Kevin Kelly, MD, PhD

Myelodysplastic Syndromes and Acute Myeloid Leukemia

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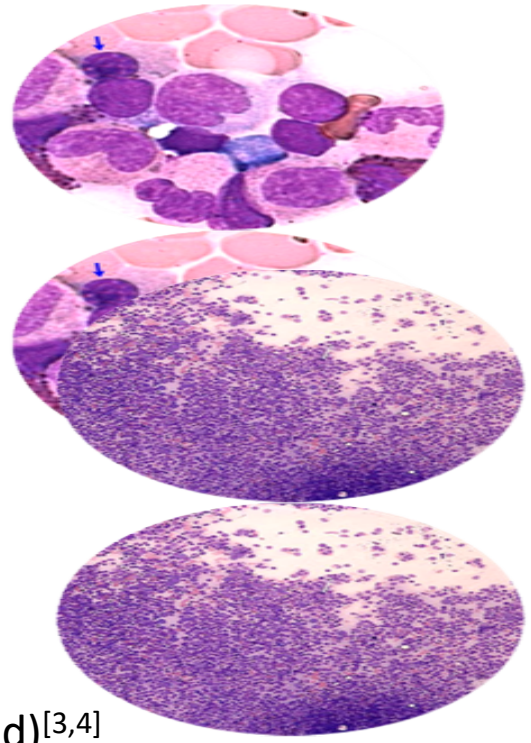
14th Annual California Cancer Conference Consortium
August 17th, 2019

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.

IPSS: A Tool for Risk Stratification of MDS

Prognostic Variable	Score Value				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts, %	< 5	5-10	--	11-20	21-30
Karyotype*	Good	Intermediate	Poor	--	--
Cytopenias†	0/1	2/3	--	--	--

Prognostic Variable	Total Score					
	0	0.5	1.0	1.5	2.0	≥ 2.5
Risk	Low	Intermediate I		Intermediate II		High
Median survival, yrs	5.7	3.5		1.2		0.4

*Good = normal, -Y, del(5q), del(20q); intermediate = other karyotypic abnormalities; poor = complex (≥ 3 abnormalities) or chromosome 7 abnormalities.
†Hb < 10 g/dL; ANC < 1500/μL; platelets < 100,000/μL.

Greenberg. Blood. 1997;89:2079.

Revised IPSS: Prognostic Values and Risk Categories

Prognostic Variable	Prognostic Score Value						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics	Very good	--	Good	--	Intermediate	Poor	Very poor
BM blast, %	≤ 2	--	> 2 to < 5	--	5-10	> 10	--
Hemoglobin, g/dL	≥ 10	--	8 to < 10	< 8	--	--	--
Platelets, x 10^9/L	≥ 100	50 to < 100	< 50	--	--	--	--
ANC, x 10^9/L	≥ 0.8	< 0.8	--	--	--	--	--

Risk	Score
Very low	≤ 1.5
Low	> 1.5 to 3.0
Intermediate	> 3.0 to 4.5
High	> 4.5 to 6.0
Very high	> 6

Greenberg. Blood. 2012;120:2454.

Somatic Mutations in MDS Predict Prognosis Independent of the IPSS-R

- Almost 80% of MDS patients carry somatic gene mutations[1]
- MDS-associated somatic mutations carry prognostic significance, independent of IPSS-R[2]
  - Adverse: *TP53, RUNX1, EZH2, NRAS, ASXL1, IDH2, etc*
  - Favorable: *SF3B1*
  - Prognostic value of individual genes may vary by clinical context and in different combinations of multiple mutations

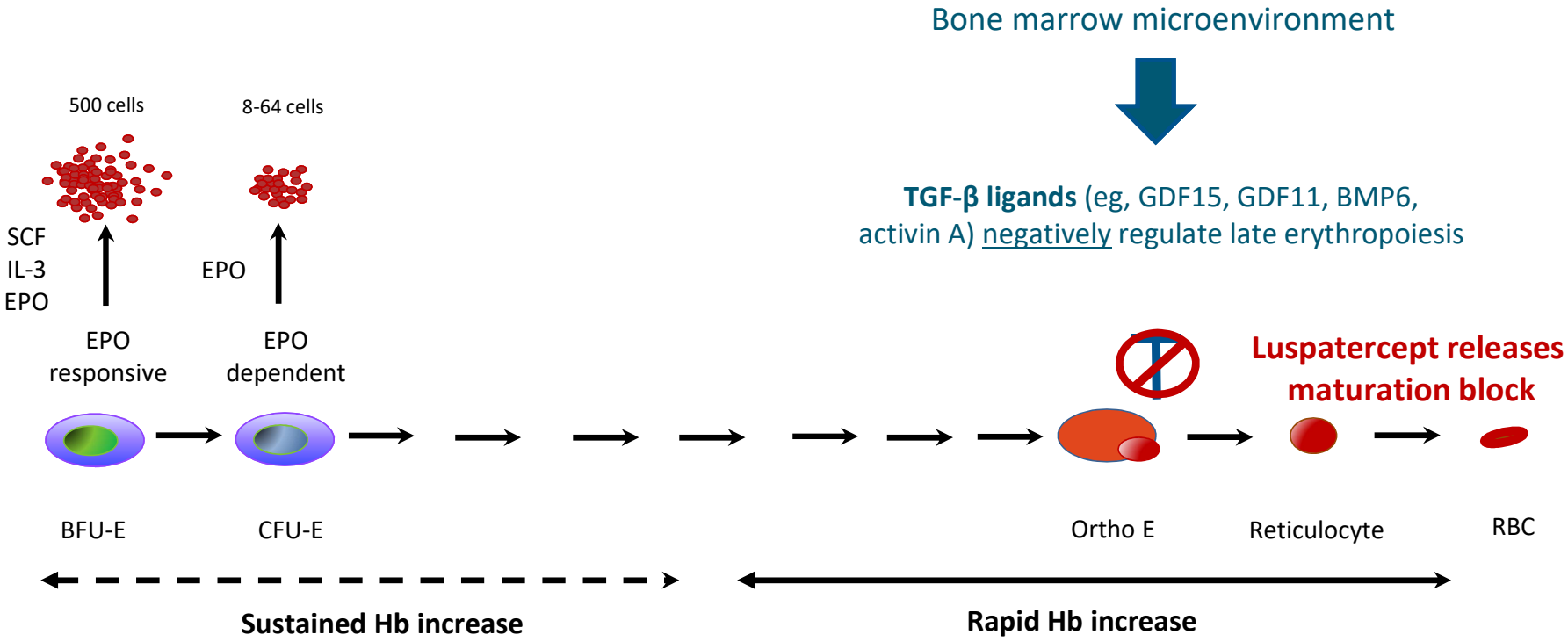
1. Papaemmanuil. Blood. 2013;122:3616. 2. Bejar. ASH 2015. Abstr 907.

Management of Patients With Lower-Risk MDS

Anemia Management in Lower-Risk MDS

- With del(5q)
  - Lenalidomide
- Without del(5q) + low serum EPO level and light transfusion burden
  - ESA followed by lenalidomide ± EPO or azacitidine
- Without del(5q) + high serum EPO level and heavy transfusion burden
  - Lenalidomide ± EPO or azacytidine for older patients
  - IST (ATG + cyclosporin A) for younger patients

Excess Smad2/3 Signaling Suppresses Late-Stage RBC Maturation in MDS

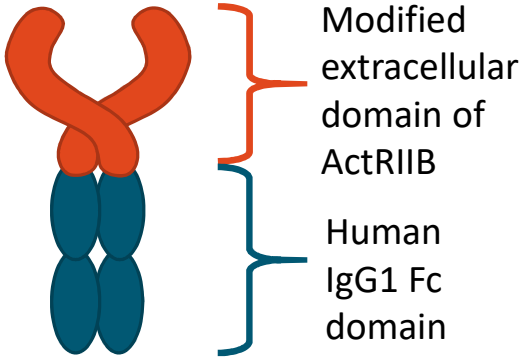


Zhou. Blood. 2008;112:3434.

Luspatercept: Mechanism of Action

- Luspatercept is an investigational first-in-class erythroid-maturation agent
- It neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models[1]
- In a phase II study in lower-risk non-del(5q) MDS, luspatercept yielded a high frequency of transfusion reduction or RBC-TI in patients with ring sideroblasts vs other subtypes[2]

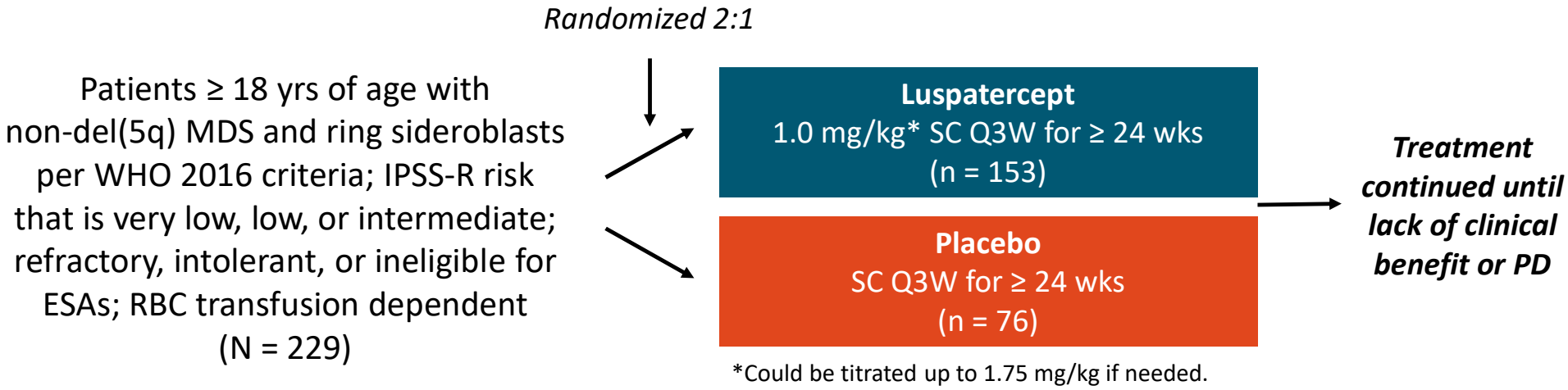
Luspatercept
ActRIIB/IgG1 Fc recombinant fusion protein



1. Suragani. Nat Med. 2014;20:408. 2. Platzbecker. Lancet Oncol. 2017;18:1338.

Phase III MEDALIST Trial of Luspatercept vs Placebo in Lower-Risk Non-del(5q) MDS

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



- Primary endpoint: RBC TI for ≥ 8 wks between Wk 1 and Wk 24
- Secondary endpoints: RBC TI for ≥ 12 wks between Wk 1 and Wk 24, modified hematologic improvement–erythroid response per IWG 2006 criteria, DoR, Hb change from baseline

Fenaux. ASH 2018. Abstr 1.

MEDALIST: Efficacy

Outcome, %	Luspatercept (n = 153)	Placebo (n = 76)	*P* Value
RBC TI ≥ 8 wks in Wks 1-24	37.9	13.2	< .0001
RBC TI ≥ 12 wks in Wks 1-24	28.1	7.9	.0002
RBC TI ≥ 12 wks in Wks 1-48	33.3	11.8	.0003
mHI-E* ≥ 8 wks in Wks 1-24	**52.9**	**11.8**	**< .0001**
▪ Reduction of ≥ 4 RBC units/8 wks	48.6	14.3	
▪ Hb increase of ≥ 1.5 g/dL	63.0	5.0	
mHI-E* ≥ 8 wks in Wks 1-48	**58.8**	**17.1**	**< .0001**
▪ Reduction of ≥ 4 RBC units/8 wks	54.2	21.4	
▪ Hb increase of ≥ 1.5 g/dL	69.6	5.0	

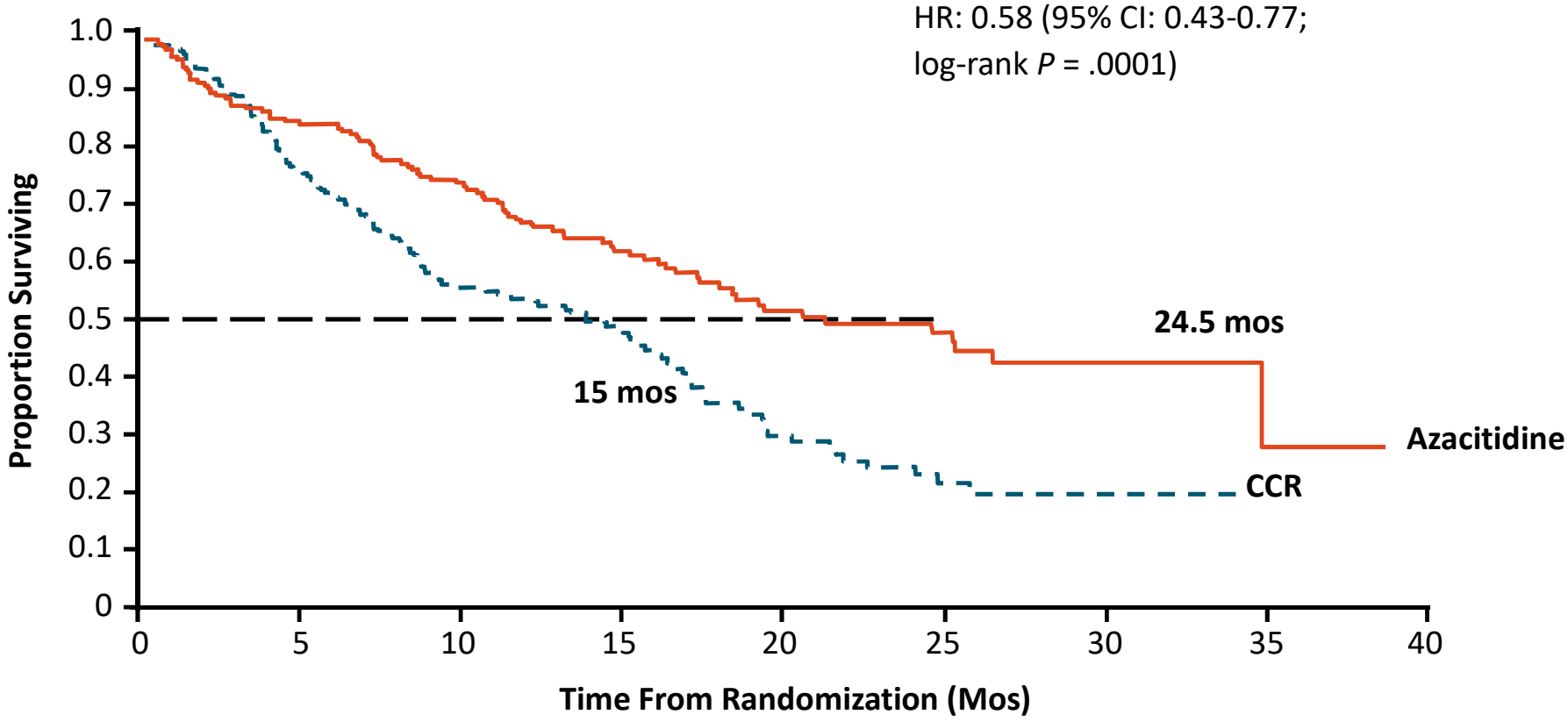
*Defined as transfusion reduction of ≥ 4 units/8 wks or mean Hb increase ≥ 1.5 g/dL/8 wks in absence of transfusions

- Among primary endpoint responders, the median duration of RBC TI response was 30.6 wks in the luspatercept arm vs 13.6 wks in the placebo arm

Fenaux. ASH 2018. Abstr 1.

Management of Patients With Higher-Risk MDS

AZA-001 Trial: Azacitidine Significantly Improves OS in Higher-Risk MDS



Fenaux. Lancet Oncol. 2009;10:223.

Phase II Trial of Immune Checkpoint Inhibitors in MDS

- Exploratory phase II basket trial*

Patients ≥ 18 yrs of age with WHO MDS, untreated or HMA failure; acceptable PS, hepatic, and renal function; no prior inflammatory or autoimmune disease (N = 76†)

HMA failure

- **Nivolumab** 3 mg/kg IV Q2W‡ (n = 15)
- **Ipilimumab** 3 mg/kg IV Q3W‡ (n = 20)

Untreated

- **5-azacitidine** 75 mg/m^2 IV x 5 days Q28d + **Nivolumab** 3 mg/kg IV Days 6, 20 (n = 20)
- **5-azacitidine** 75 mg/m^2 IV x 5 days Q28d + **Ipilimumab** 3 mg/kg IV Days 6 (n = 21)

Stopping rules for toxicity and response

Primary endpoints:

- ORR (CR + PR + HI) in patients with HMA failure
- ORR in untreated patients

*Data for 2 cohorts (ipilimumab + nivolumab and 5-azacitidine + ipilimumab + nivolumab) not included in this analysis. †Maximum 20 patients/cohort. ‡5-azacitidine added back if no response after 6 cycles of ICI.

Garcia-Manero. ASH 2018. Abstr 465.

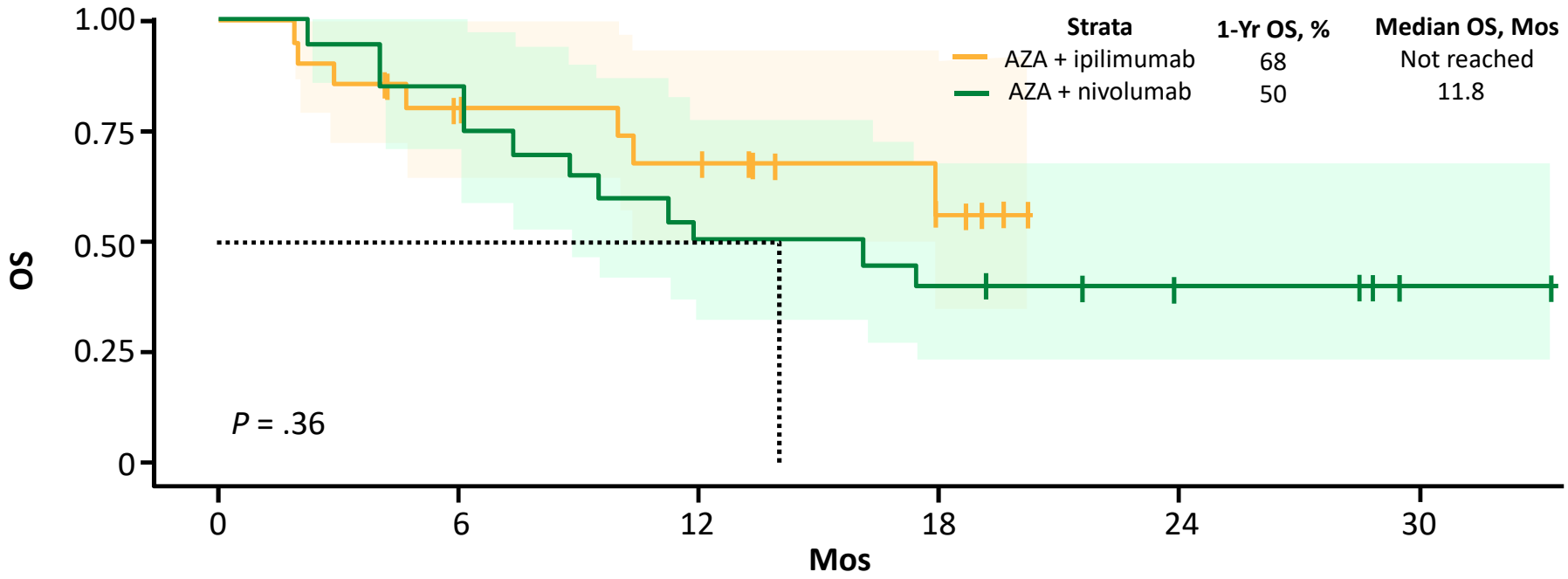
Checkpoint Inhibitors in MDS: Response

Response, n (%)	Frontline		HMA Failure	
	Nivo + AZA (n = 20)	Ipi + AZA (n = 21)	Nivo (n = 15)	Ipi (n = 20)
ORR	14 (70)	13 (62)	0	6 (30)
CR	8 (40)	3 (14)	0	0
mCR + HI	2 (10)	0	0	1 (5)
mCR	3 (15)	7 (33)	0	3 (15)
HI	1 (5)	3 (14)	0	3 (15)
SD	0	1 (5)	0	0
NR	5 (25)	5 (24)	15 (100)	13 (65)

- 3 patients were not evaluable
- Median number of cycles: 4 (range: 1-29)
- Median number of cycles to response: 3 (range: 1-15)

Garcia-Manero. ASH 2018. Abstr 465.

Checkpoint Inhibitors in MDS: OS in Untreated Patients

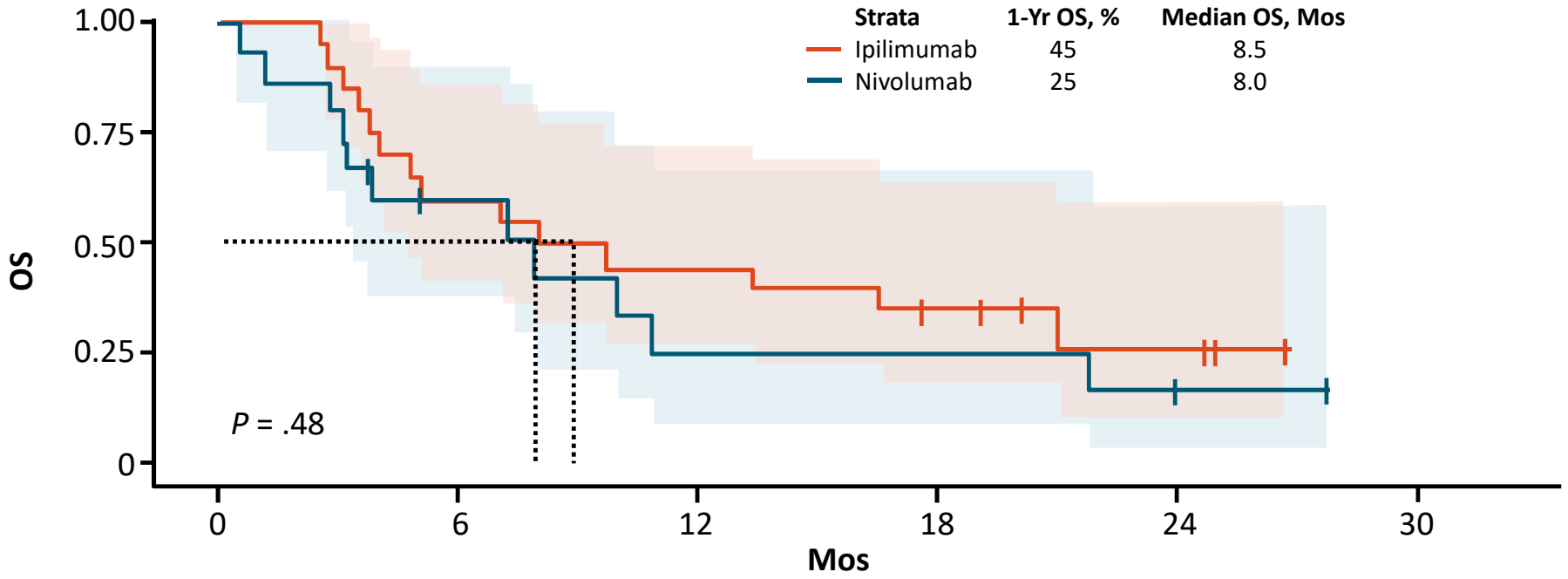


Patients at Risk, n

AZA + ipilimumab	21	14	11	4	0	0
AZA + nivolumab	20	17	10	8	4	1

Garcia-Manero. ASH 2018. Abstr 465.

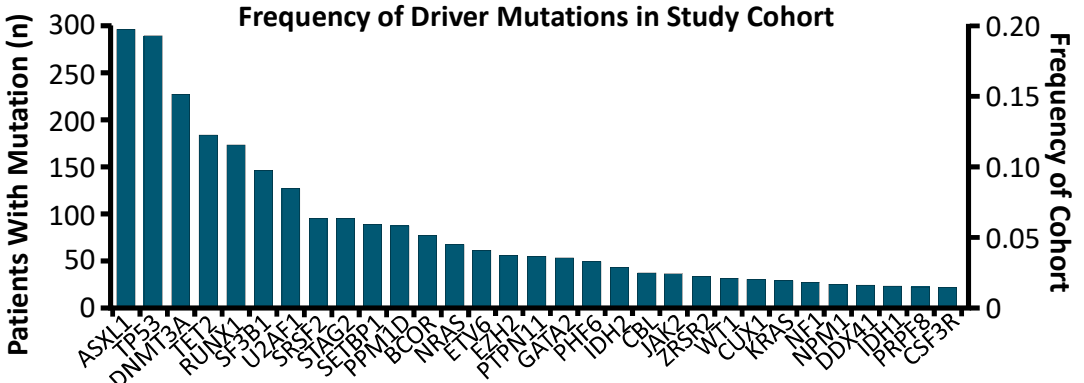
Checkpoint Inhibitors in MDS: OS after HMA Failure

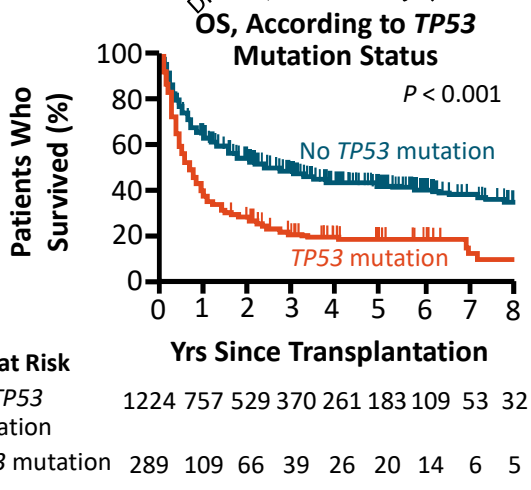


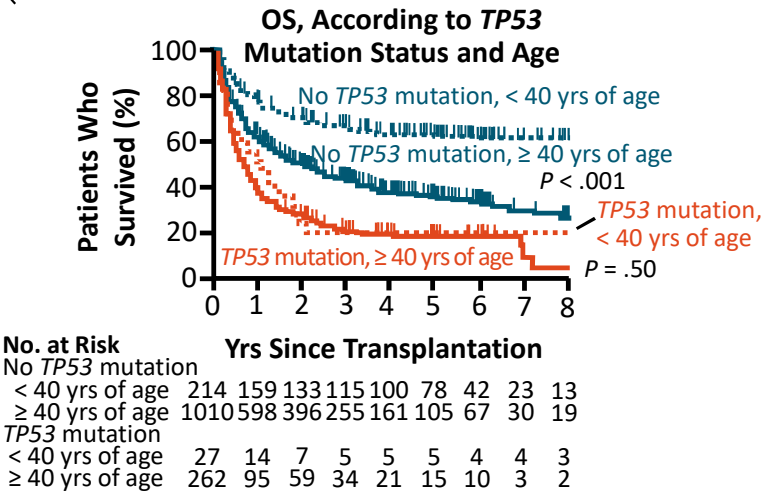
Garcia-Manero. ASH 2018. Abstr 465.

TP53 Mutation Is Associated With Inferior OS Overall and Post AlloSCT in Patients With MDS[1,2]

Risk Factor	HR (95% CI)	*P* Value
Age ≥ 55 yrs vs < 55 yrs	1.81 (1.20-2.73)	.004
IPSS risk group		
▪ Intermediate 1 vs low	2.29 (1.69-3.11)	< .001
▪ Intermediate 2 vs low	3.45 (2.42-4.91)	< .001
▪ High vs low	5.85 (3.63-9.40)	< .001
Mutational status		
▪ *TP53*+ vs *TP53*-	2.48 (1.6-3.84)	< .001
▪ *EZH2*+ vs *EZH2*-	2.13 (1.36-3.33)	< .001
▪ *ETV6*+ vs *ETV6*-	2.04 (1.08-3.86)	.03
▪ *RUNX1*+ vs *RUNX1*-	1.47 (1.01-2.15)	.047
▪ *ASXL1*+ vs *ASXL1*-	1.38 (1.00-1.89)	.049







1. Bejar. NEJM. 2011;364:2496.
2. Lindsley. NEJM. 2017;376:536.

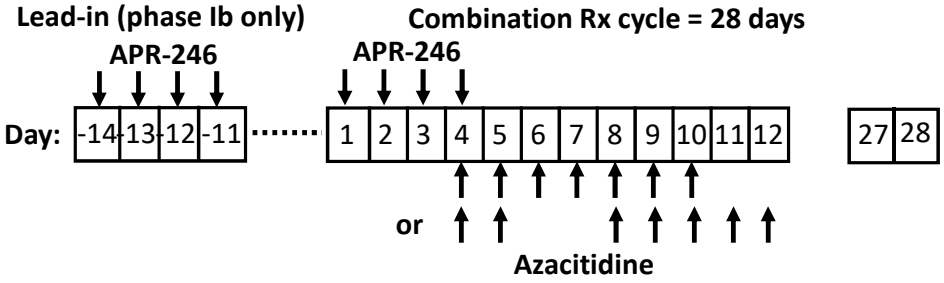
Phase Ib/II Trial of APR-246 and Azacitidine in *TP53*-Mutated MDS and AML

- *TP53*-mutated (m*TP53*) HMA-naive MDS and AML (≤ 30% blasts)

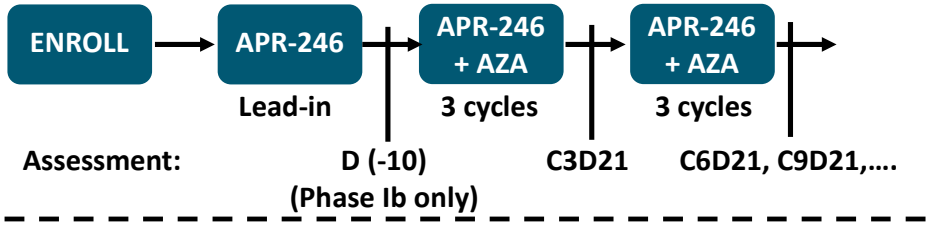
Dosing

Drug	Dose	Admin.	Duration
APR-246	PhIb: 50/75/100 mg/kg LBM PhII: 4500 mg fixed dose	IV	6 hrs
Azacitidine	75 mg/m^2	SC (or IV)	

Dosing Schedule



Assessment Schedule

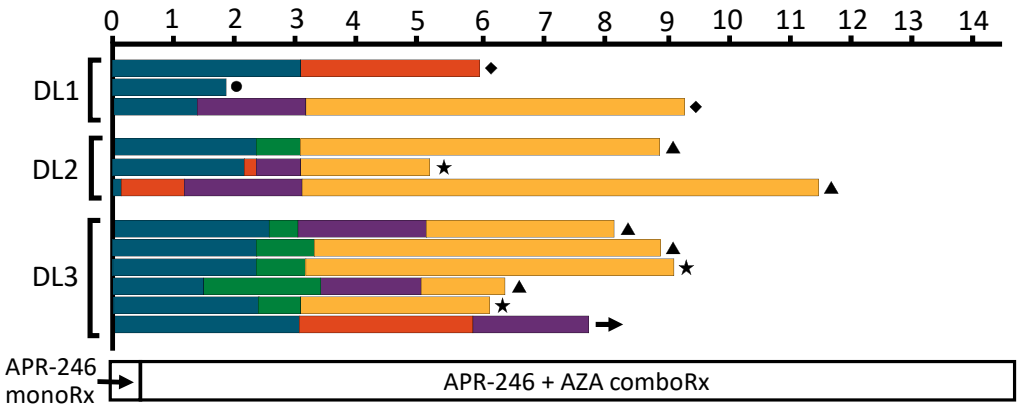


Endpoints

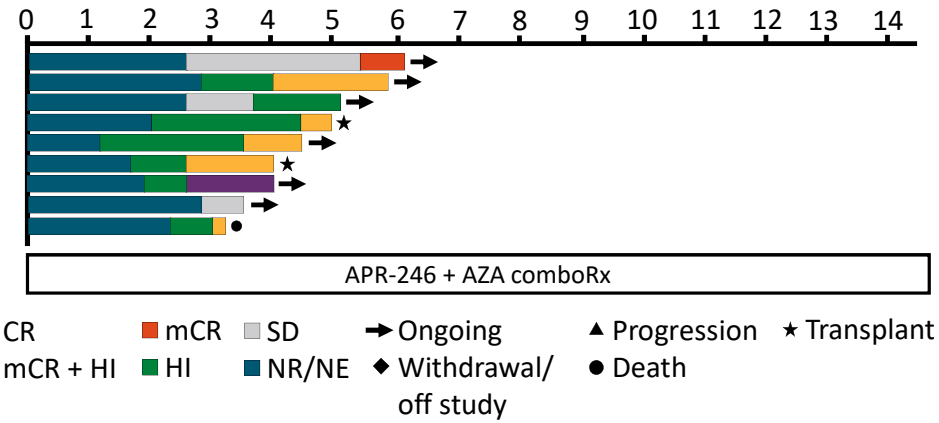
	Phase Ib	Phase II
Primary:	Safety	CR rate
Secondary:	ORR, PFS, OS, *TP53* VAF	ORR, PFS, OS, *TP53* VAF

Phase Ib/II APR-246 + AZA Trial: Treatment Duration and Response

Phase Ib Treatment Duration (Mos)



Phase II Treatment Duration (Mos)



Best Response at Cutoff

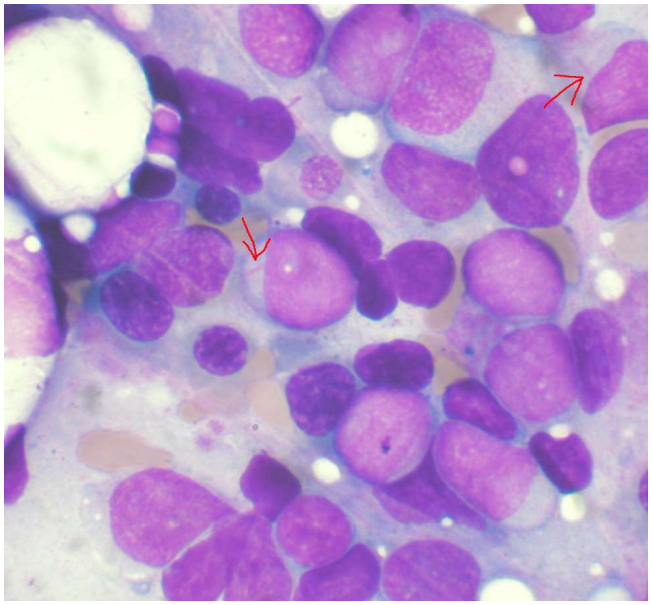
	Phase Ib	Phase II	MDS	AML	Total	AZA Historical
Evaluable patients, n	11	9	15	5	20	
ORR, %	100	89	93	100	95	30-50
CR, %	82	56	67	80	70	20-30

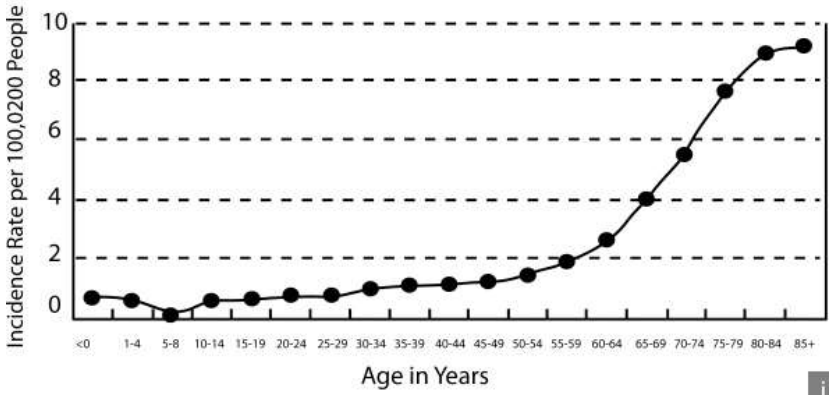
Sallman. ASH 2018. Abstr 3091.

Slide credit: clinicaloptions.com

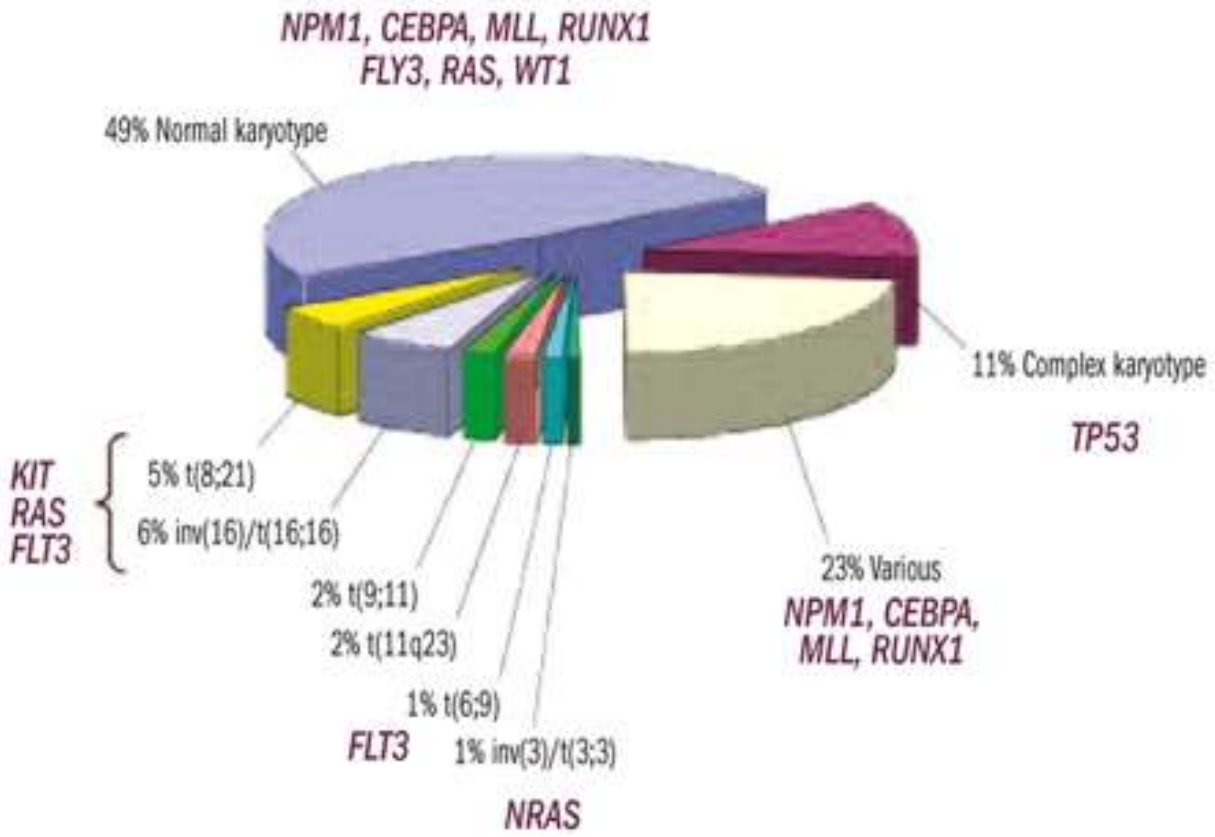
Acute Myeloid Leukemia

- 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





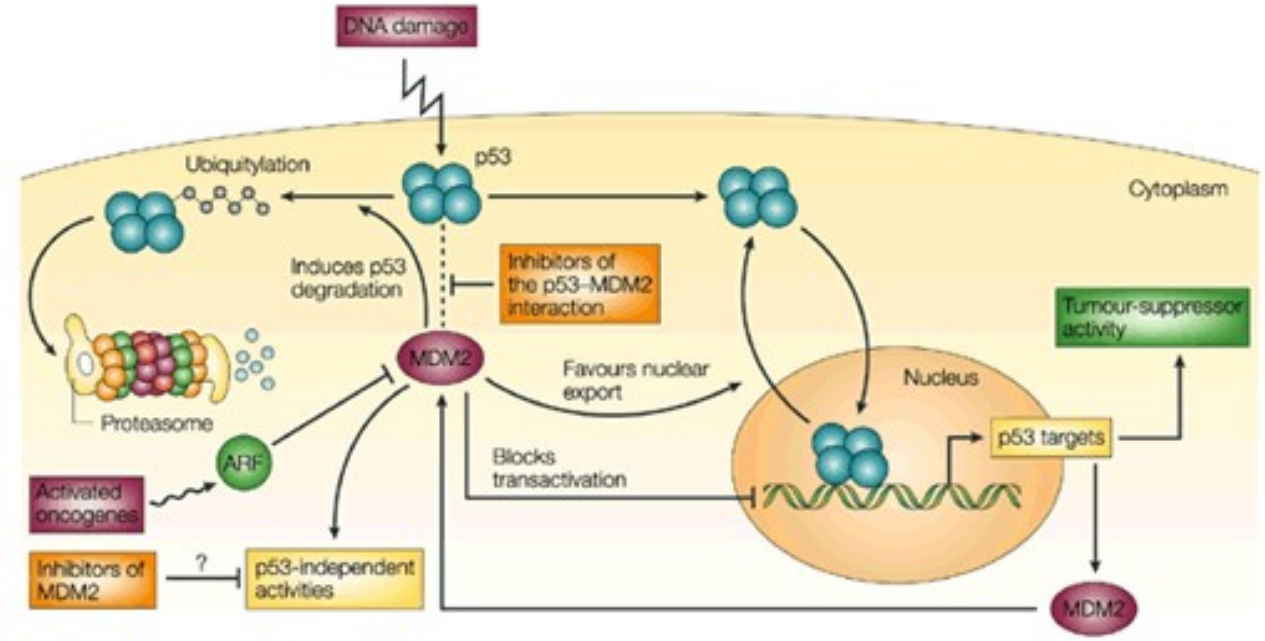
Major cytogenetic subgroups of AML and associated gene mutations

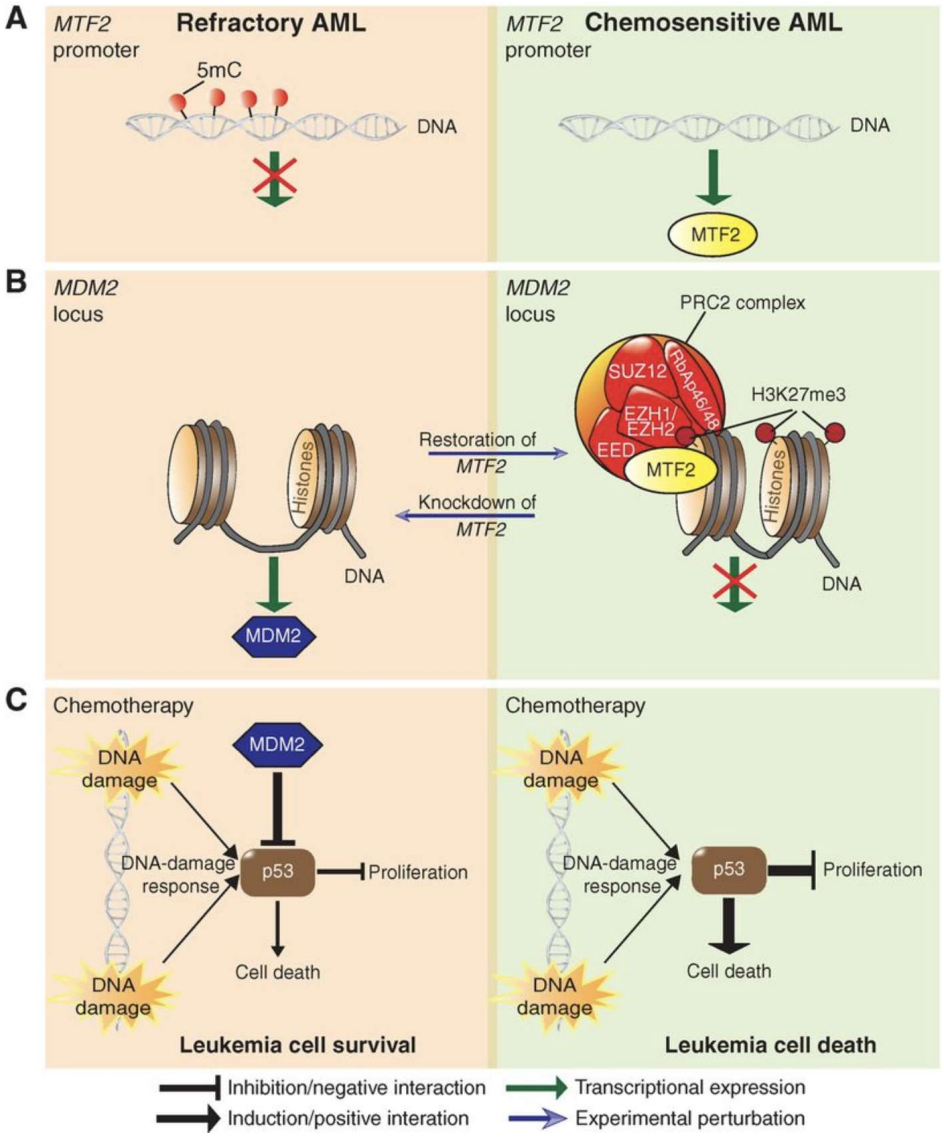


Novel Target in AML: Protein Homeostasis

- MDM2
- NEDDylation

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



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.

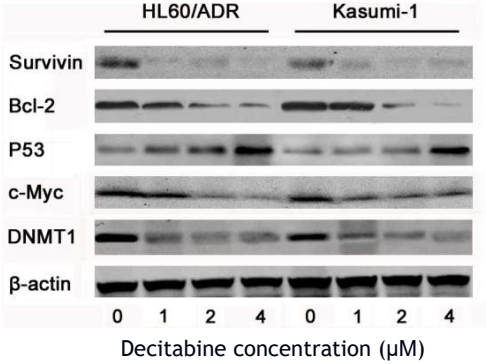
Refractory AML cells resist Chemo-induced DNA damage through MDM2-mediated depletion of p53.

MDM2i renders refractory cells sensitive to chemotherapy.

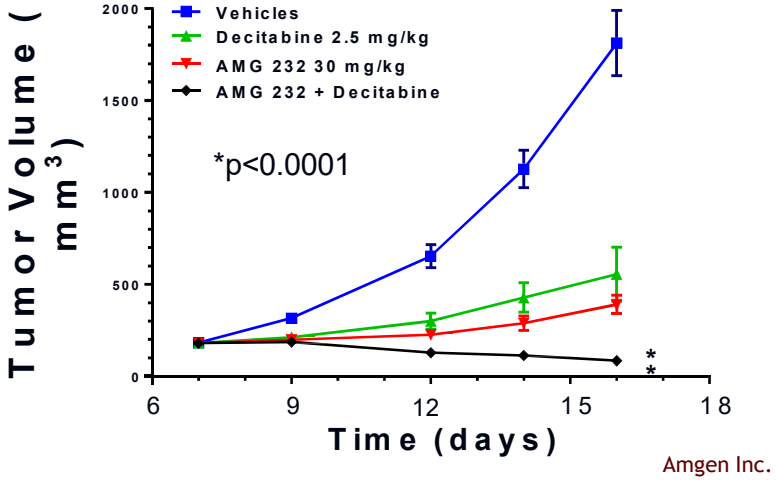
Rationale for the combination of KRT-232 with Decitabine in AML

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

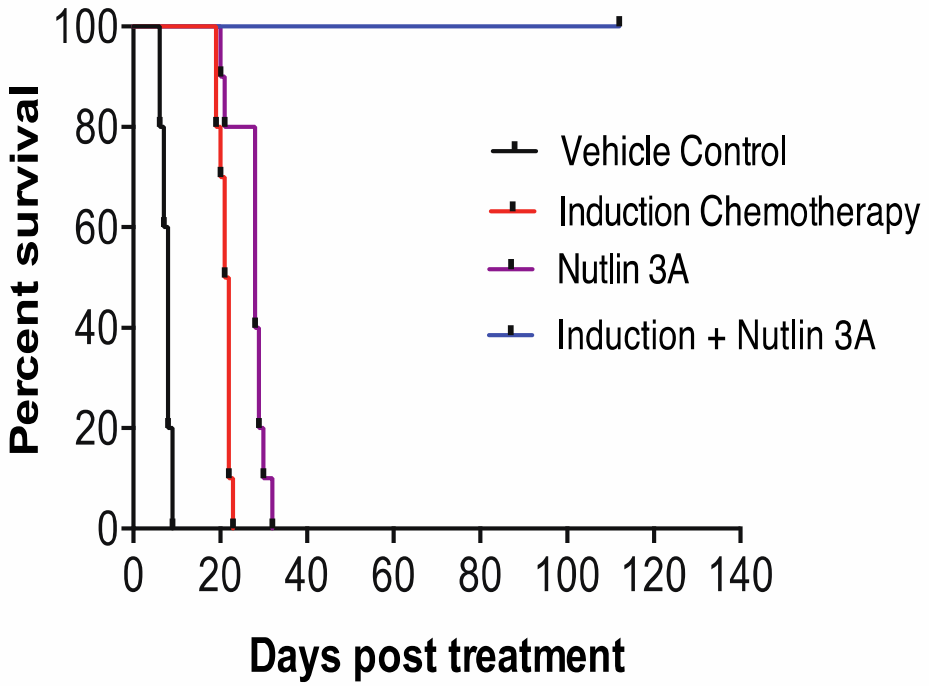


Jiang X, et al *Oncotarget*, 2015

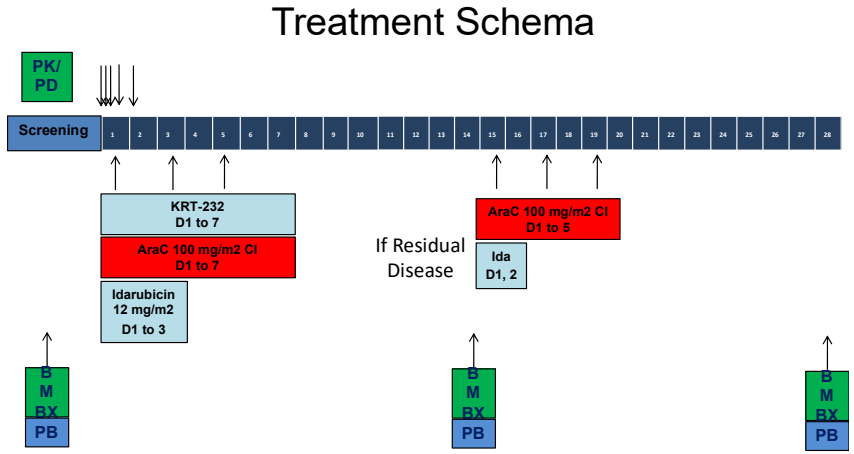


Amgen Inc.

PDX Mice Treated with MDM2 Inhibitor Plus Induction Drugs Survive

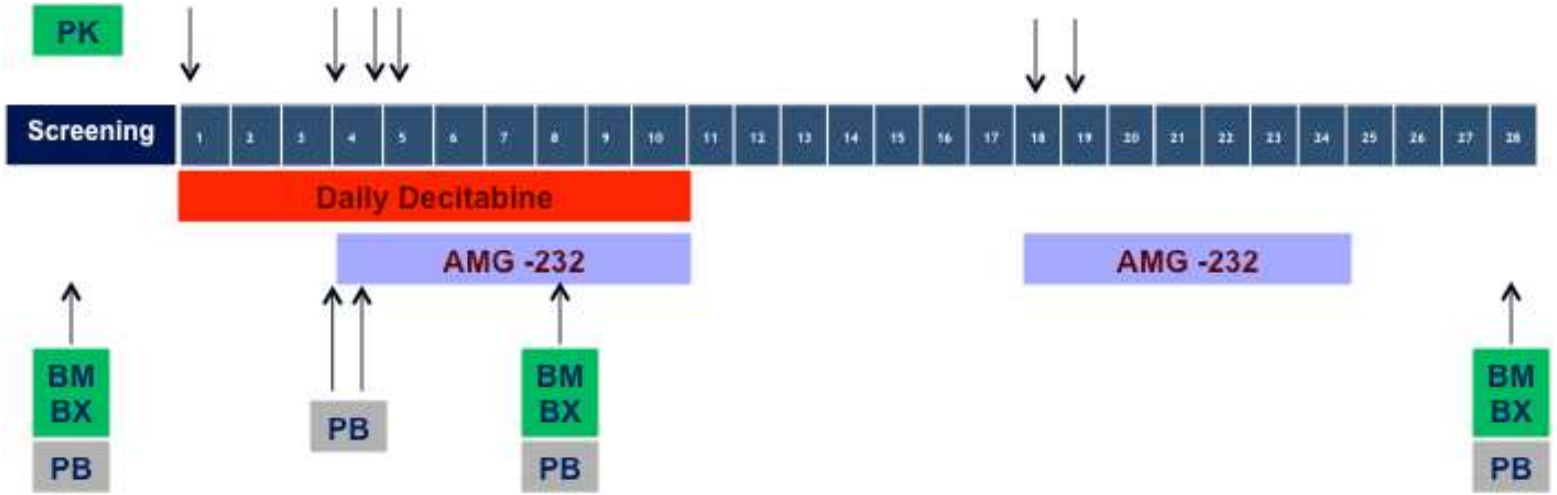


PDX Mice Treated with MDM2 Inhibitor Plus Induction Drugs Survive. Kaplan-Meier curve of NSG mice transplanted with MTF2-deficient AML patient BM cells were treated with vehicle control, induction drugs, MDM2 inhibitor Nutlin 3A or induction + Nutlin 3A. n=4 refractory AML samples; n=8 mice per treatment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



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

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. 2 patients enrolled.

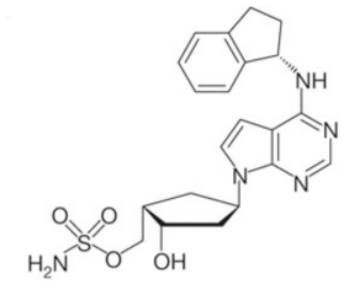
Profile of Complete Responders				
Cohort	**Age**	**Cytogenetics**	**Prior Tx**	**Genomic Alterations**
1	67	Normal	7+3+M	**FLT3 TKD**, NRAS, **RUNX1** and U2AF1
2	64	- 9, +21	7+3, AlloTX, Vidaza Maintenance, TLI, HIDAC salvage, Mylotarg. Ipi. Aza/Ven	CEPBA DM. KIT, IKZF1, **FLT3 TKD**
2	44	Normal	7+3+C. DC Allo. AraC. Haplo. FLT3i.	BCORL1, **EZH2**, IKZF1, NF1, NLRP1

MLN4924/ Pevonedistat

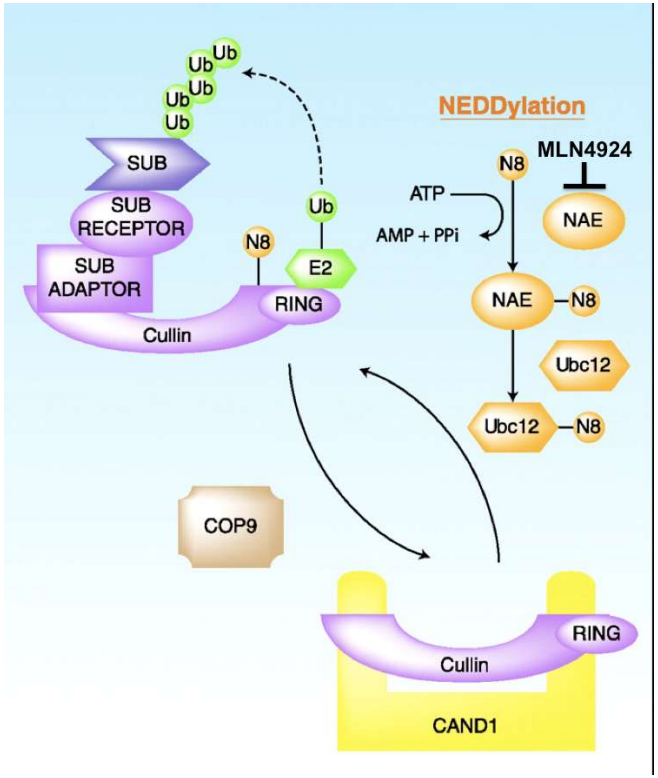
- First-in-class small molecule inhibitor of NEDD8-activating enzyme (NAE), the proximal regulator of the NEDD8 conjugation pathway, developed by Millennium Pharmaceuticals

- 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

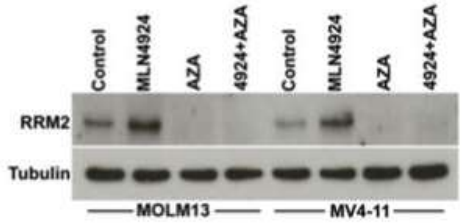


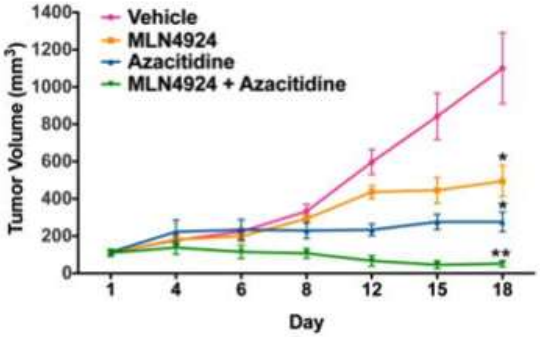
MLN4924



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

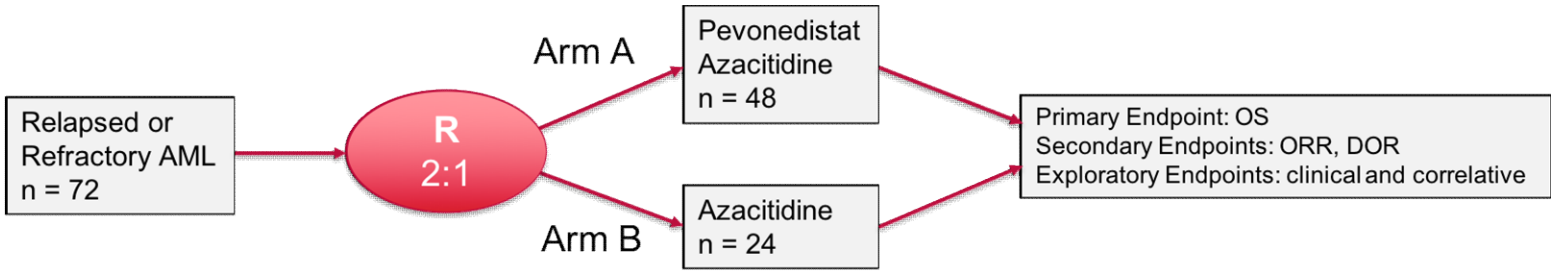
- Pevonedistat induces AML cell death (including AML leukemia stem cells) and synergizes with azacitidine in preclinical models[1-4]
- Pevonedistat activity and safety was confirmed in R/R AML (NCT00911066)[5-6]
- Pevonedistat plus azacitidine was studied in unfit older AML patients (NCT01814826)[7-8]
  - 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.**





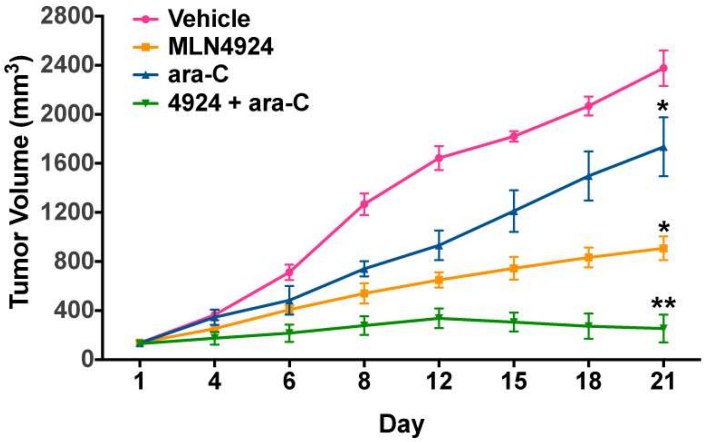
1 Swords et al, Blood 2010.
2 Smith et al, ASH 2011 Abstract 578.
3 Sen et al, ASH 2011 Abstract 1414.
4 Traore et al, EHA 2012 Abstract 1066.
5 Swords et al, BJH 2015.
6 Swords et al, Blood Cancer Journal, 2017.
7 Swords et al, ASH 2016 Abstract 98.
8 Swords et al, Blood 2018.

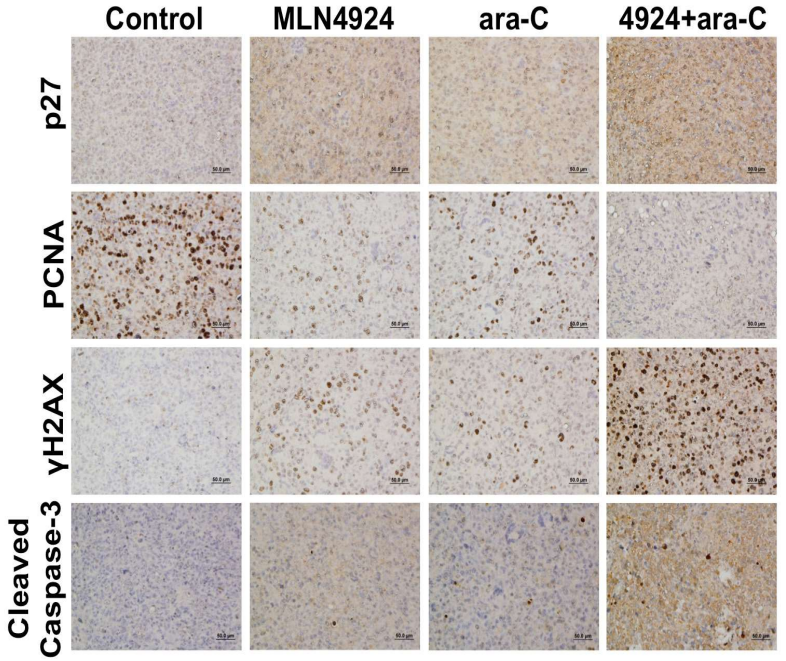
Study Design: A Randomized Phase II Trial of MLN4924 (Pevonedistat) with Azacitidine versus Azacitidine in Adult Relapsed or Refractory Acute Myeloid Leukemia (NCI Study #10247)



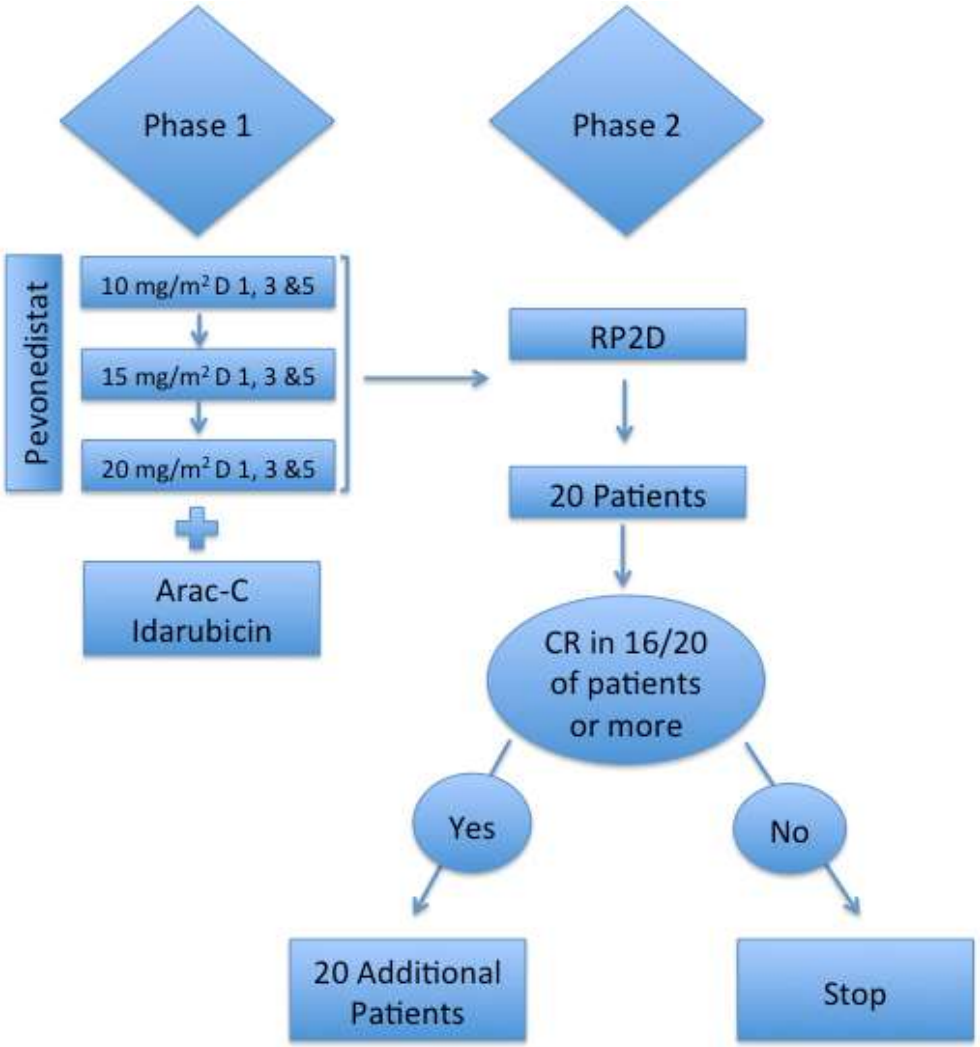
- **Treatment continues until transplant, progression, lack of clinical benefit, unacceptable toxicity, withdrawal of informed consent, etc.**
  - **Note, patients with PD may stay on study if it is judged they are deriving a clinical benefit from doing so**
- **Disease assessments after 2, 4, and 6 cycles of treatment**
  - **Using European Leukemia Net response criteria**
- **Patients followed for survival after cessation of study treatment**
- **There is one interim analysis for futility after 50% of events reached**

In Vivo Benefit of MLN4924/ara-C Combination





Clin Cancer Res 21:439-47, 2015


Phase 1
Phase 2
Pevonedistat
10 mg/m² D 1, 3 &5
15 mg/m² D 1, 3 &5
20 mg/m² D 1, 3 &5
Arac-C
Idarubicin
RP2D
20 Patients
CR in 16/20 of patients or more
Yes
No
20 Additional Patients
Stop

Cohort	Age	Cytogenetics	Genomic Alterations	Mid Tx Marrow	Response
Cohort 1 (PEV 15 mg/m^2)					
1	61	Normal	TET2, NPM1, FLT3	<5% Blasts	CR $_{\text{MRD-ve}}$
2	64	+8	DNMT3A, SF3B1, SRSF2 SH2B3, NF1	<5% Blasts	CR $_{\text{MRD-ve}}$
3	60	Normal	IDH2, SRSF2, STAG2, RAD21	<5% Blasts	MLFS, (MRD-ve)
Cohort 2 (PEV 20 mg/m^2)					
1	65	+8, t(2,16)	PTPN11	<5% Blasts	CR $_{\text{MRD-ve}}$
2	64	NED	ASXL1, IDH2, KRAS, SRSF2	<5% Blasts	CR $_{\text{MRD-ve}}$
3	65	NED	MPL	<5% Blasts	Relapse
4	73	Normal	IDH2, ASXL1, and DNMT3A	<5% Blasts	
5	66	Normal	DNMT3A, NPM1, CEBPA	<5% Blasts	
6	47	-7, -7q, Loss of MLL, RUNX1T1			

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.