Kevin Kelly, MD, PhD

Myelodysplastic Syndromes and Acute Myeloid Leukemia

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Speakers bureau: Janssen, Seattle Genetics, Celgene, Karyopharm, Epizyme
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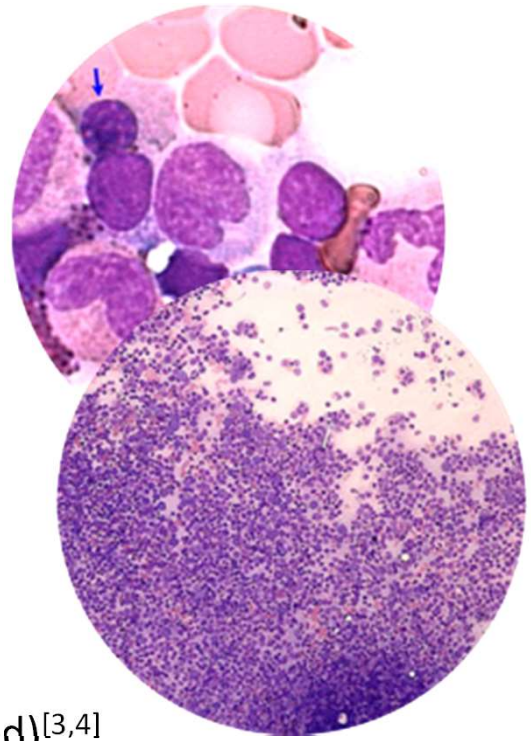
16th Annual California Cancer Conference Consortium
October 31st, 2020

Overview of Myelodysplastic Syndromes

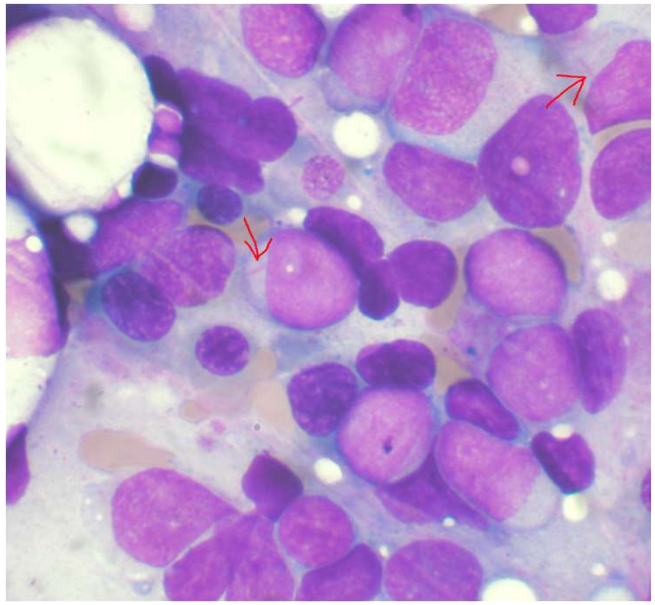
- A group of malignant hematopoietic stem cell disorders characterized by[1]
  - Bone marrow failure with resultant cytopenias and related complications
  - Macrocytic anemia is most common presentation
  - Dysplastic morphology is disease hallmark
  - Genetic abnormalities (acquired) are common
  - Tendency to progress to AML
- Age-adjusted incidence 4.5/100,000[2]
- Approximately 10,000/yr in United States (likely underestimated)[3,4]

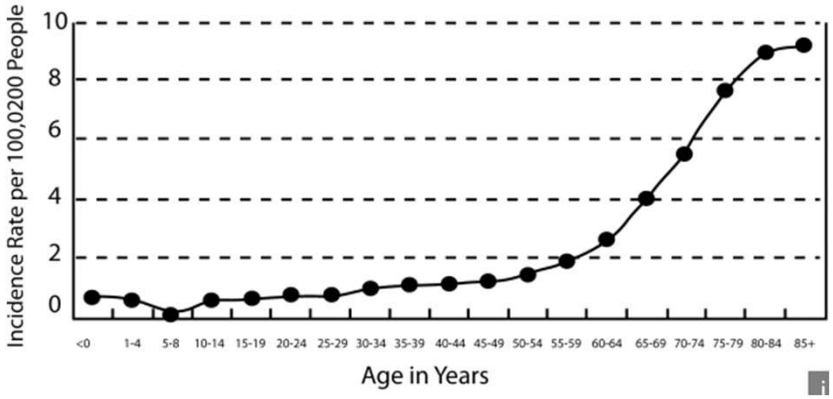


1. Greenberg. J Natl Compr Canc Netw. 2013;11:838. 2. SEER 21 Data. 2012-2016.
3. Ma. Cancer. 2007;109:1536. 4. Ma. Am J Med. 2012;125:S2.

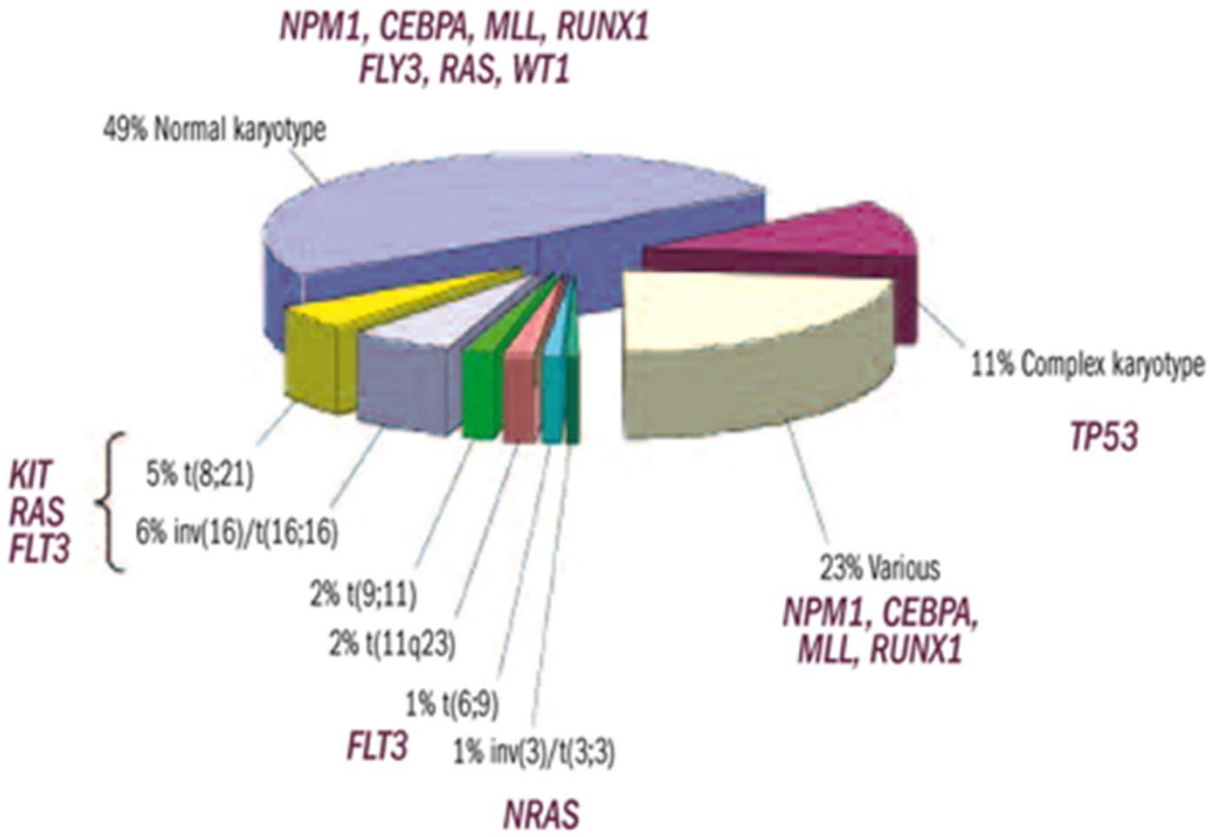
Acute Myeloid Leukemia

- Most common acute leukemia in adults.
- 3 to 5 cases per 100,000.
- Median Age 65 years.
- Treatment unchanged for 30 years.
- Challenges:
  - Advanced Age
  - Co-morbidities
  - Complex Molecular Heterogeneity





Major cytogenetic subgroups of AML and associated gene mutations



AML in 2017-2020, FDA Approvals

- **Midostaurin** (FLT3 inhibitor) for de novo younger AML (≤60 yrs), FLT3 mutation—April 2017
- **Gilteritinib** (FLT3 inhibitor) for FLT-3 + R-R AML—November 2018
- **Enasidenib** (IDH2 inhibitor) for R-R AML and IDH2 mutation—August 2017
- **Ivosidenib** (IDH1 inhibitor) for R-R AML—July 2018
- **CPX 351** (daunorubicin + cytarabine) for newly Dx Rx-related AML and post MDS AML—August 2017
- **Gemtuzumab ozogamicin** revival for frontline AML Rx— September 2017

Midostaurin PI. Gilteritinib PI. Enasidenib PI. Ivosidenib PI. CPX 351 PI. Gemtuzumab ozogamicin PI.

AML in 2017-2020, FDA Approvals

- **Venetoclax** for newly Dx older/unfit for intensive chemo, with AZA/DAC, ara-C—November 2018
- **Glasdegib** for newly Dx older/unfit, with ara-C—November 2018
- Data + with FLT3 inhibitor **quizartinib**
- **Oral azacitidine 2020**

Venetoclax PI. Glasdegib PI. Quizartinib PI. Oral Azacitidine PI. NCT02668653. NCT01757535.

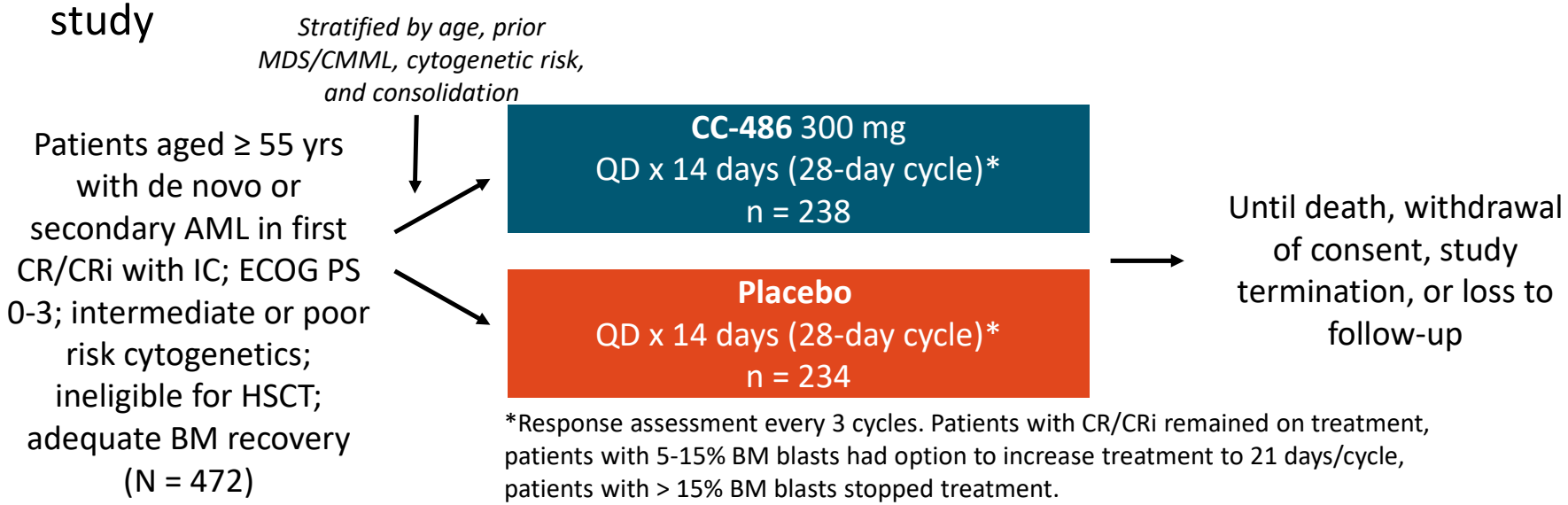
QUAZAR AML-001: Background

- Azacitidine tablets, CC-486: investigational oral formulation of the hypomethylating agent azacitidine that allows for extended dosing (> 7 days/cycle)
- QUAZAR AML-001: double-blind phase III trial of CC-486 vs placebo as maintenance therapy in patients ≥ 55 yrs of age with AML in first CR or CRi after induction therapy
  - CC-486 dosing: 300 mg PO QD x 14 days of 28-day cycle
  - CC-486 prolonged OS (24.7 vs 14.8; HR: 0.69; 95% CI: 0.55-0.86; *P* = .0009) and RFS (10.2 vs 4.8; HR: 0.65; 95% CI: 0.52-0.81; *P* = .0001)[1]

1. Wei. ASH 2019. Abstr LBA-3. 2. Dohner. ASCO 2020. Abstr 7513.
3. Roboz. ASCO 2020. Abstr 7533. 4. Ravandi. ASCO 2020. Abstr 7530.

Phase III QUAZAR AML-001: CC-486 as Maintenance Therapy in First-Remission AML—Study Design

- International, multicenter, randomized, placebo-controlled, double-blind, phase III study

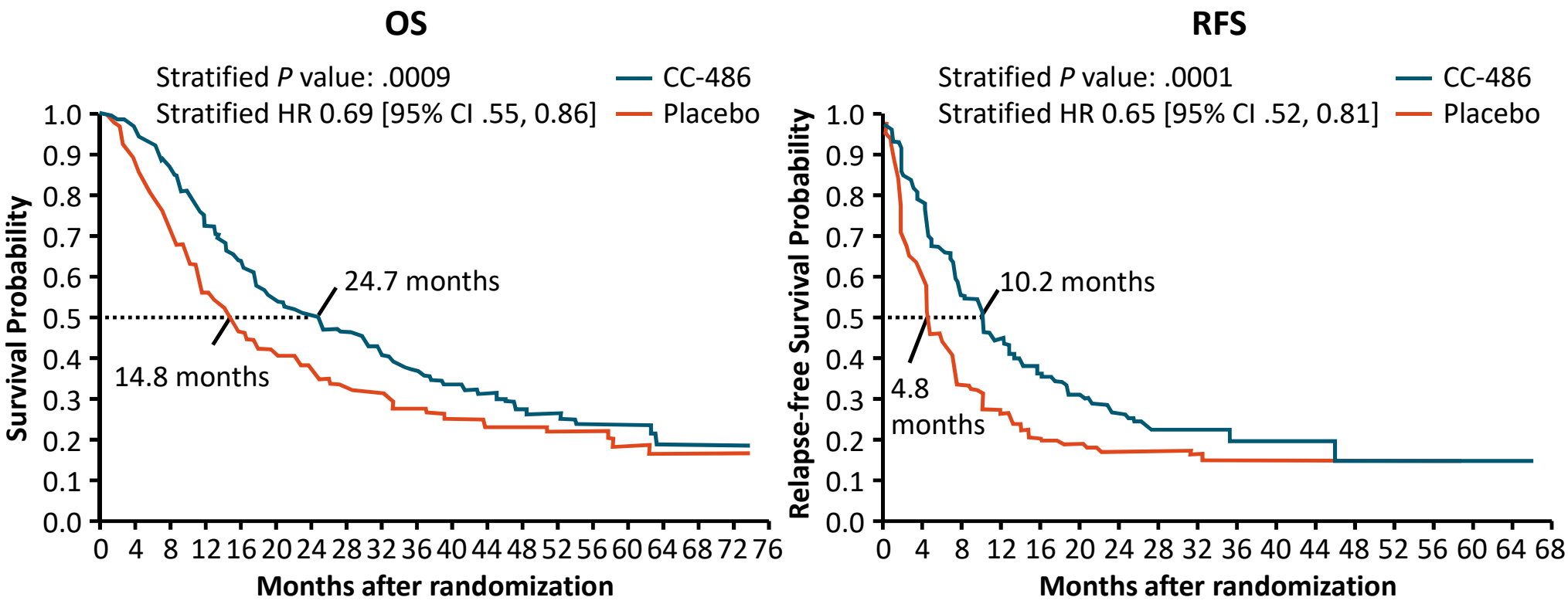


*Response assessment every 3 cycles. Patients with CR/CRi remained on treatment, patients with 5-15% BM blasts had option to increase treatment to 21 days/cycle, patients with > 15% BM blasts stopped treatment.

- Primary endpoint: overall survival
- Key secondary endpoints: relapse-free survival, health-related QoL, and safety

Wei. ASH 2019. Abstr LBA_3.

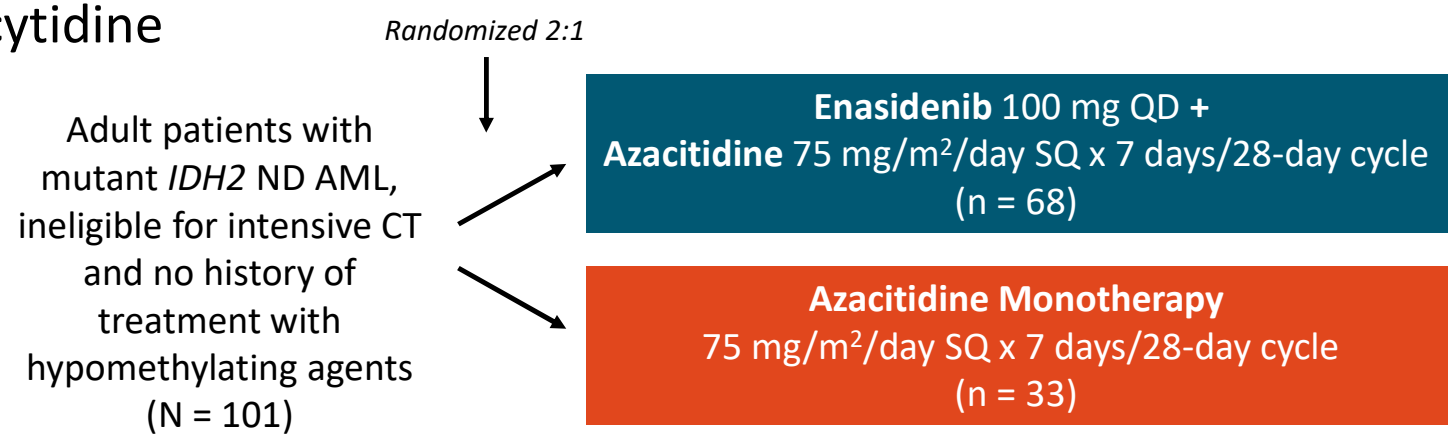
Phase III QUAZAR AML-001: Survival and RFS



Wei. ASH 2019. Abstr LBA_3.

AG221-AML-005: Enasidenib Plus AZA vs AZA in Mutant *IDH2* Newly Diagnosed AML—Phase II Study Design

- Randomized phase I/II study
  - Phase I portion consisted of 3 + 3 dose-finding for enasidenib + azacytidine

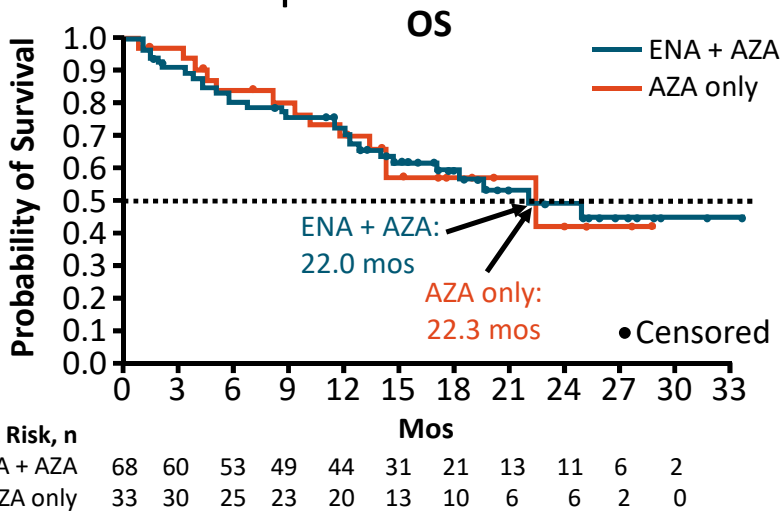


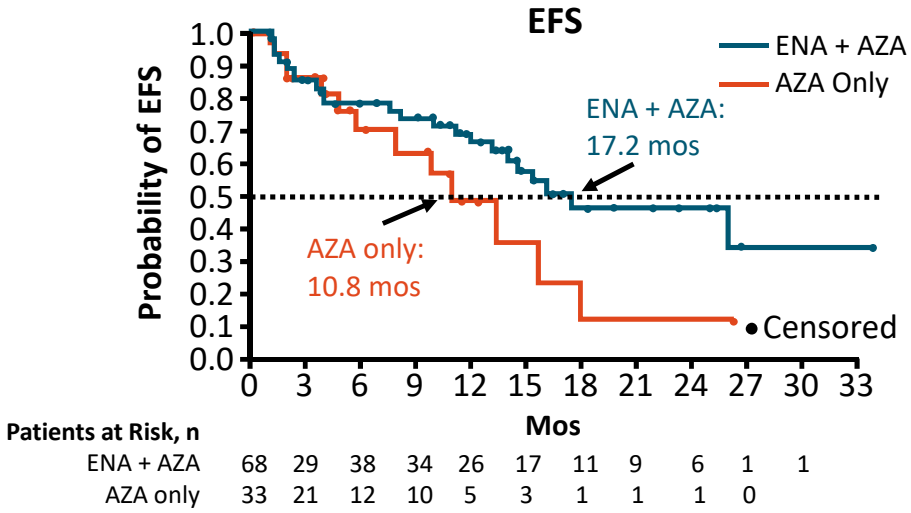
- Primary endpoint: ORR
- Key secondary endpoints: CR, safety, OS, EFS

DiNardo. ASH 2019. Abstr 643.

AG221-AML-005: OS and EFS

- Median follow-up in both arms: 14 mos





Endpoint	Enasidenib + Azacitidine (n = 68)	Azacitidine Monotherapy (n = 33)	HR (95% CI)	*P* Value
Median OS, mos	22.0	22.3	0.99 (0.52-1.87)	.9686
Median EFS, mos	17.2	10.8	0.59 (0.30-1.17)	.1278

- ENA + AZA CR 53%; estimated 1-year survival >90%

DiNardo. ASH 2019. Abstr 643.

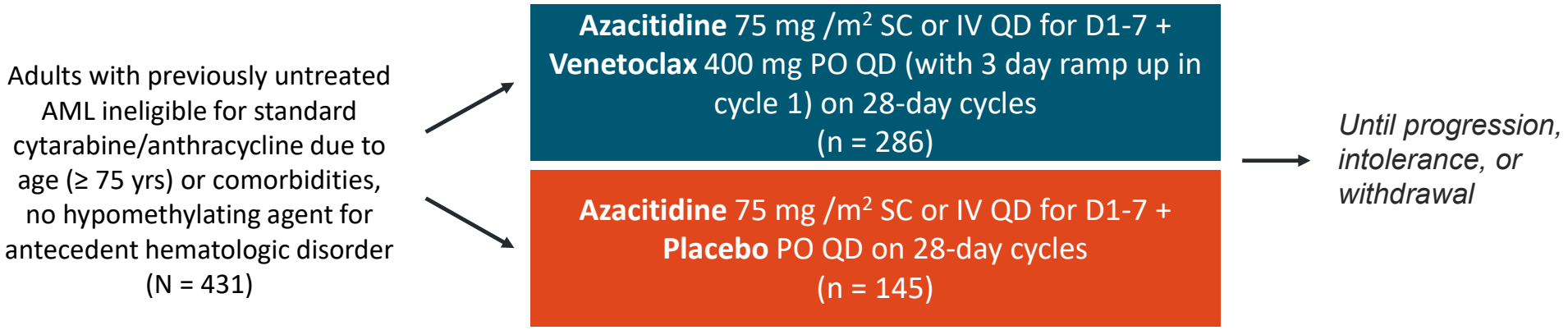
Ivosidenib + Azacitidine in Newly Diagnosed AML

- 23 pts; median age 76 yrs (61-88); age ≥ 75 yrs 52%
- CR 61%; CRh 9%; CR + CRh 70%
- 12-mos OS 82%
- IDH1 mutation clearance in 63% of CR-CRh

DiNardo. EHA 2019. Abstr PS1023.

VIALE-A: Azacitidine ± Venetoclax in Treatment-Naive Patients With AML Ineligible For Standard Induction Therapy

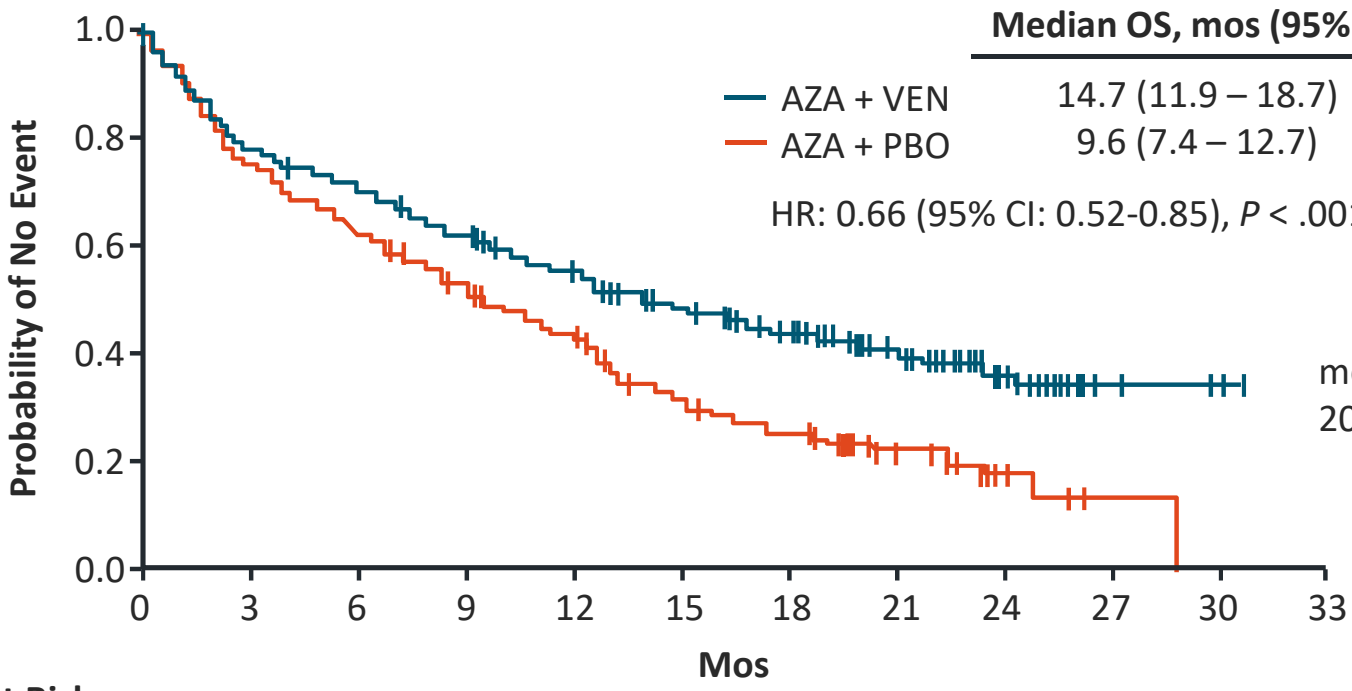
- Multicenter, double-blind, placebo-controlled, randomized phase III trial



- Primary endpoint: OS, rate of CR + CRi (outside the US)
- Other endpoints: composite CR or CRi, EFS, OS by molecular subtype, QoL, CR, transfusion independence

DiNardo. EHA 2020. Abstr. LB2601. NCT02993523.

VIALE-A: OS



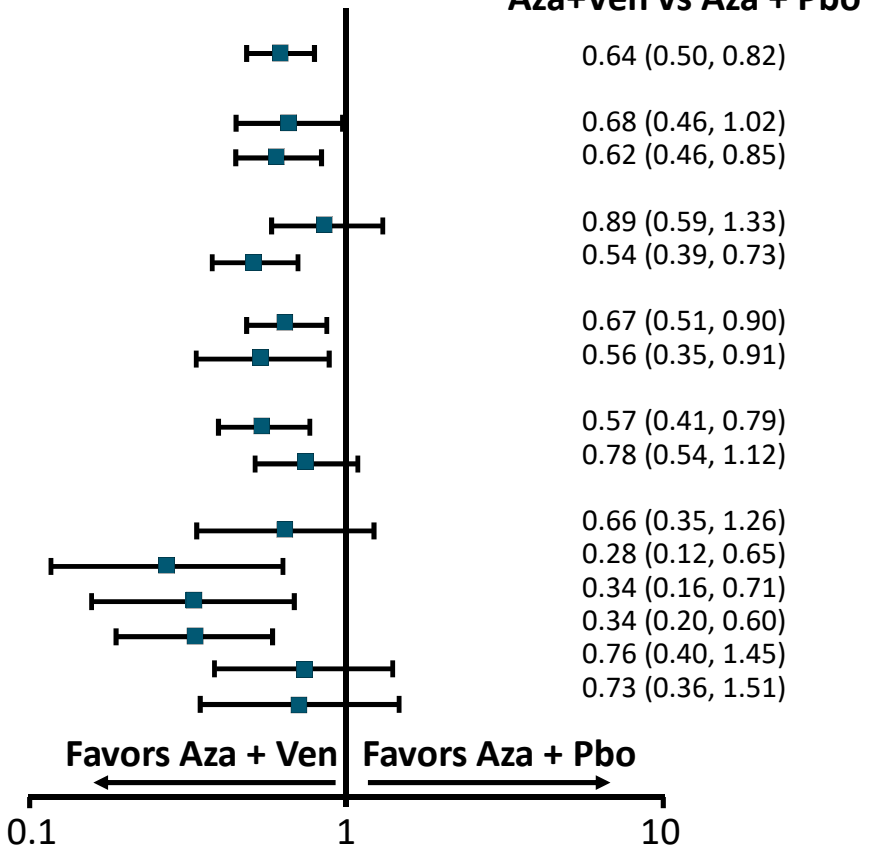
No. at Risk

Aza + Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza + Pbo	145	109	92	74	59	38	30	14	5	1	0	0

DiNardo. EHA 2020. Abstr. LB2601.

VIALE-A: Survival by Subgroups

	Aza+Ven, n/N (%)	Aza+Pbo, n/N (%)	HR (95% CI) Aza+Ven vs Aza + Pbo
All subjects	161/286 (56.3)	109/145 (75.2)	0.64 (0.50, 0.82)
Gender			
Female	61/114 (53.5)	41/58 (70.7)	0.68 (0.46, 1.02)
Male	100/172 (58.1)	68/87 (78.2)	0.62 (0.46, 0.85)
Age, yrs			
< 75	66/112 (58.9)	36/58 (62.1)	0.89 (0.59, 1.33)
> 75	95/174 (54.6)	73/87 (83.9)	0.54 (0.39, 0.73)
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)	0.28 (0.12, 0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16, 0.71)
IDH1/2	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. EHA 2019. Abstr. LB2601.

VIALE-A: Response and EFS

	Aza + Ven (n = 286)	Aza + Pbo (n = 145)	*P* value
CR + CRi rate (95% CI), %	66.4 (60.6-71.9)	28.3 (21.1-36.3)	<.001
CR + CRi by start of cycle 2 (95% CI), %	43.4 (37.5-49.3)	7.6 (3.8-13.2)	<.001
CR rate (95% CI), %	36.7 (31.1-42.6)	17.9 (12.1-25.2)	<.001
Transfusion independence* (95% CI), %			
▪ RBC	59.8 (53.9-65.5)	35.2 (27.4-43.5)	<.001
▪ Platelets	68.5 (62.8-73.9)	49.7 (41.3-58.1)	<.001
CR + CRi rate in subgroups (95% CI), %			
▪ *IDH1/2*	75.4 (62.7-85.5)	10.7 (2.3-28.2)	<.001
▪ *FLT3*	72.4 (52.8-87.3)	36.4 (17.2-59.3)	.021
▪ *NPM1*	66.7 (46.0-83.5)	23.5 (6.8-49.9)	.012
▪ *TP53*	55.3 (38.3-71.4)	0	<.001
EFS (95% CI), mo	9.8 (8.4-11.8)	7.0 (5.6-9.5)	<.001

- Median age (range): 76 yrs (49-91)

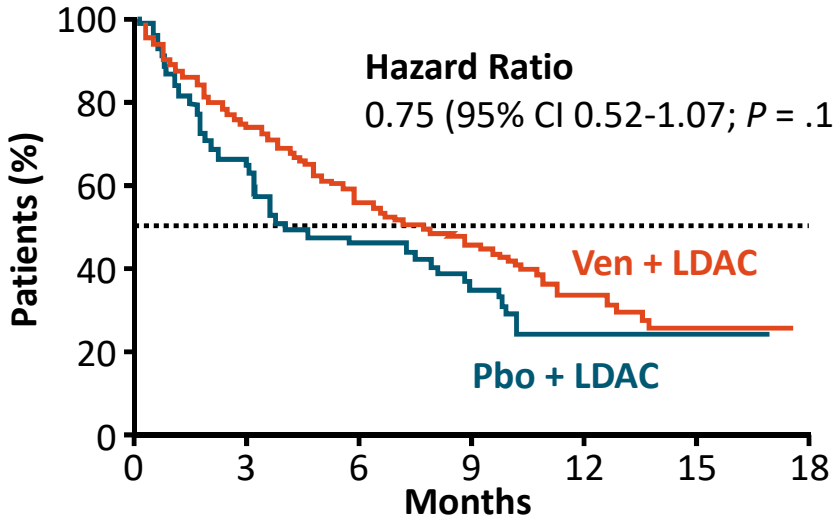
*defined as ≥ 56 days with no RBC or platelet transfusion between first and last day of treatment

DiNardo. EHA 2020. Abstr. LB2601. NCT02993523.

Low-dose Cytarabine ± Venetoclax in AML: Efficacy

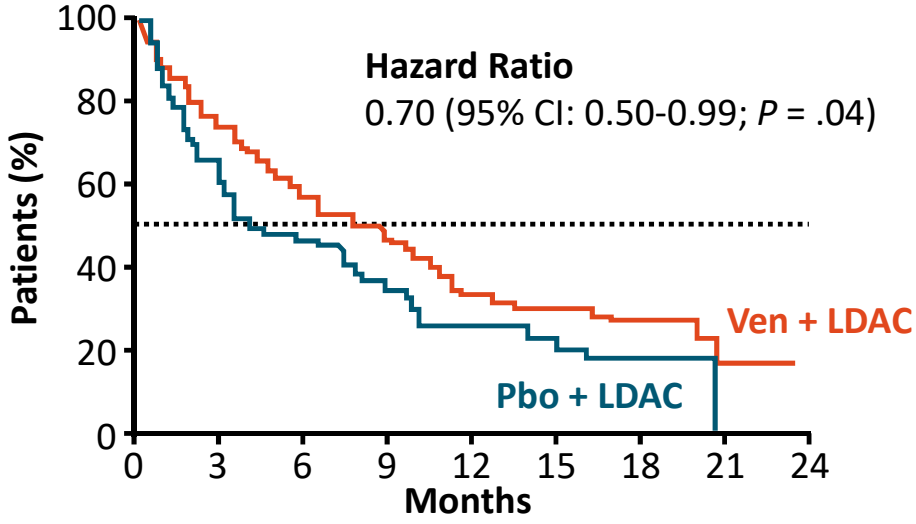
	Response Rate	mOS, m (95% CI)	Transfusion Independence	QoL
VEN + LDAC	48%	8.4 (5.9-10.1)	375	Improved
PBO + LDAC	13%	4.1 (3.1-8.1)	16%	--

OS, Primary endpoint



Ven + LDAC	143	102	61	49	24	6
Pbo + LDAC	68	43	26	18	8	1

OS, +6-month follow-up



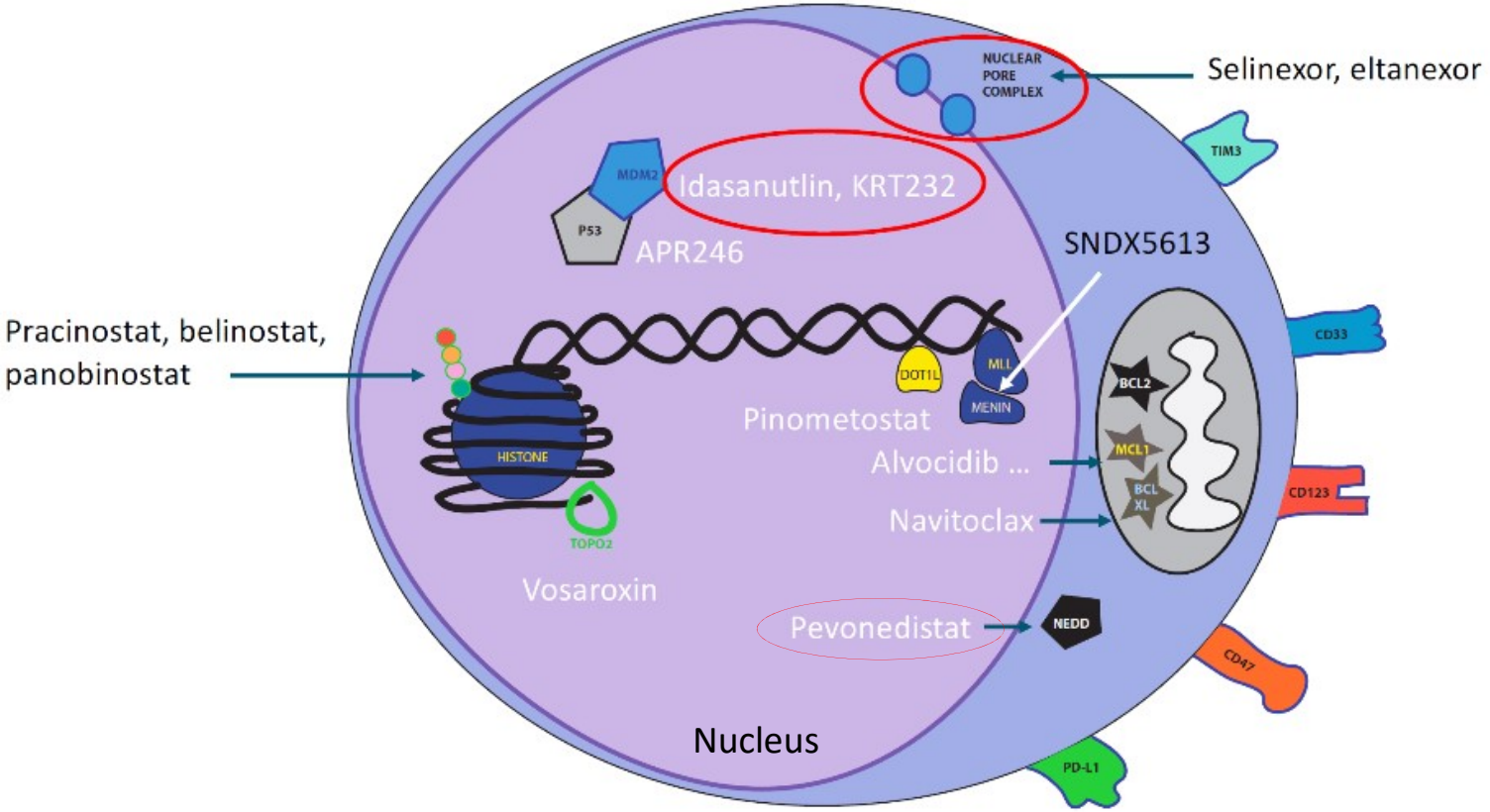
Ven + LDAC	143	103	78	64	35	30	14	3
Pbo + LDAC	68	43	30	22	14	12	6	0

Wei. Blood. 2000;135:2137.

Overview of Presentation

- Review of intracellular targets for investigational small molecules
  - Focus on two example drug classes
  - MDM2, XPO1
- Review of extracellular targets for investigational immune and cellular therapies
  - Example agent: CD47
  - Example class: bispecific T-cell engager (BiTE)
- Review novel combinations of approved drugs under investigation

Intracellular Targets for Investigational AML Therapies



Permission by Dillon

Targeting P53 Dysfunction in AML

Mutations		
TP53 mutated	**Gene therapy**	Gendicine/Advexin ONYX-015
	Vaccinating against p53	P53-SLP INGN-225
	Reactivation of mutant p53	PRIMA-1/APR-246 MIRA-1/3 STIMA-1 CP-31398
TP53 wild-type	**MDM2 (-p53 interaction) inhibitors**	Nutlins/RG7112 MI compounds PXN727/822 JNJ-26854165 RITA

Kojima. Exp Hematol. 2016;44:791.

MDM2 Inhibition in AML

MDM2 modulates p53 activity by:

1. Directly inhibiting p53 transcriptional activity
2. Transporting p53 out of the nucleus
3. Ubiquitinating and tagging p53 for proteasomal degradation

Khurana. Onco Targets Ther. 2019;16:2903.

MIRROS Phase III Study of Idasanutlin: Study Design

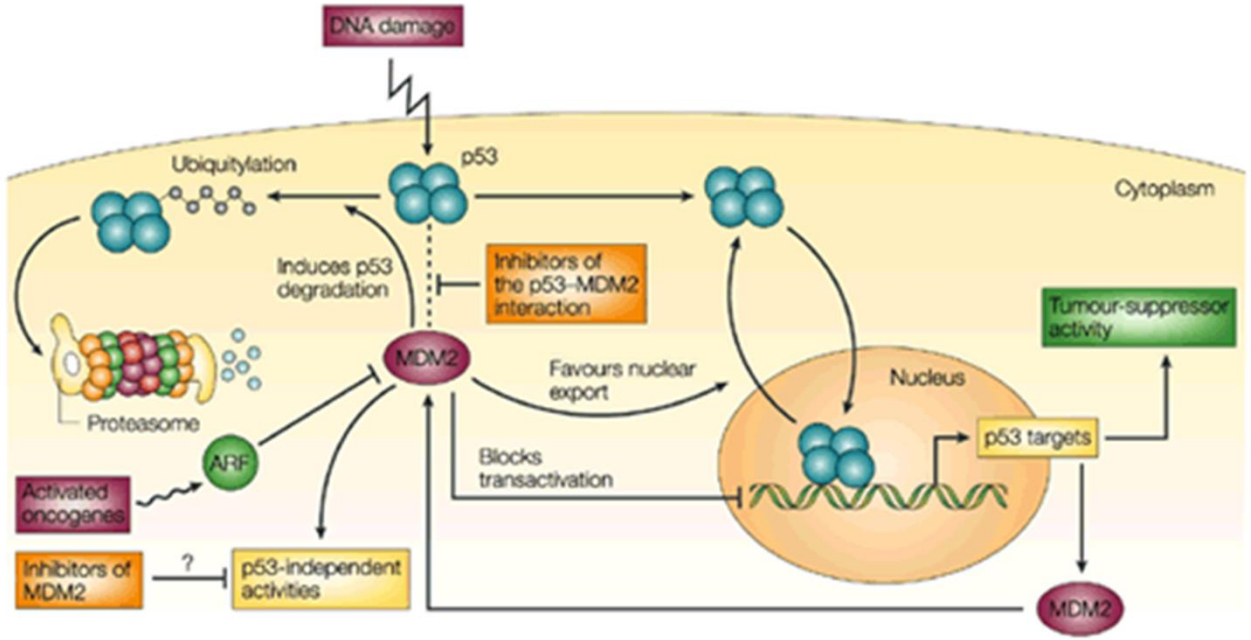
- Phase Ib CR rate 27% (idasanutlin + cytarabine)[1]
- Phase II CR + CRi rate 33% (idasanutlin + venetoclax)[2]

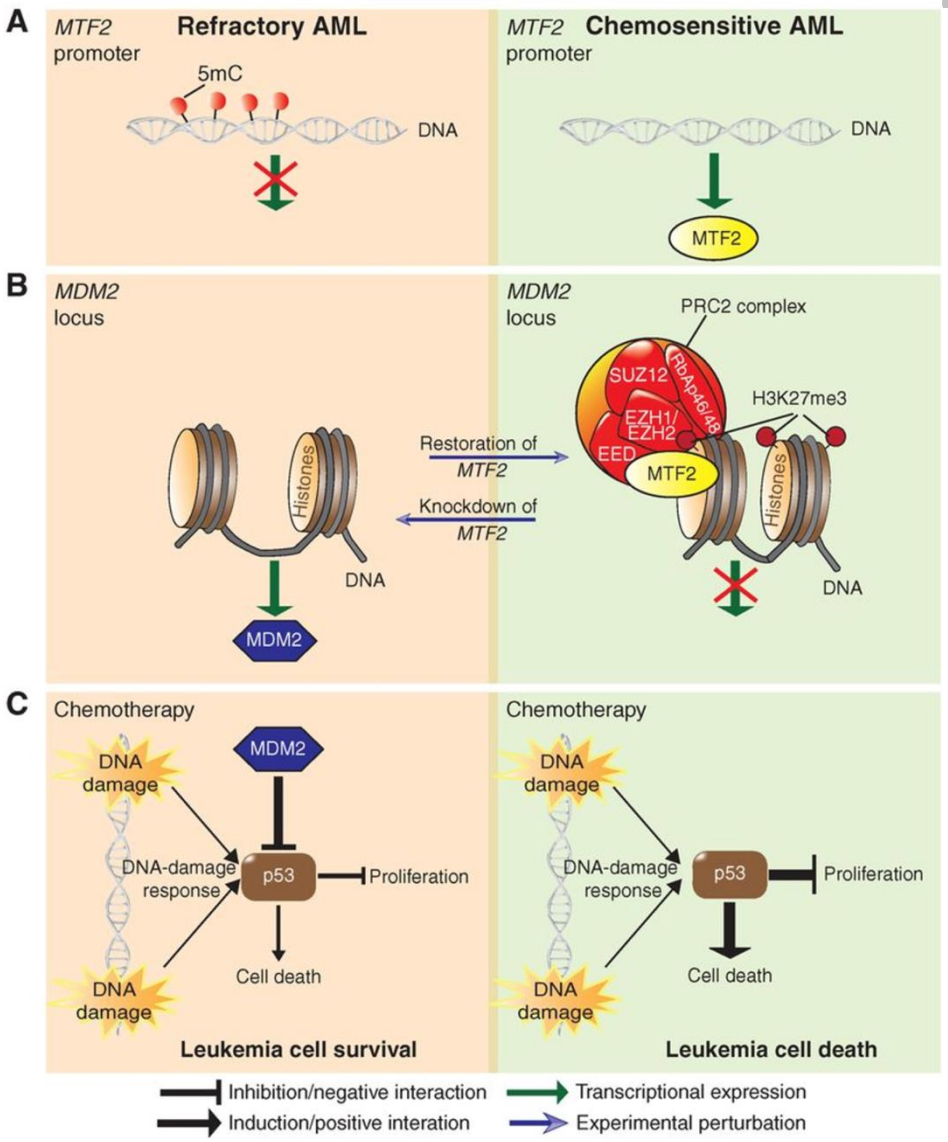
Primary analysis: OS in TP53-WT population

Futility interim analysis: safety and efficacy (120 pts with TP53-WT disease)

1. Martinelli. EHA 2016. Abstr S504. 2. Daver. ASH 2017. Abstr 813. 3. Montesinos. ASCO 2019. Abstr TPS7063

MDM2


DNA damage
p53
Ubiquitylation
Cytoplasm
Induces p53 degradation
Inhibitors of the p53–MDM2 interaction
Tumour-suppressor activity
MDM2
Favours nuclear export
Nucleus
Proteasome
p53 targets
ARF
Blocks transactivation
Activated oncogenes
Inhibitors of MDM2
?
p53-independent activities
MDM2



[redacted]

MTF2 promoter is hypermethylated in MTF2-deficient AMLs -refractory AML

MTF2 mediates silencing of *MDM2* in Chemo AML, whereas refractory, MTF2-deficient AMLs exhibit abundant levels of MDM2.

PRC2-mediated silencing of the *MDM2* locus renders leukemia cells sensitive to Chemo through activation of the p53 pathway in response to DNA damage.

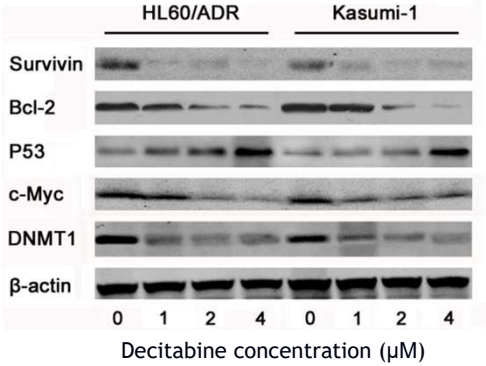
Refractory AML cells resist Chemo-induced DNA damage through MDM2-mediated depletion of p53.

MDM2i renders refractory cells sensitive to chemotherapy.

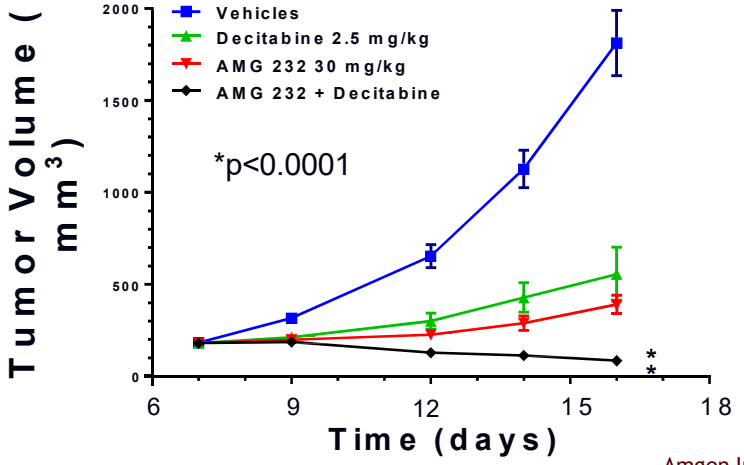
Rationale for the combination of KRT-232 with Decitabine in AML

Agent \ Cell Line	MCF7 (Breast)	RKO (Colon)	KS-1 (GBM)	A427 (NSCLC)	SJSA-1 (Sarcoma)	SW982 (Sarcoma)	MKN45 (Stomach)	NCI-SNU-1 (Stomach)	EOL-1 (AML)	MOLM-13 (AML)	HT-29 (Colon)	PC-3 (Prostate)
AMG 232 x Cisplatin				0.70							0.19	0.48
AMG 232 x Oxaliplatin		0.85									0.08	0.18
AMG 232 x Doxorubicin	4.63								4.37	8.63	1.14	2.14
AMG 232 x Etoposide					2.16	9.05	2.86	1.88			1.92	0.52
AMG 232 x Irinotecan		1.69									0.95	0.67
AMG 232 x Temozolomide			2.61								0.04	0.18
AMG 232 x Cytarabine									6.90	8.70	0.56	1.33
AMG 232 x Decitabine									12.48	14.67	0.07	0.86

Decitabine induces p53 in AML

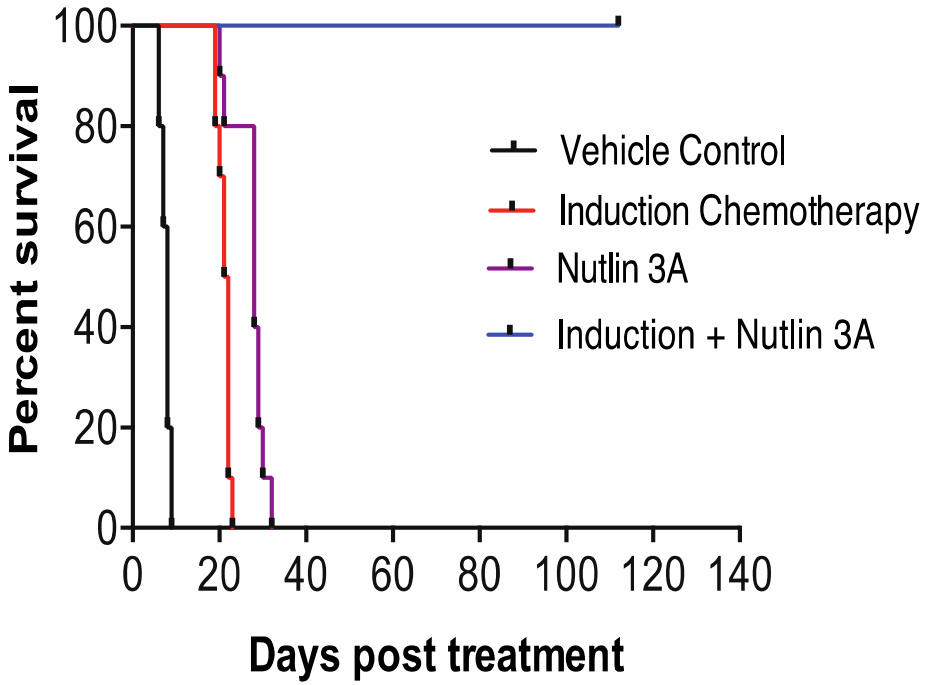


Jiang X, et al *Oncotarget*, 2015



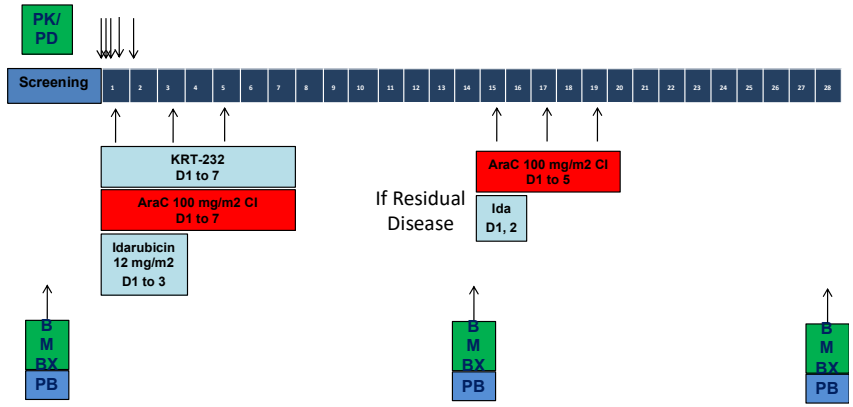
Amgen Inc.

PDX Mice Treated with MDM2 Inhibitor Plus Induction Drugs Survive



PDX Mice Treated with MDM2 Inhibitor Plus Induction Drugs Survive. Kaplan-Meier curve of NSG mice transplanted with MTF2-deficient AML patient BM cells were treated with vehicle control, induction drugs, MDM2 inhibitor Nutlin 3A or induction + Nutlin 3A. n=4 refractory AML samples; n=8 mice per treatment group, n=32 mice total.

Treatment Schema



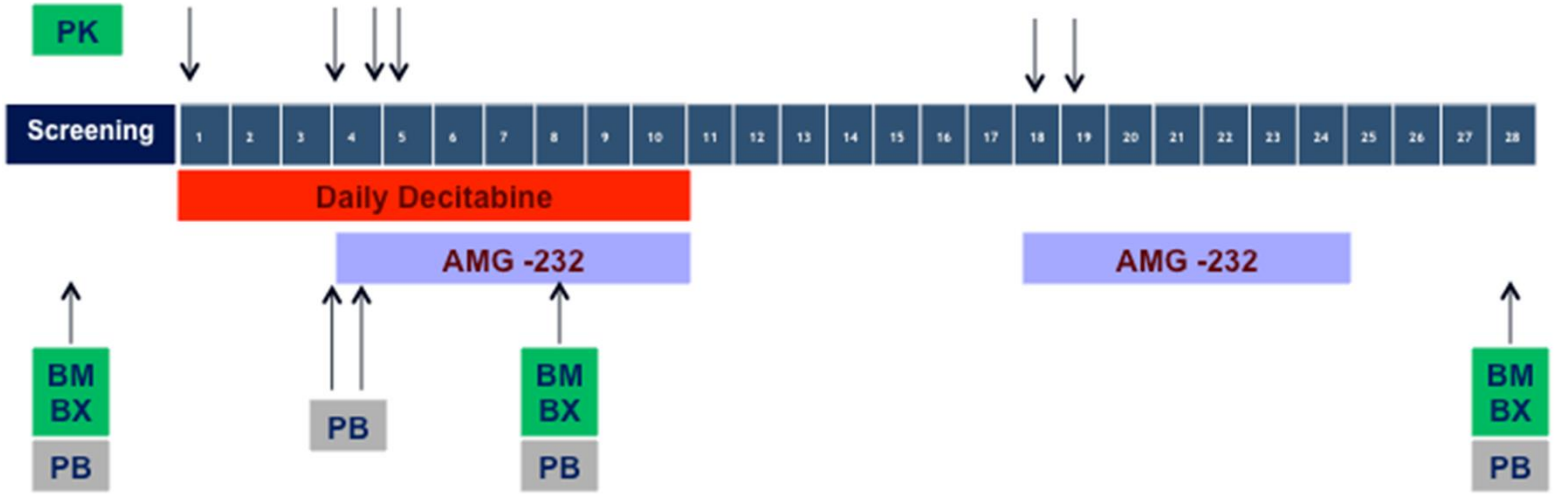
BM Bx = Bone Marrow Biopsy; PB = Peripheral Blood AML Blasts; PK= Pharmacokinetic Sample; PD=Pharmacodynamic Sample.

Dose Escalation Schedule

Dose Level	Dose		
	KRT-232 (AMG 232) (mg; PO)	*Cytarabine* (mg/m^2; IV)*	*Idarubicin* (mg/m^2; IV)*
Level -2	60	200	12
Level -1	90	200	12
Level 1**	120	200	12
Level 2	180	200	12
Level 3	240	200	12
Level 4	300	200	12
Level 5	360	200	12

* Dose rounding per institutional guidelines is allowed.
**Starting Dose Level

A Phase 1B study of KRT-232 in combination with Decitabine in Acute Myeloid Leukemia



Decitabine: 20 mg/m^2/day IV for 10 days per cycle on Days 1 to 10
AMG-232: **PO** Days 4 to 10, 18 to 24

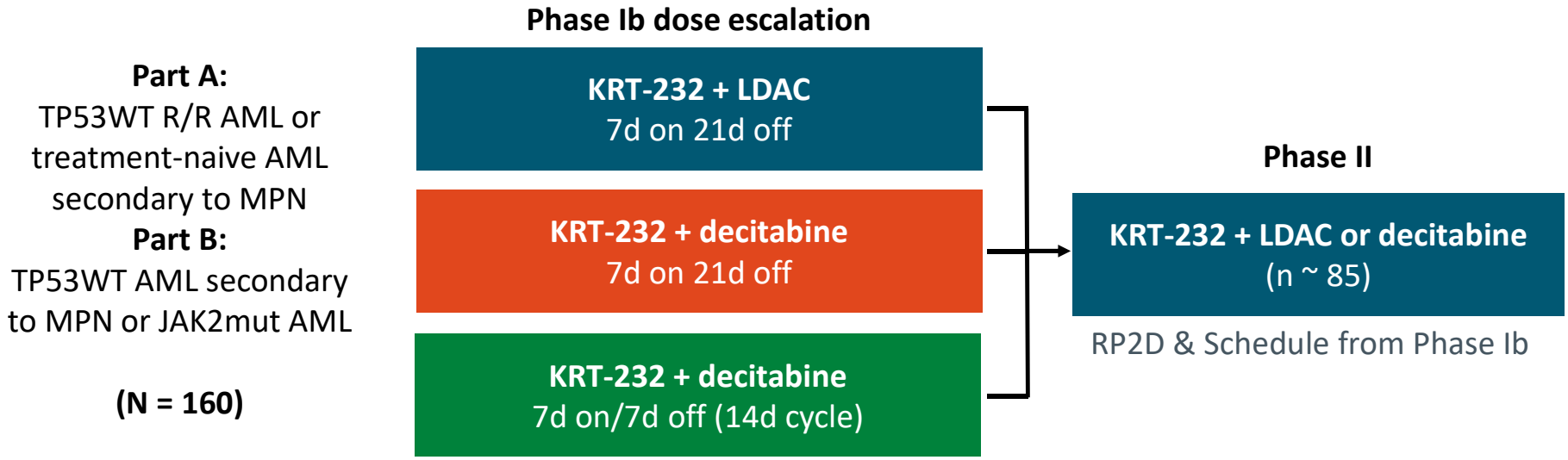
- Repeated treatment cycles until disease progression or unacceptable toxicity

BM Bx = Bone Marrow Biopsy; PB = Peripheral Blood AML Blast

PHI-92: A Phase 1B study of KRT-232 in combination with Decitabine in Acute Myeloid Leukemia

- Cohort 1. 60 mg KRT-232. 5 patients enrolled. 1 CR, 1 MLFS
- Cohort 2. 90 mg KRT-232. 3 patients treated. 2 CRs.
- Cohort 3. 120 mg KRT-232. 3 patients enrolled.
- Cohort 3 180 mg KRT-232 3 patients enrolled 1 PR, 1 MLFS
- Cohort 4 240 mg KRT-232 3 patients enrolled
- Cohort 5 300 mg KRT-232 4 patients enrolled

Phase Ib/II Study of KRT-232 Plus LDAC or Decitabine: Study Design



- Primary endpoint
  - Part A: DLT in combination with LDAC or decitabine
  - Part B: proportion pts achieving CR/CRh
- Secondary endpoints for Part A
  - CR, CRh per 2017 ELN criteria
  - MLFS, CRi, CRc, PR

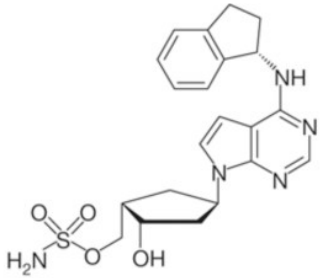
NCT04113616

MLN4924/ Pevonedistat

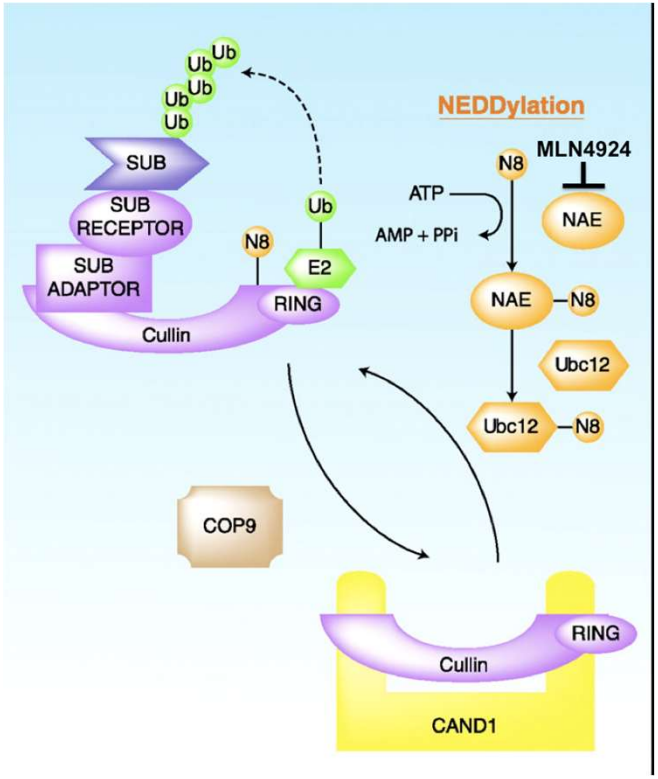
- First-in-class small molecule inhibitor of NEDD8-activating enzyme (NAE), the proximal regulator of the NEDD8 conjugation pathway, developed by Millennium Pharmaceuticals

- Disrupts NEDD8-mediated protein turnover and has demonstrated broad-spectrum anticancer activity in preclinical studies

- Has been evaluated in Phase I clinical trials for patients with advanced solid tumors, MM & lymphomas, and MDS/AML

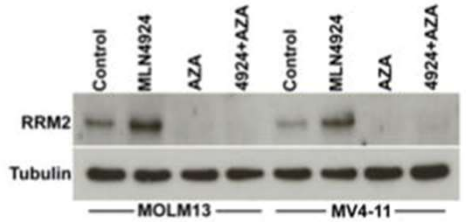


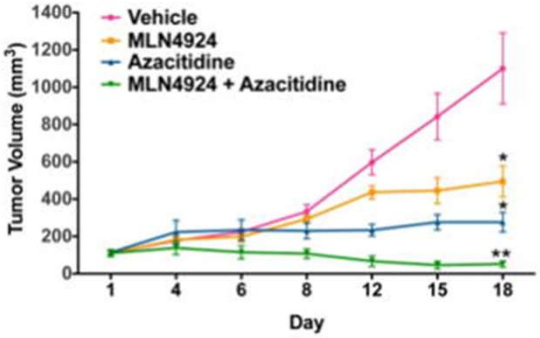
MLN4924



Introduction to Agent: Pevonedistat in R/R and Treatment Naïve AML

- Pevonedistat induces AML cell death (including AML leukemia stem cells) and synergizes with azacitidine in preclinical models[1-4]
- Pevonedistat activity and safety was confirmed in R/R AML (NCT00911066)[5-6]
- Pevonedistat plus azacitidine was studied in unfit older AML patients (NCT01814826)[7-8]
  - RP2D Pev 20mg/m2 IV days 1, 3 and 5 with Aza 75mg/m2 IV for 7 days every 28 days
  - ORR 50%, CR/CRi 39% (not influenced by de novo vs secondary, BM blast count or cytogenetic risk)
  - Med DoR 8.3mo
  - Med OS 7mo and 1yr OS 45%
  - Most common G≥3 AE: anemia (30%), febrile neutropenia (30%), thrombocytopenia (23%), neutropenia (20%), pneumonia (17%)
  - Two subjects with asymptomatic and reversible G4 AST/ALT elevation (8%)
  - No effect of Aza on Pev PK
- **There is a critical unmet need for novel, safe and more effective regimens for R/R AML. The activity of Pev plus Aza in R/R AML is unknown. There is a strong preclinical and clinical rationale for the study of Pev in combination with azacytidine in R/R AML.**





1 Swords et al, Blood 2010.
2 Smith et al, ASH 2011 Abstract 578.
3 Sen et al, ASH 2011 Abstract 1414.
4 Traore et al, EHA 2012 Abstract 1066.
5 Swords et al, BJH 2015.
6 Swords et al, Blood Cancer Journal, 2017.
7 Swords et al, ASH 2016 Abstract 98.
8 Swords et al, Blood 2018.

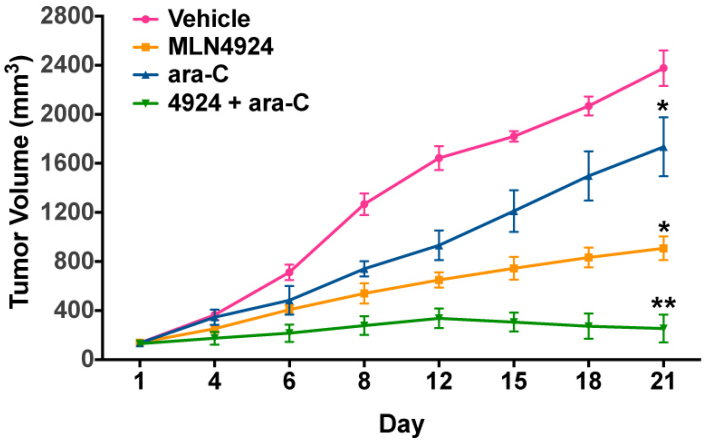
Phase 2: Pev+Aza vs Aza

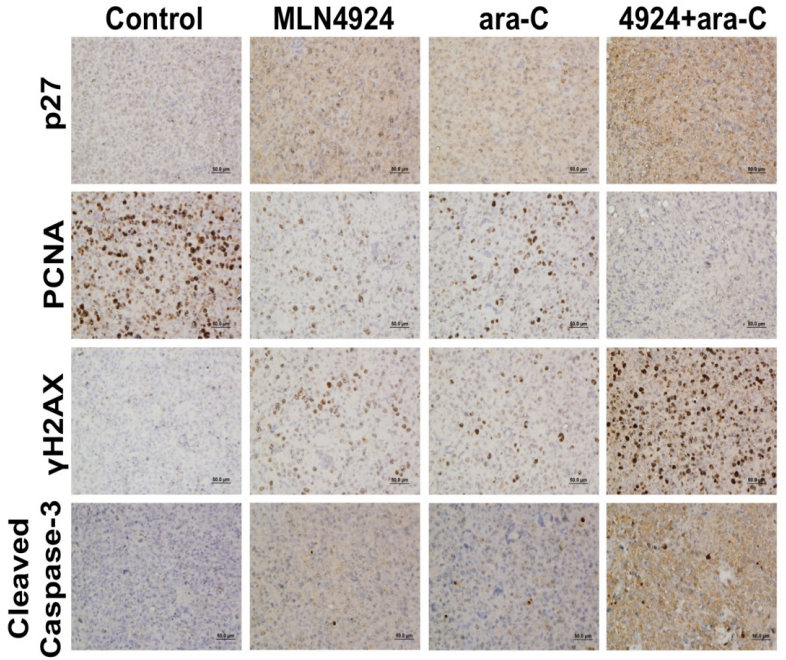
TABLE 1: Outcomes With Pevonedistat Plus Azacitidine in Higher-Risk MDS

Outcome	Pevo/Aza (n = 58)	Aza	HR; *P* Value
Intent-to-Treat			
Event-free survival	21.0 months	16.6 months	0.539; *P* = .045
Overall survival	21.8 months	19.0 months	0.802; *P* = .334
Higher-Risk MDS			
Event-free survival	20.2 months	14.8 months	0.539; *P* = .045
Overall survival	23.9 months	19.1 months	0.701; *P* = .240
ORR	79%	57%	NA
Complete response	52%	27%	NA
Median DOR	34.6 months	13.1 months	NA
Low-Blast AML			
Overall survival	23.6 months	16.6 months	0.494; *P* = .081

AML = acute myeloid leukemia; Aza = azacitidine; DOR = duration of response; HR = hazard ratio; ORR = objective response rate; MDS = myelodysplastic syndromes; NA = not applicable; Pevo = pevonedistat.

In Vivo Benefit of MLN4924/ara-C Combination





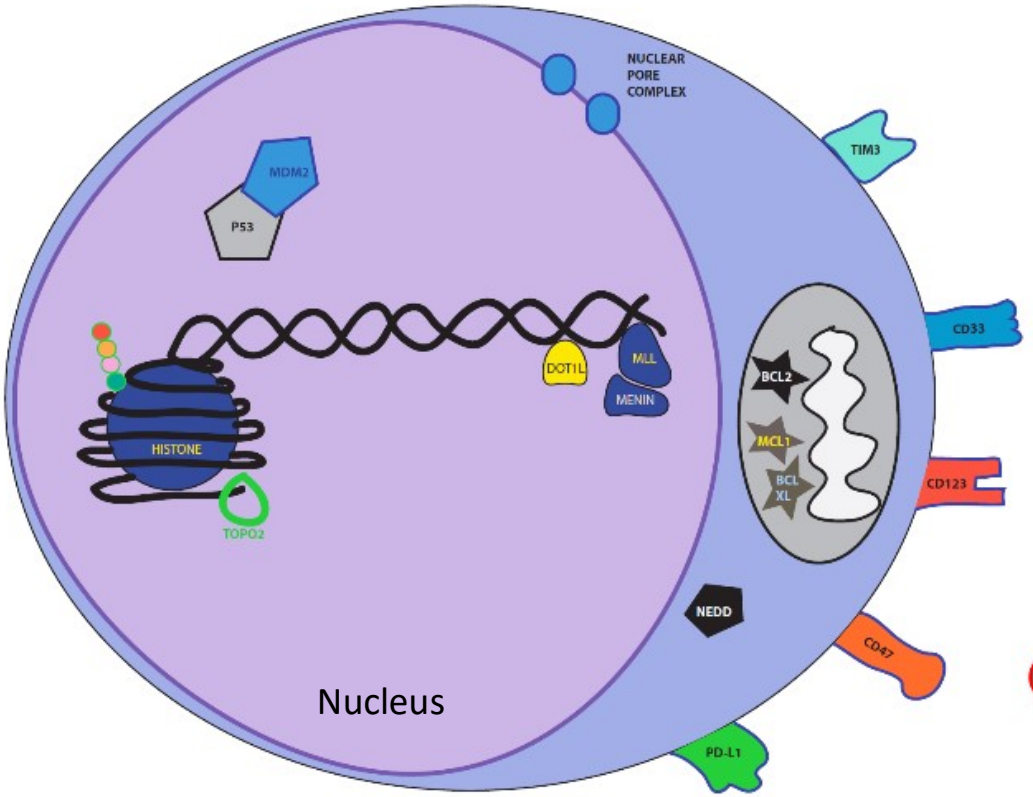
Clin Cancer Res 21:439-47, 2015

Best Overall Response, n (%)	1L AML (n = 15)
ORR	12 (80)
CR	10 (67)
MLFS/marrow CR	2 (13)

Patient Update

Cohort	Age	Cytogenetics	Genomic Alterations	Mid Tx Marrow	Response
Cohort 1 (PEV 15 mg/m²)					
1	61	Normal	TET2, NPM1, FLT3	<5% Blasts	CR $_{MRD-ve}$
2	64	+8	DNMT3A, SF3B1, SRSF2 SH2B3, NF1	<5% Blasts	CR $_{MRD-ve}$
3	60	Normal	IDH2, SRSF2, STAG2, RAD21	<5% Blasts	MLFS, (MRD-ve)
Cohort 2 (PEV 20 mg/m²)					
4	65	+8, t(2,16)	PTPN11	<5% Blasts	CR $_{MRD-ve}$
5	64	NED	ASXL1, IDH2, KRAS, SRSF2	<5% Blasts	MLFS, (MRD-ve)
6	65	NED	MPL	<5% Blasts	Relapse
7	73	Normal	IDH2, ASXL1, and DNMT3A	<5% Blasts	CR $_{MRD-ve}$
8	66	Normal	DNMT3A, NPM1, CEBPA	<5% Blasts	CR $_{MRD-ve}$
9	47	-7, -7q, Loss of MLL,	RUNX1T1	Persistent Disease	Persistent Disease
10	61	Normal	DMT3A	<5% Blasts	CR $_{MRD-ve}$
11	65	Normal	DDX41	<5% Blasts	CR $_{MRD-ve}$
12	61	46,XY,der(10)t(10;11)(p12;q14)[14]/ 46,XY[6] gain of 11q23 (KMT2A) (97.5%)	PICALM-MLL10 Fusion U2AF1 p.(S34F)c.101C>T	Persistent Disease (received re-induction)	CR $_{MRD-ve}$
13	57	Karyotype: 57~72<3n>,X,-X,-X,+1,-2,-3,-4,+5,add(5)(q11.2)x2,+6,-6,-7,+8,+9,-9,+11,der(11;12)(q10;q10),-12,-15,-16,-17,-17,-18,-19,+20,+21,+22,+2-5mar[cp20] - FISH analysis (Genoptix) for MECOM, t(6;9), t(8;21), KMT2A (MLL), t(15;17), and inv(16)/t(16;16): Fish: ABNORMAL results with 6p+, 8q+, 9q+, 11q+, 16p+, 16q- and 21q+.	JAK2 /c.1592A>G; p.H531R /MISSENSE /48% UNCERTAIN TP53 /ALL/ c.638G>C; p.R213P MISSENSE/ 88%	Persistent Disease	Persistent Disease
14	61	Normal	IDH2 (R140Q, MAF = 47.9%), RUNX1 (H404Pfs*196, 46.1%) and STAG2 (Y636Pfs*5, 91.5%)	<5% Blasts	CR $_{MRD-ve}$
15	54	46,XX,t(11;19)(q23.3;p13.3)[17]/47,idem,+8[3].	PTPN11	<5% Blasts	CR $_{MRD-ve}$
16	70	CBFB (16q22), +8			

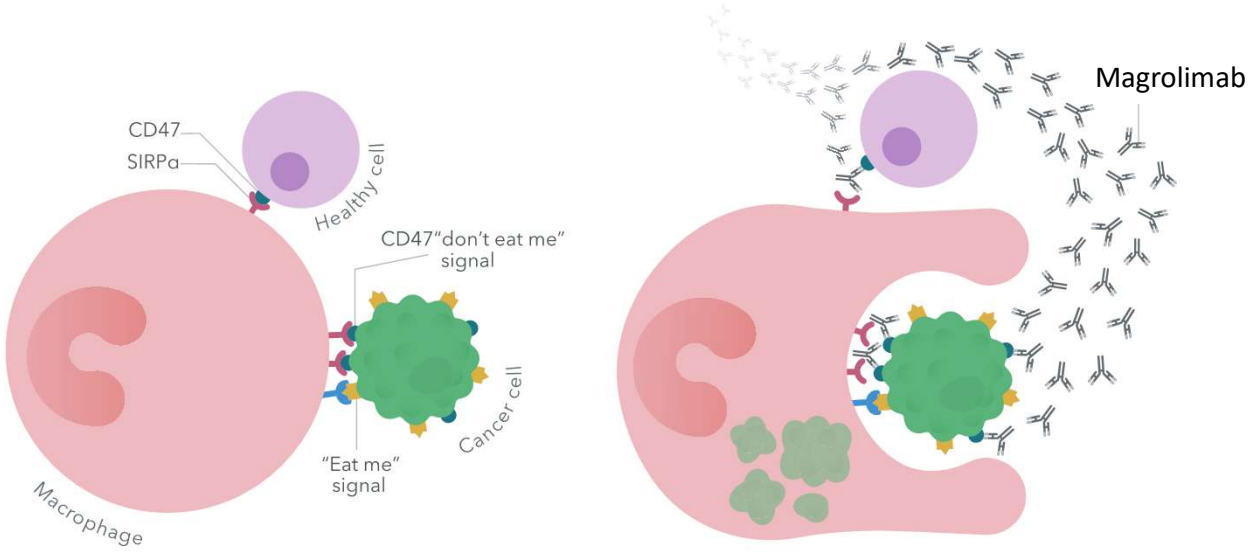
Extracellular Targets for Investigational AML Therapies



Agent	Modality
MBG453	Monoclonal Ab
AMV564	BITE
UCAR123	CAR-T
Magrolimab	Monoclonal Ab
Nivolumab	Monoclonal Ab

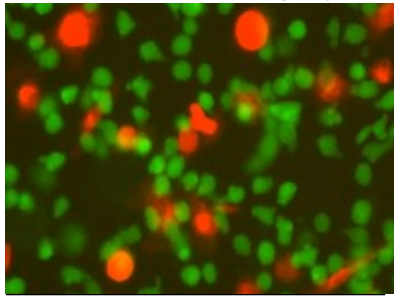
Permission by Dillon

Magrolimab Is a Macrophage Checkpoint Inhibitor

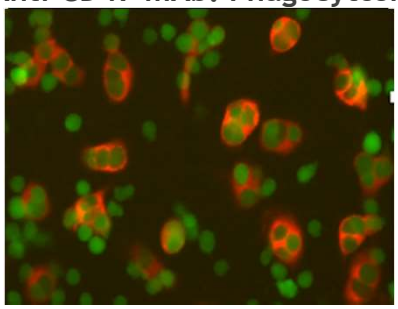


- Magrolimab is an IgG4 anti-CD47 monoclonal antibody that eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dosed

Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis

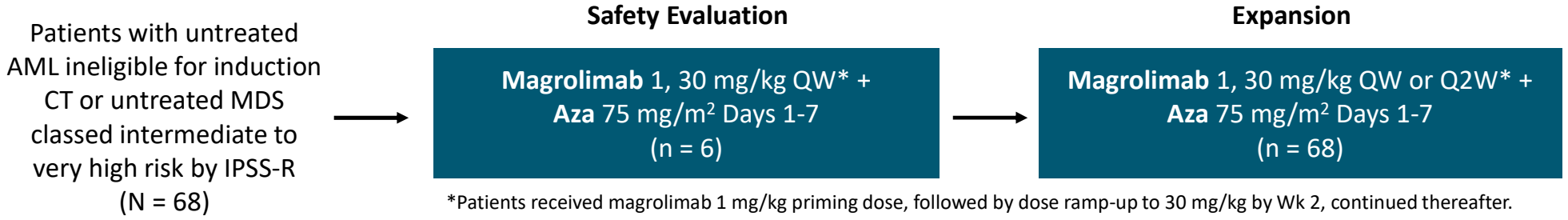


Macrophages Cancer cells

Daver. EHA 2020. Abstr S144.

Magrolimab + Aza in Patients With MDS and AML: Study Design

- Multicenter, single-arm phase Ib study
  - Current analysis reports data from expansion phase



*Patients received magrolimab 1 mg/kg priming dose, followed by dose ramp-up to 30 mg/kg by Wk 2, continued thereafter.

- Primary endpoints: safety, efficacy
- Secondary endpoints: magrolimab PK, PD, immunogenicity
- Exploratory endpoints: CD47 receptor occupancy, immune activity markers, molecular profiling

Daver. EHA 2020. Abstr S144.

Magrolimab + Aza in Patients With MDS and AML: Baseline Characteristics

Characteristic	MDS (n = 39)	AML (n = 29)
Median age, yrs (range)	70 (47-80)	74 (60-89)
ECOG PS, n (%)		
▪ 0	11 (81)	7 (24)
▪ 1	26 (67)	20 (69)
▪ 2	2 (5)	2 (7)
Cytogenetic risk, n (%)		
▪ Favorable	0	0
▪ Intermediate	11 (28)	2 (7)
▪ Poor	25 (64)	21 (72)
▪ Unknown/missing	3 (8)	6 (21)
WHO AML classification, n (%)		
▪ MRC		19 (66)
▪ Recurrent genetic abnormalities	NA	2 (7)
▪ Therapy related		3 (10)
▪ NOS		5 (17)

Characteristic	MDS (n = 39)	AML (n = 29)
WHO MDS classification, n (%)		
▪ RS and single/multilineage dysplasia	1 (3)	NA
▪ Multilineage dysplasia	7 (18)	
▪ RS with multilineage dysplasia	3 (8)	
▪ Excess blasts	22 (56)	
▪ Unclassifiable/unknown/missing	6 (15)	
IPSS-R (MDS), n (%)		
▪ Intermediate	13 (33)	NA
▪ High	19 (49)	
▪ Very high	6 (15)	
▪ Unknown/missing	1 (3)	
Therapy-related MDS, n (%)	12 (31)	NA
▪ Unknown/missing	1 (3)	
TP53 mutation, n (%)	5 (13)	13 (45)

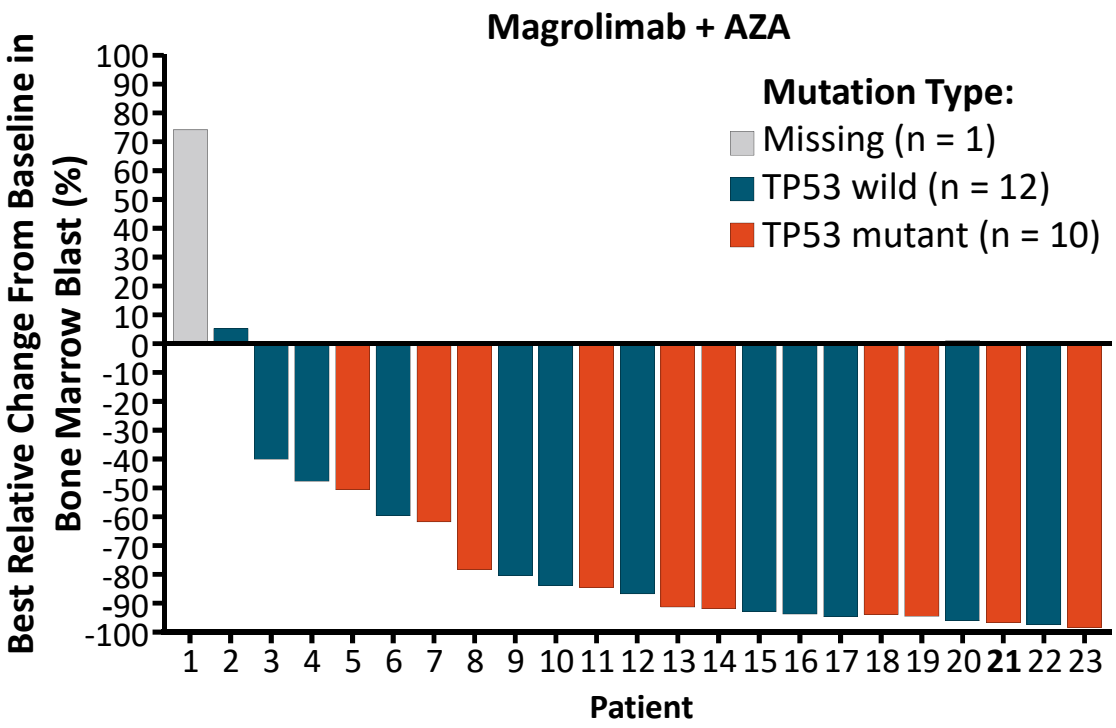
Sallman. ASCO 2020. Abstr 7507.

AZA + MAGRO: Response

Best Overall Response, n (%)	1L AML (n = 25)
ORR	16 (64)
CR	10 (40)
CRi	4 (16)
PR	1 (4)
MLFS/marrow CR	1 (4)
SD	8 (32)
PD	1 (4)

Response per 2017 AML ELN criteria

Pts with ≥1 post-treatment response shown

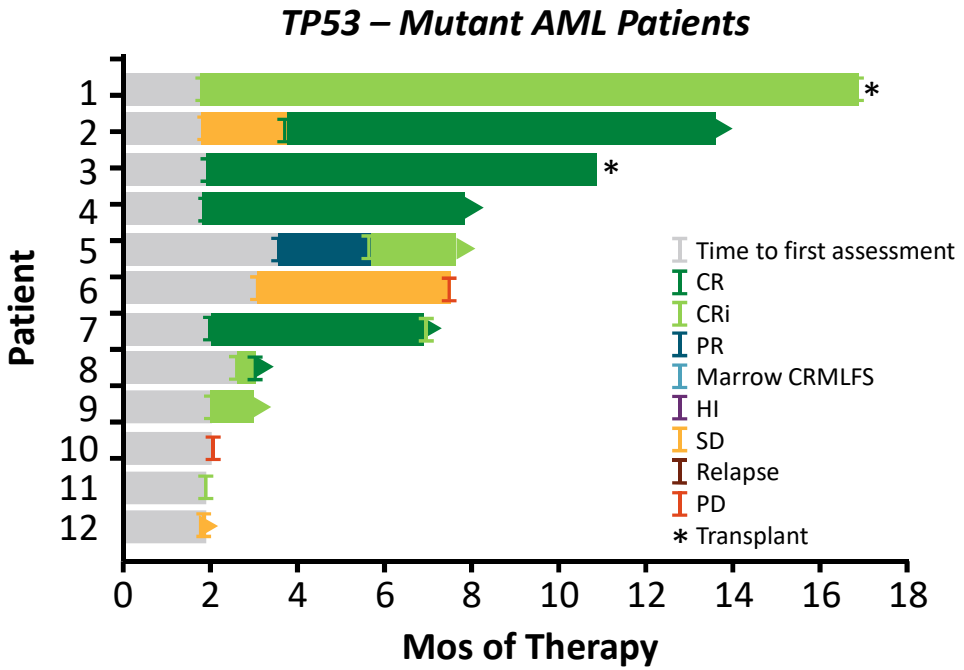


< 5% blasts imputed as 2.5%. Two patients not shown due to missing values.

AZA + MAGRO: Response in Patients With TP53 Mutations

Outcome	AML *TP53* Mutant (n = 12)
ORR, n (%)	9 (75)
CR, n (%)	5 (42)
CRi/marrow CR, n (%)	4 (33)
Complete cytogenetic response, n/N (%)*	4/8 (50)
MRD negativity in responders, n/N (%)	4/9 (44)
Median DoR, mos	NR (0.03+ to 15.1+)
6-mo survival probability, %	91
Median follow-up, mos (range)	8 (1.9 to 16.9)

*Responding pt with abnormal cytogenetics at baseline

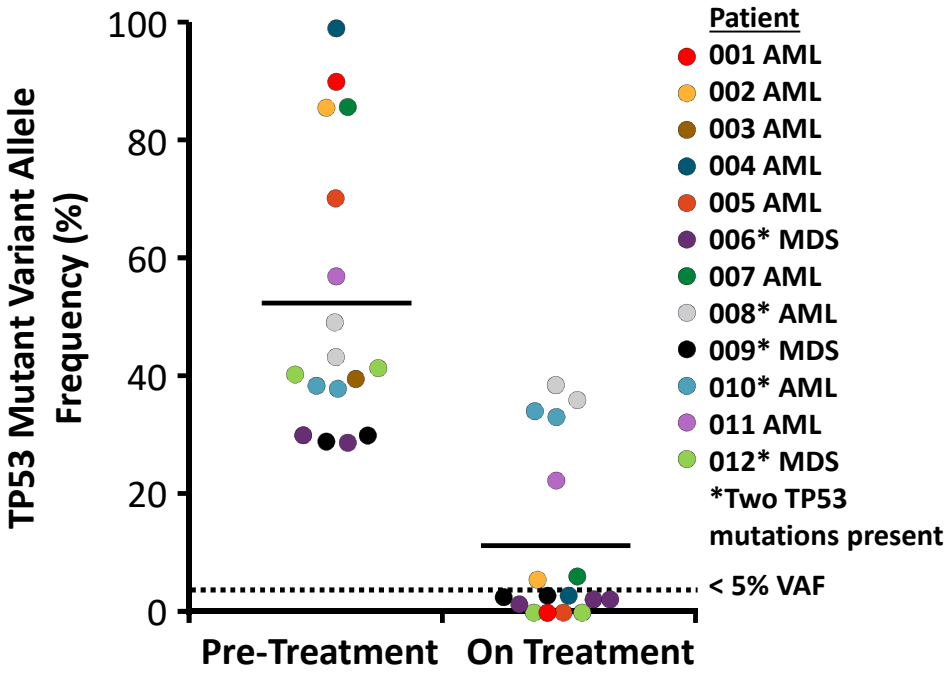


- High response rate with magrolimab + AZA; estimated 6-mo survival of 91%
- Median DoR and OS not yet reached

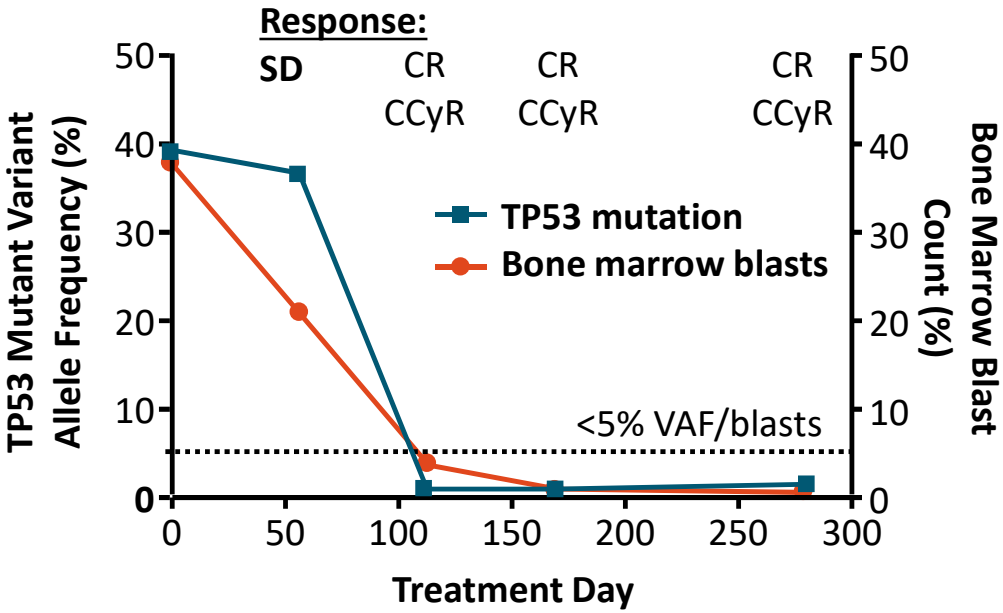
Daver. EHA 2020. Abstr S144.

MRD-reduction in Patients With *TP53* Mutations

***TP53* Mutation Burden on Treatment**



65F therapy-related, complex karyotype, and *TP53* mutant AML: Achieved CR, CyCR, clearance of *TP53* mutations at Cycle 5 and ongoing



Patient data available for analysis. **Best overall reduction is shown. NGS data shown.**

Daver. EHA 2020. Abstr S144.

CyCr: complete cytogenetic response

BiTE Antibodies in AML: Mechanism of Action and Targets

Target	Agent
CD33	AMG330
	AMG673
CD123	**Flotetuzumab**
FLT3	AMG427

Einsele. Cancer. 2020;126:3192. Uy. ASH 2019. Abstr 733.

Summary

- Recent flurry of new drug approvals - treatment landscape for MDS acute myeloid leukemia has expanded
- New questions about how to incorporate those drugs into patient care.
- Novel and targeted agents, many specifically going after mutational by products, are yielding some great results and raising hopes for better survival outcomes.