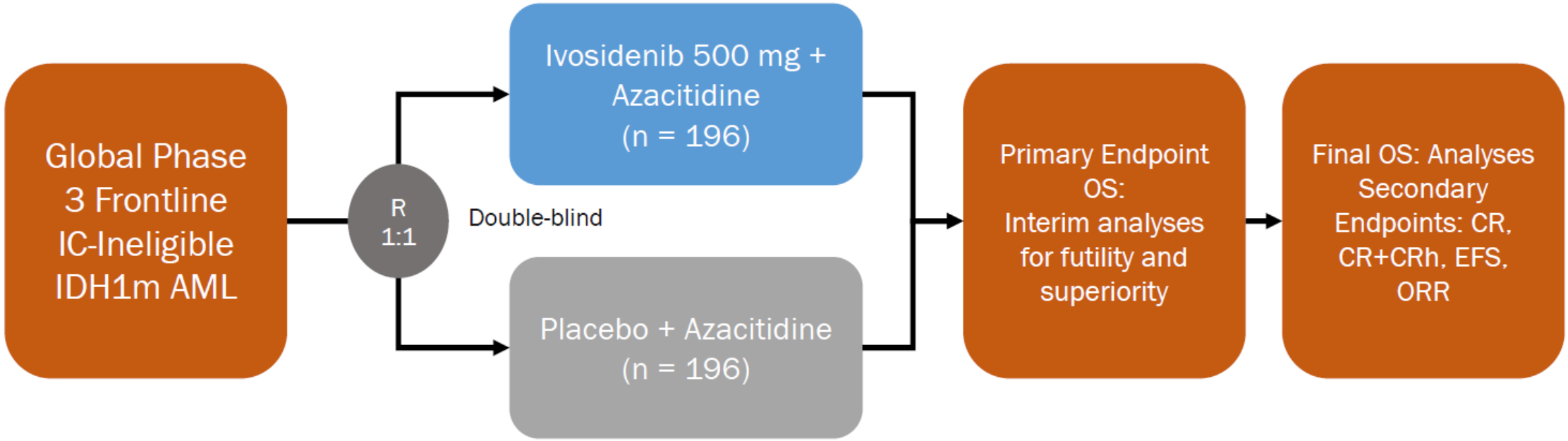


**Non-Blinded Study, In the AZA Only arm,
8 patients (24%) received subsequent treatment with enasidenib monotherapy

DiNardo CD et al, ASCO 2020

Courtesy of Courtney D DiNardo, MD, MSCE

AGILE Study: AZA +/- Ivosidenib for Newly Dx AML



*155 sites worldwide, enrolling primarily ex-US due to AZA + VEN approval in the US for front-line treatment.

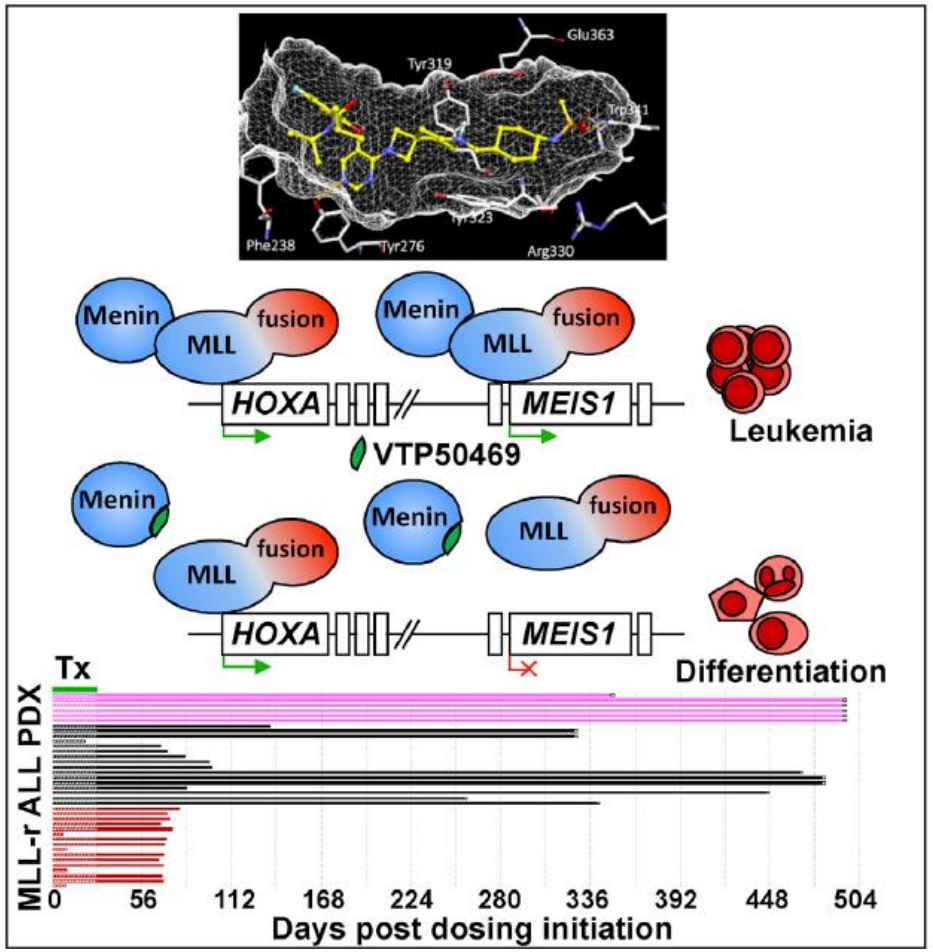
*Amendment has modified primary endpoint to event-free survival (EFS)

Press Release 8/2/2021 with Improved EFS and OS; ORR 78%, CR 57% Trial stopped early

Courtesy of Dinardo C et al

MOFFITT CANCER CENTER

Menin Inhibitors (SNDX-5613 and KO-539) in *MLL-r* AML



SNDX-5613

Pt #	Age	# Prior Tx	Mutational status	Dose	Meets target PK profile^	DLT period	Response Assessment
2	69	2	MLL-r t(10;11) FLT3 ITD	226 q12 → 113 q12	Yes	No DLTs Grade 2 QTc, resolved with dose reduction	**Day 28 CRi - improved to CR** FISH neg, Flow neg, on study
4	30	>3	None*	226 q12	PK pending	Inevaluable	**Progressive Disease** off study
5	79	2	MLL PTD	226 q12	PK pending	No DLTs	Day 28: **No Response** on study
6	61	3	MLL-r t(9;11)	113 q12 → 113 QD	PK pending	No DLTs Grade 1 QTc, resolved with dose reduction	**Day 28 PRi** blast count 40%→ 20%; peripheral blood counts improving; FISH positive on study

**Patient did not have either MLLr or NPM1 mutant AML; ^Target PK profile defined as: (1) maintaining steady state levels above IC_{95} (~600 ng/mL) for most of dosing interval, (2) maintaining Cmin level above projected IC_{90} (~300 ng/mL) and (3) achieving a minimum 24 h AUC of ~30,000 ng*h/mL*

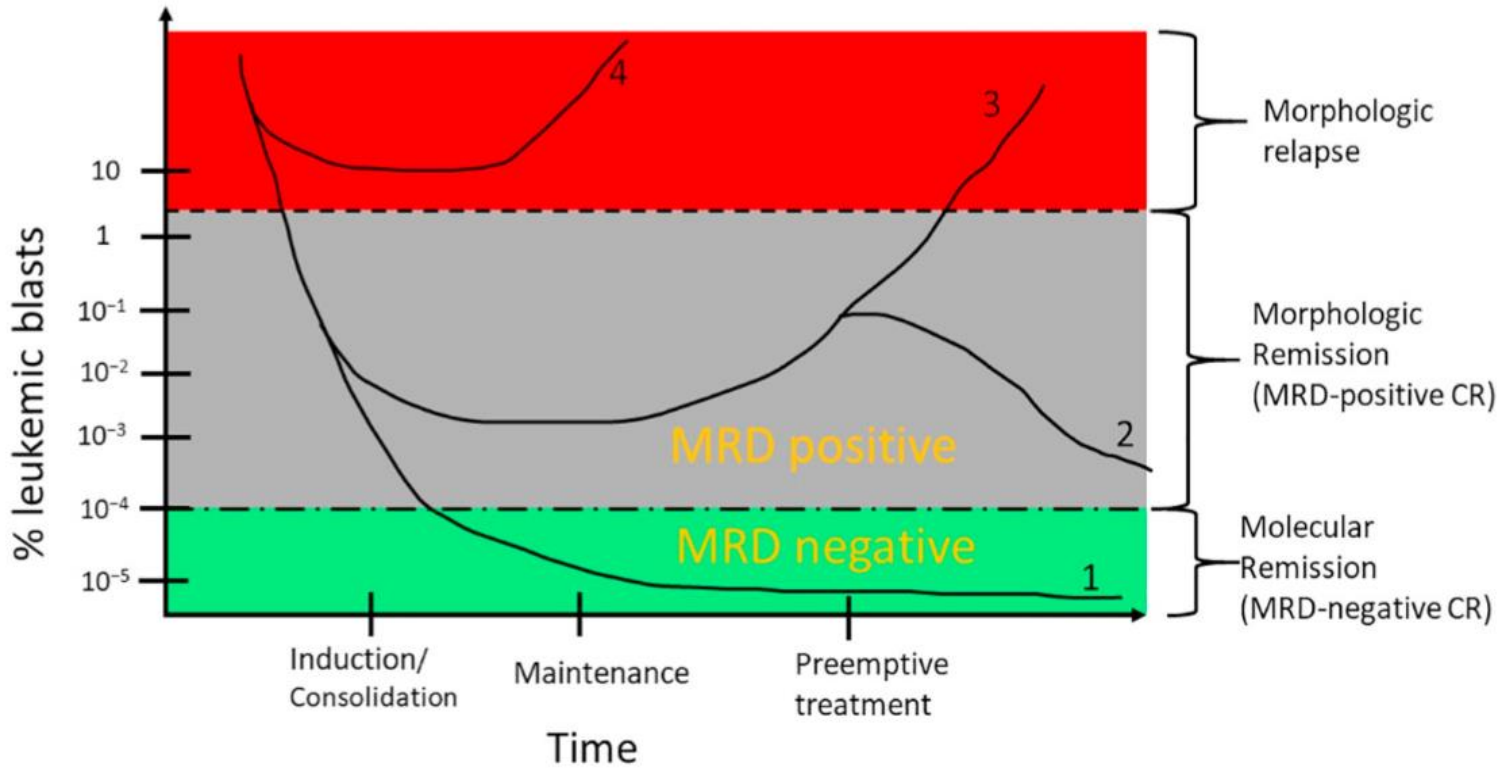
KO-539

Clinical activities observed in 6 patients (efficacy evaluable = 8)				
Dose	Mutational Profile	CYP3A4 inhibitor	# of prior regimens	Clinical Activity
400 mg	RUNX1, SRSF2, ASXL1, TET2, STAG2, BCOR, PTPN11	Yes	3	Decreased peripheral blasts
200 mg	U2AF1, TET2, p53, DNMT3A, PTPN11	No	4	Stable disease
	NPM1, FLT3-ITD, TET2, CUX1	Yes	4	Morphological leukemia-free state
	NPM1, DNMT3A, KMT2D	Yes	7	CR, MRD-
100 mg	SETD2, RUNX1	Yes	2	CR, MRD+
50 mg	KMT2A-r	Yes	2	Decreasing hydrea requirement

Krivtsov A et al., *Cancer Cell* 2019; McGeehan, J et al., AACR 2020; Wang E et al., ASH 2020

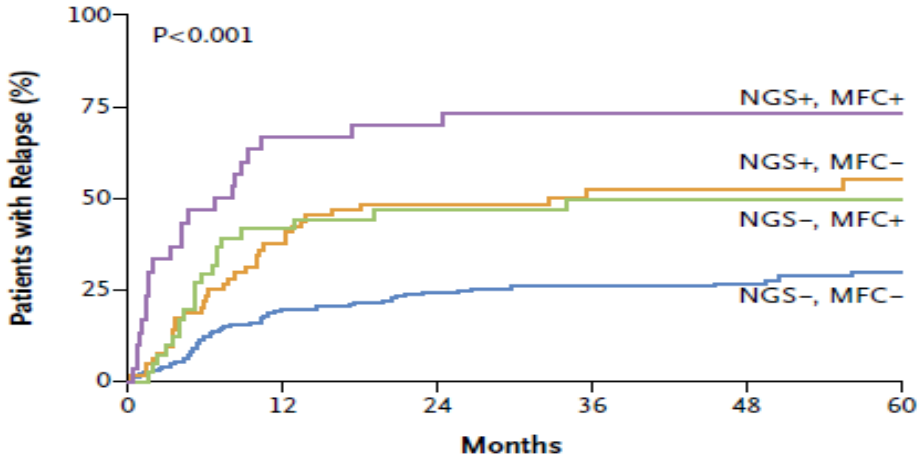
What is MRD – “The Minimal that Kills”

- 5 year OS ~ 25% of patients, even in younger patients treated with intensive therapy



Bewersdorf J et al *Blood Reviews* 2019

Combinatorial MRD technologies can further improve prognosis



No. at Risk						
NGS+, MFC+	30	8	7	5	4	4
NGS–, MFC+	41	22	18	14	11	7
NGS+, MFC–	64	39	30	22	15	11
NGS–, MFC–	205	153	130	101	69	42

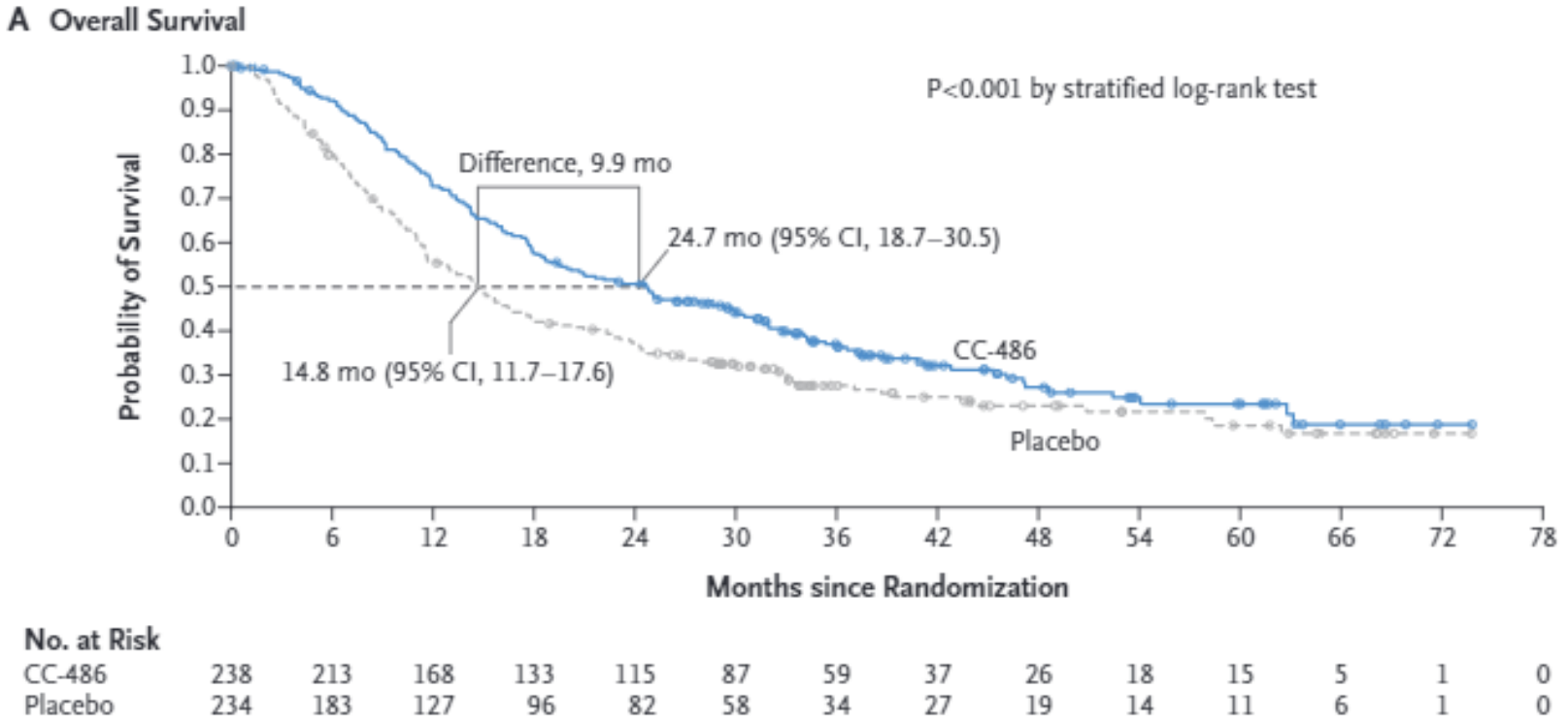
Figure 3. Rate of Relapse According to Results of Next-Generation Sequencing and Multiparameter Flow Cytometry.

Shown is the cumulative incidence of relapse, according to the presence of positive (+) or negative (–) results for the detection of persistent non-*DTA* mutations during complete remission on next-generation sequencing (NGS) and on multiparameter flow cytometry (MFC).

Jongen-Lavrencic M et al. NEJM 2018

MOFFITT CANCER CENTER

Oral Azacitidine and MRD



37% Converted to MRD negative by MFC in CC-486 group

Roboz G et al., ASH 2020; Wei A et al., NEJM 2020

MOFFITT CANCER CENTER

MRD Directed Therapy

- As MRD is strongly concordant with OS, MRD negativity may prove to be an approvable registrational endpoint in future studies
- Currently 100s of ongoing studies for risk-adapted MRD directed therapy for patients with AML
  - Including targeted therapy, HMA +/- ven and other novel agents, checkpoint inhibitors, CAR-T, bispecific agents, novel IO, and others

What are the next step for AML Patients

- Multiple Phase 1-3 studies with triplet trials on top of a HMA + venetoclax backbone (both targeted and non-targeted) for elderly AML
- ?s on how targeted inhibitors should be incorporated into the treatment paradigm (sequential vs combinatorial; based on MRD???)
  - What happens if have both FLT3 and IDH?
- Discussions of toxicity issues with triplet studies (cytopenias, financial)
- Can we cure some patients?
- Can we discontinue therapy based on MRD status?
- What about young patients with non-good risk disease?
- Will Intensive Chemotherapy go away?

MOFFITT CANCER CENTER

Acknowledgements

Moffitt Cancer Center

Amy McLemore
Kathy McGraw
Rami Komrokji
Eric Padron
Jeffrey Lancet
Amy Aldrich
Lisa Nardelli
Seongsuk Yun
Najla Ali
Ling Zhang
Qianxing Mo
Jiqiang Yao
Kendra Sweet
Chetasi Talati
John Puskas
Anthony Hunter

MDACC

Guillermo Garcia-Manero

Emory

Anthony Hunter

GFM

Thomas Cluzeau
Pierre Fenaux

Alan List

AA&MDSIF • MDS CLINICAL RESEARCH CONSORTIUM
Supported by the Edward P. Evans Foundation

mds foundation
the myelodysplastic syndromes foundation, inc.

VERA and JOSEPH DRESNER FOUNDATION