AML and MDS
New Directions

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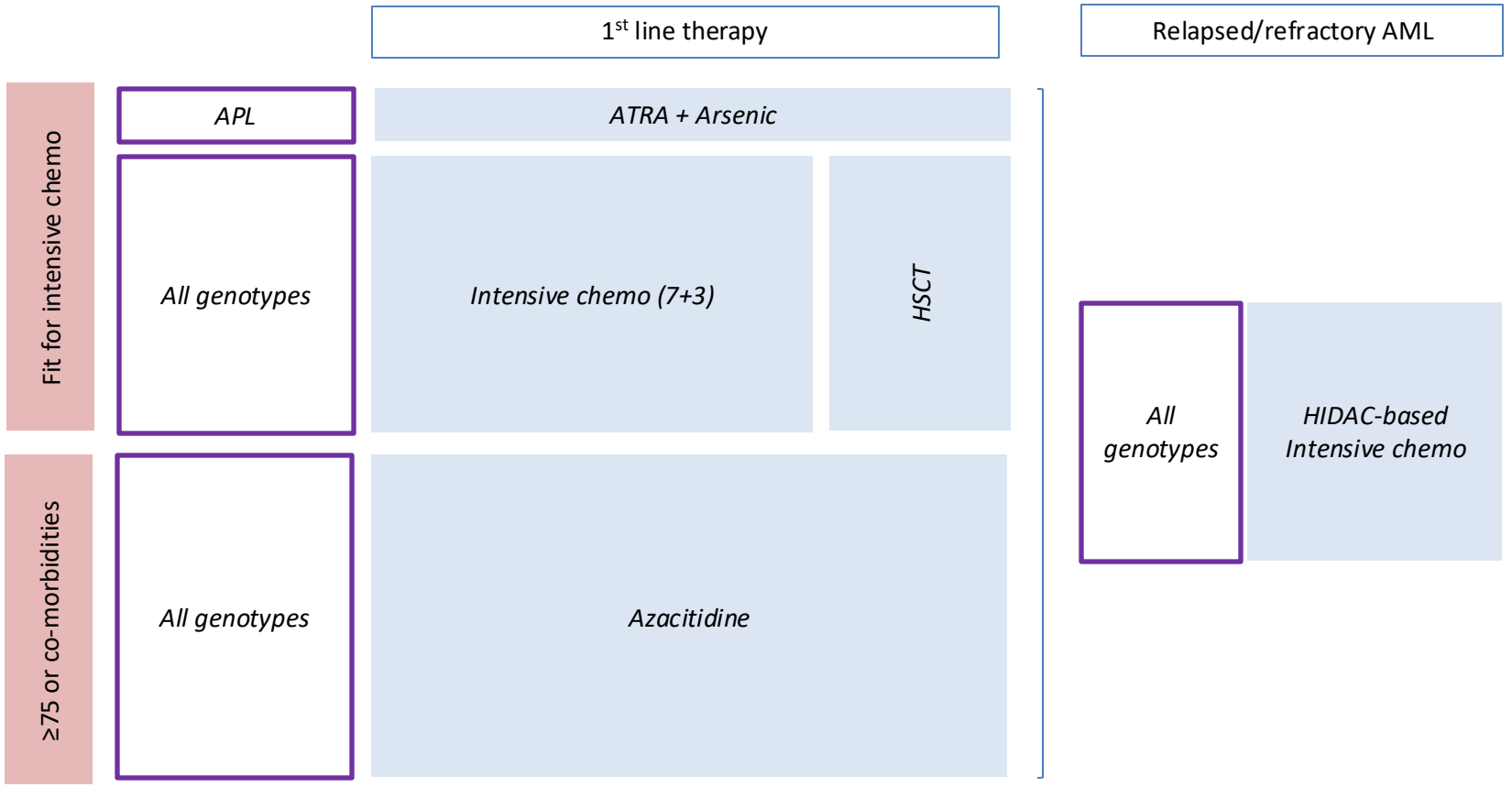
Learning Objectives

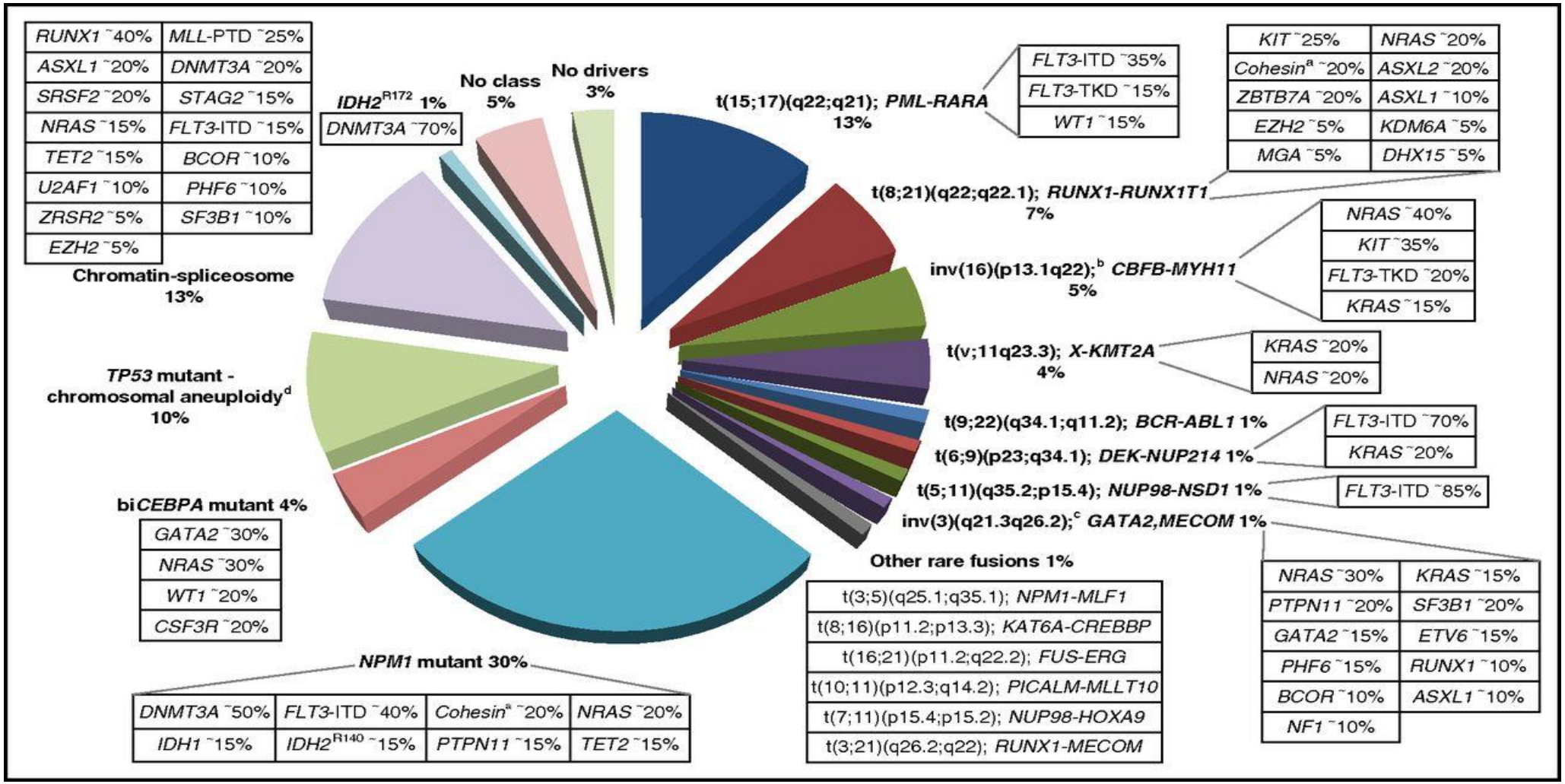
- To understand the biologic and clinical heterogeneity of AML and MDS
- To discuss contemporary approaches for AML and MDS
- To discuss novel therapeutic targets in AML and MDS

Historical treatment landscape in AML



Courtesy Andrew Wei, ASCO 2022

AML is heterogeneous and biologically complex



Döhner H, et al. *Blood.* 2017;129:424-447.

AML Risk Stratification/Prognosis

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*#

5-yr OS: 55-65%

5-yr OS: 24-41%

5-yr OS: 5-14%

Other Poor Prognosis Groups

-AML arising from chronic myeloid neoplasms (MPN, MDS, CMML)

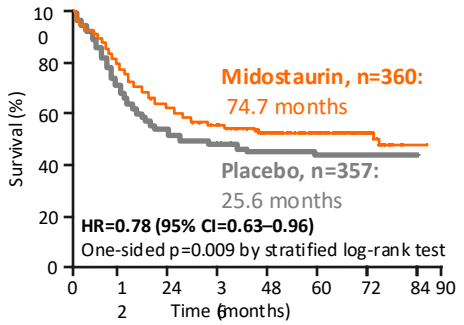
-AML with myelodysplastic changes

-treatment-related AML

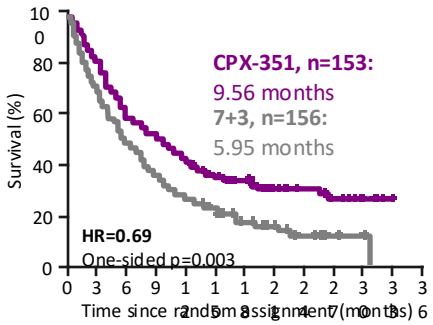
Dohner et al. Blood 2017

Randomized outcomes for FDA-approved drugs for AML

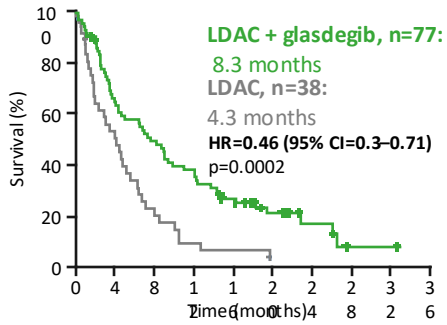
7+3 + midostaurin[1]



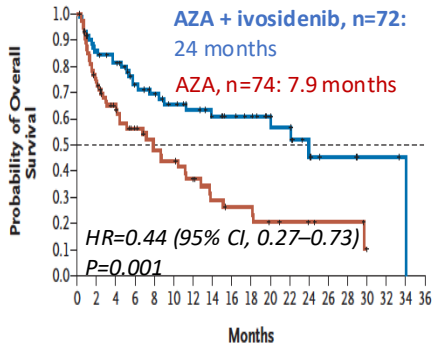
CPX-351[2]



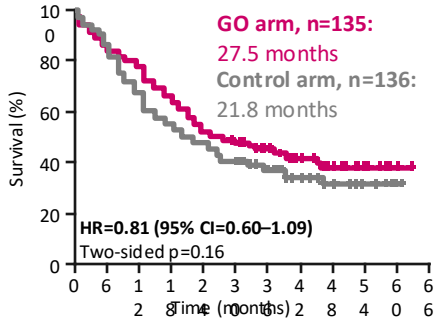
LDAC + glasdegib[3]



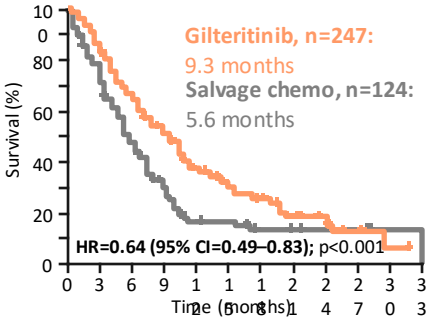
AZA + ivosidenib[4]



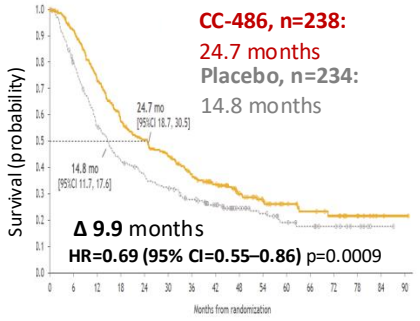
7+3 + GO[5]



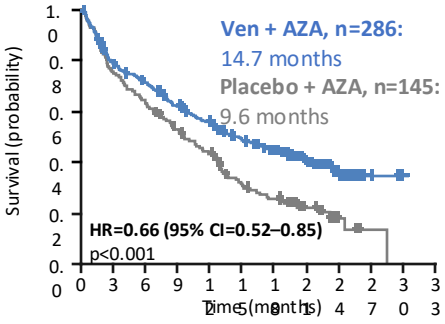
Gilteritinib[6]



CC-486[7]



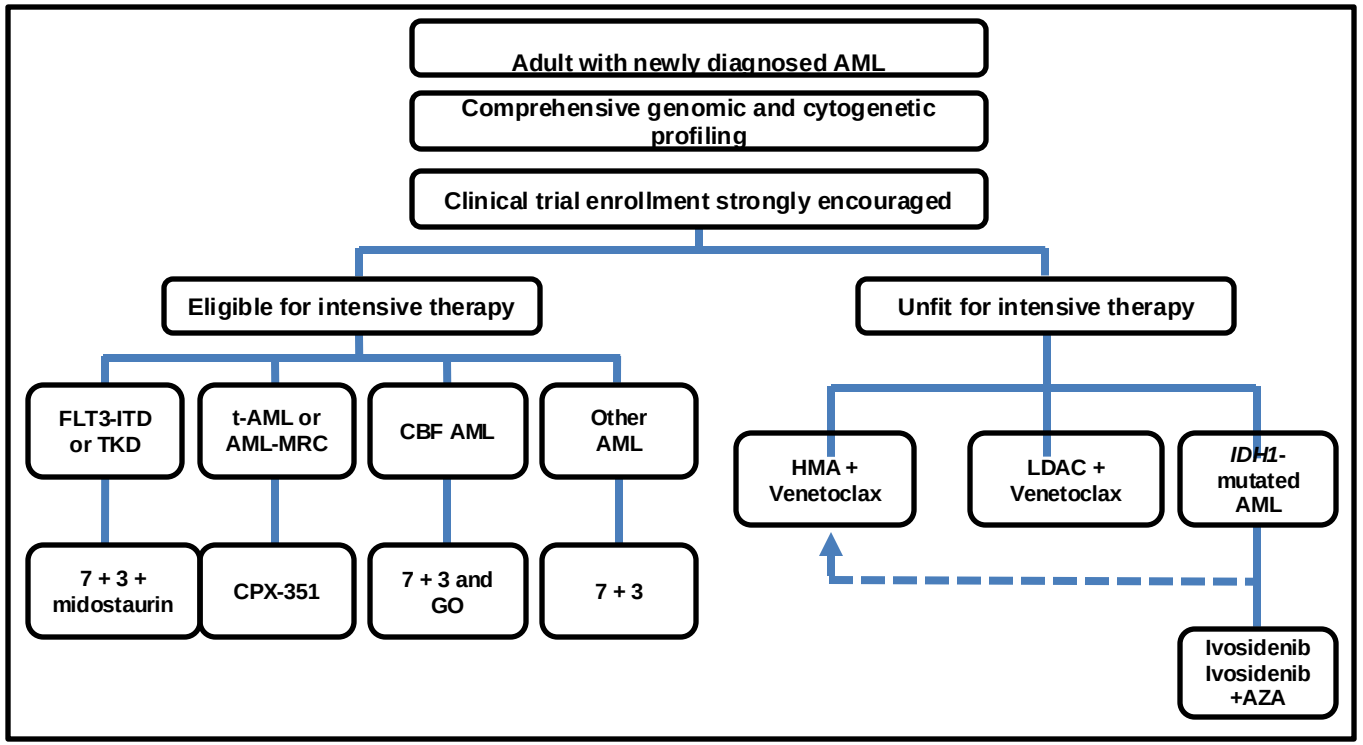
AZA + venetoclax[8]



AZA, azacitidine; ENA, enasidenib; GO, gemtuzumab ozogamicin; LDAC, low-dose cytarabine; Ven, venetoclax.

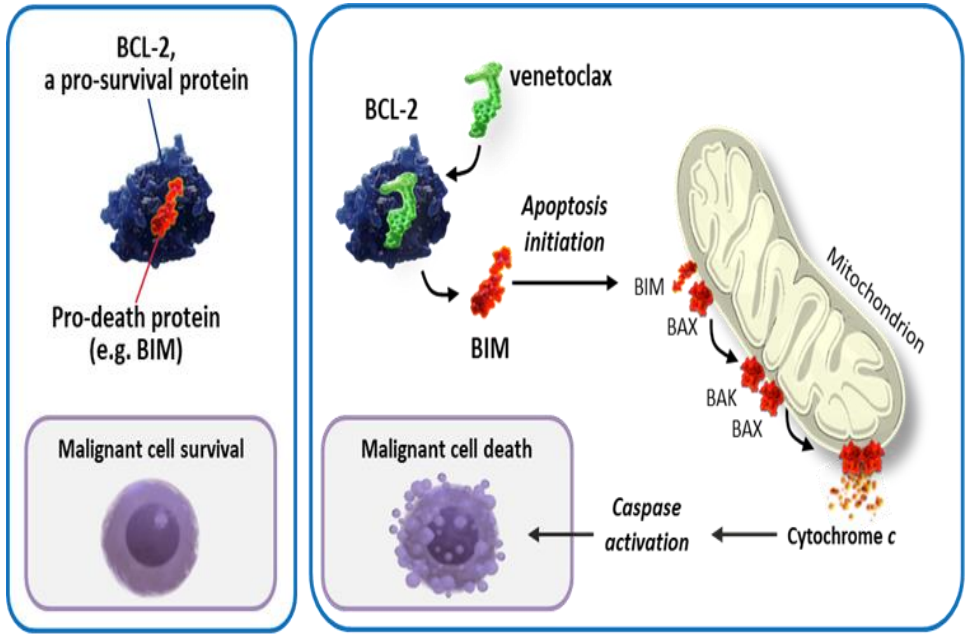
1. Stone M, *et al. N Engl J Med* 2017; **377:**454–464; 2. Lancet JE, *et al. J Clin Oncol* 2018; **36**:2684–2692; 3. Cortes et al, *Leukemia* 2019;33, 379-389;
4. Montesinos, P et al. *N Engl J Med* 2022; 1519-31 5. Lambert J, *et al. Haematologica* 2019; **104**:113–119; 6. Perl AE, *et al. N Engl J Med* 2019; **381:**1728–1740;
7. Wei AH, *et al.NEJM 2020; 383, 2526*; 8. DiNardo CD, *et al. N Engl J Med* 2020; **383**:617–629.

Approach to frontline treatment of AML



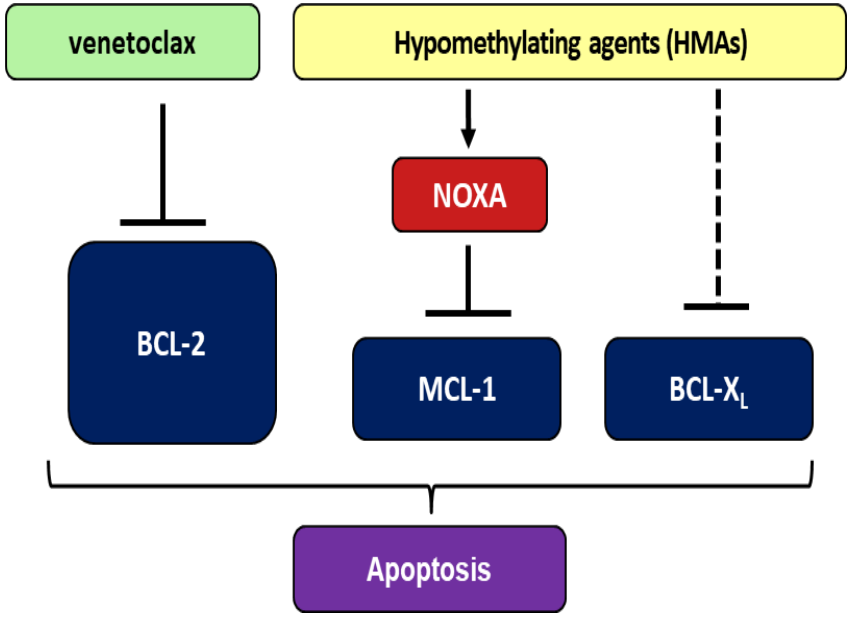
Modified from: Cahill and Odenike, Advances in Oncology 2021

Venetoclax is a potent and selective BCL2 inhibitor



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins [1-3]

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis)[4-6]



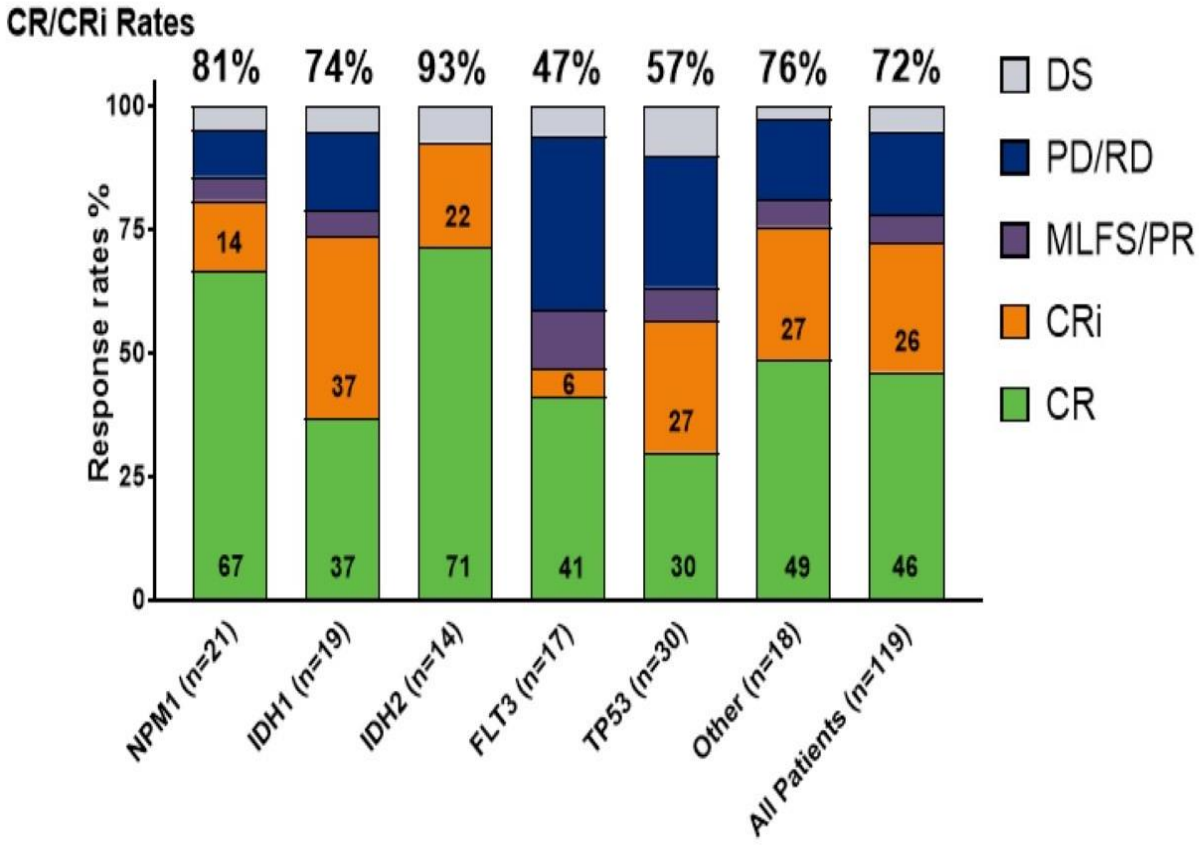
Azacitidine and decitabine indirectly increase sensitivity to BCL-2 inhibition in AML cells by modifying the relative levels of BCL-2 family members[2,3]

1. Leverson JD, et al. *Sci Transl Med* 2015; 7:279ra40. 2. Czabotar, et al. *Nature Reviews* 2014;15:49-63. 3. Plati J, Bucur O, Khosravi-Far R. *Integr Biol (Camb)* 2011;3:279–296. 4. Certo M, et al. *Cancer Cell*. 2006;9(5):351-65. 5. Souers AJ, et al. *Nat Med*. 2013;19(2):202-8. 6. Del Gaizo Moore V et al. *J Clin Invest*. 2007;117(1):112-21.

Azacitidine+venetoclax in AML early phase experience

Subgroup	CR + CRi, n (%)
All patients	97 (67)
Cytogenetic risk	
Intermediate	55 (74)
Poor	42 (60)
Age	
≥75 y	40 (65)
<75 y	57 (69)
AML	
De novo	73 (67)
Secondary	24 (67)

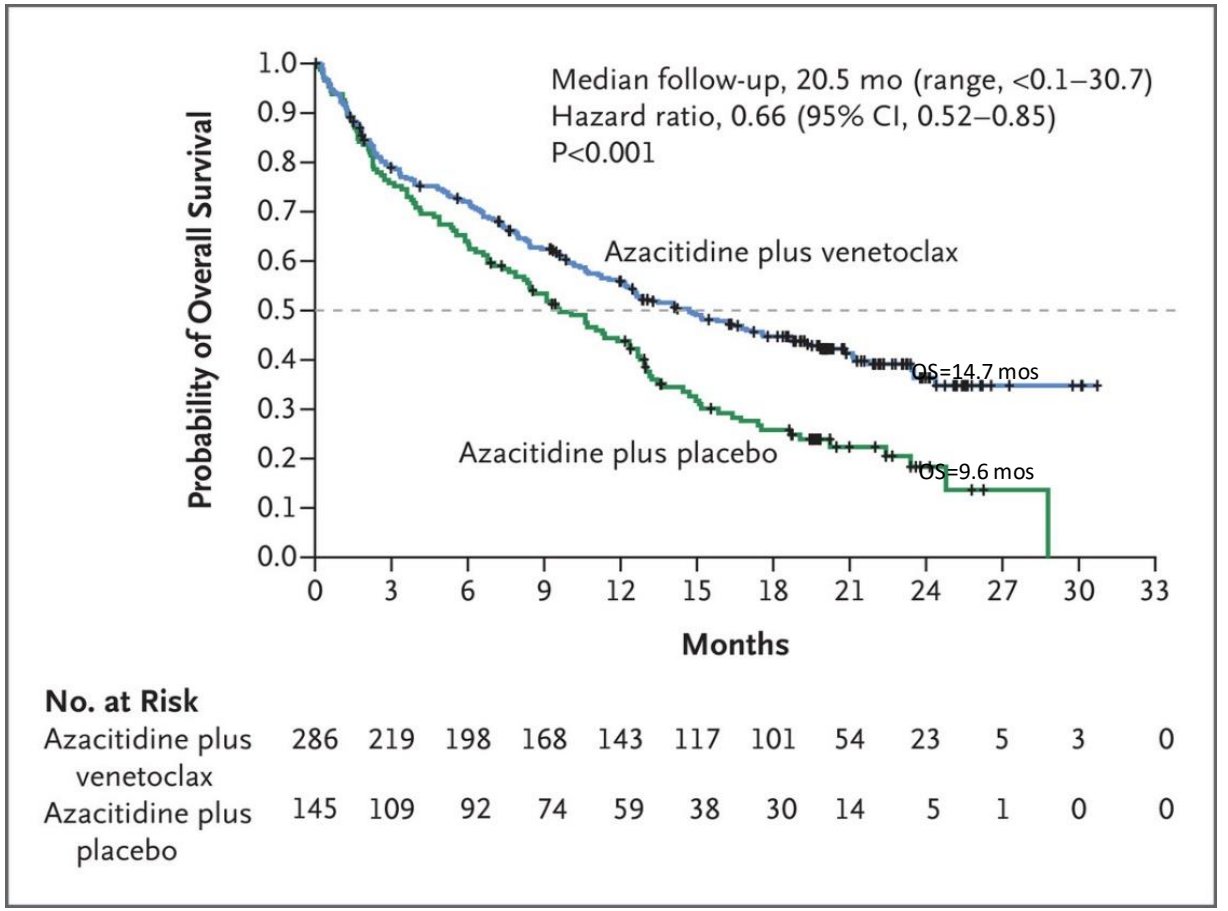
DiNardo et al, Blood 2019



Chyla et al, ASH 2019

Azacitidine+venetoclax confers a survival advantage: Results of Phase III VIALE-A trial (n=431).

- **Populations excluded from VIALE A**
  - **Favorable risk cytogenetics**
  - **Prior HMA**
  - **Prior MPN**
  - **Younger fit patients**



- **Febrile neutropenia:**
  - **30% vs 10%**
- **30 day mortality**
  - **7% vs 6%**
- **CRc**
  - **66% vs 28%**
- **MRD $<10^{-3}$**
  - **41% of those achieving CRc**
- **FDA approved:**
  - **Adults ≥75y/o or with comorbidities that preclude intensive chemo**

CD DiNardo et al. N Engl J Med 2020;383:617-629; Pratz K, JCO, 2021

Of note, 60% enrolled in VIALE A were ≥ 75y/o, 55% were ECOG 0-1, 45% had 2 or more reasons for ineligibility

Outstanding Questions

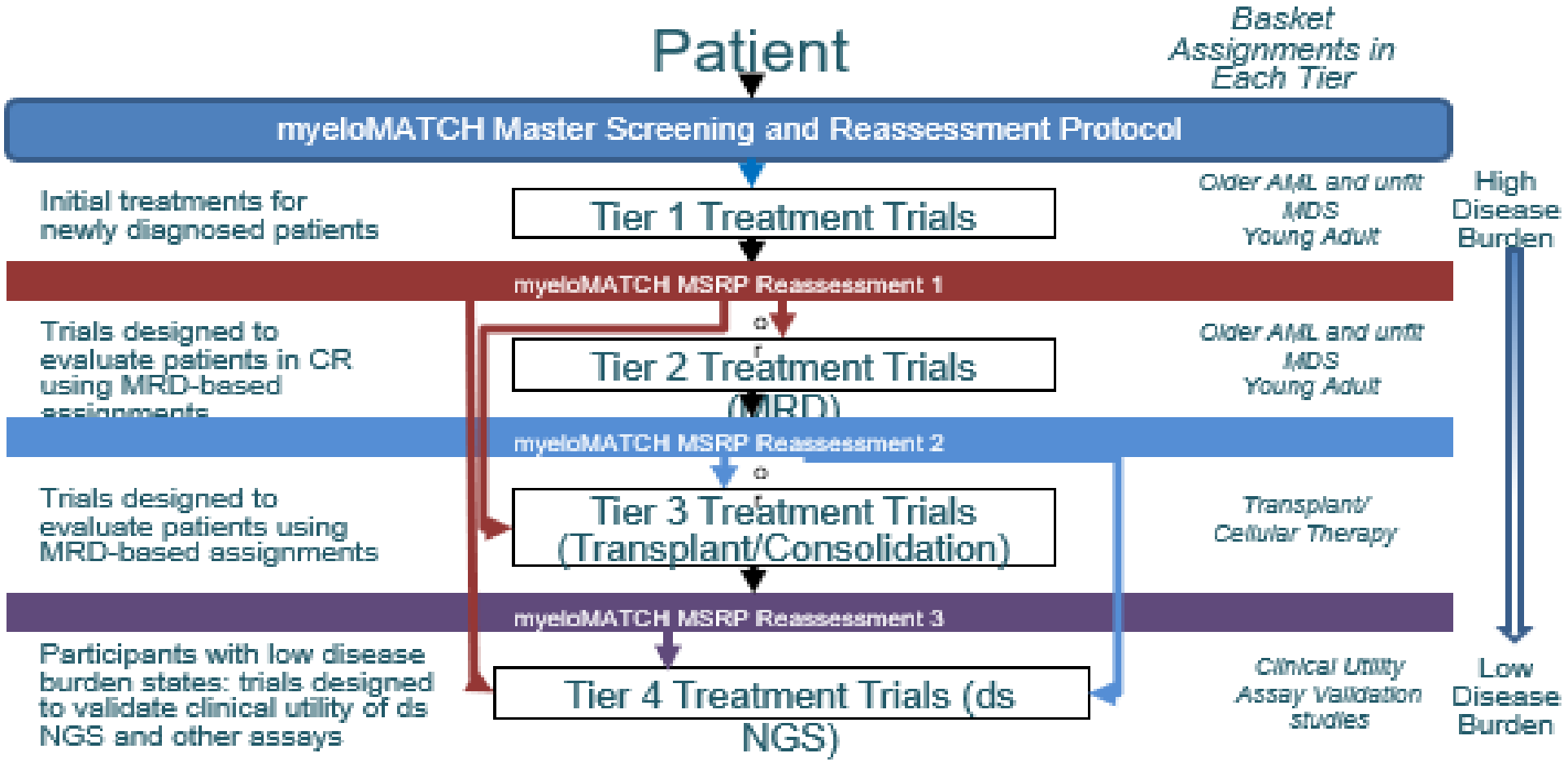
- **Relative magnitude of benefit of lower intensity therapies in AML**
  - **For both fit and unfit populations**
- **In specific targeted subsets e.g IDH or FLT3 mutated AML unfit for intensive therapies**
  - **HMA/venetoclax versus triplet therapies?**
- **In very poor risk subsets-*TP53* mutated subset**
  - **Role of novel agents/approaches under investigation**
- **Path to cure?**
  - **Transplantation; novel immunotherapeutic approaches; MRD erasers?**

NCI Myeloid Malignancies Molecular Analysis for Therapy Choice Precision Medicine Trial
myeloMATCH

- Collaborative effort between NCI, academic investigators and industry partners to accelerate the development of precision medicine trials through the NCTN for patients with myeloid malignancies

- Provision of a framework that facilitates the career development of early career investigators

myeloMATCH Launch date! May 16, 2024



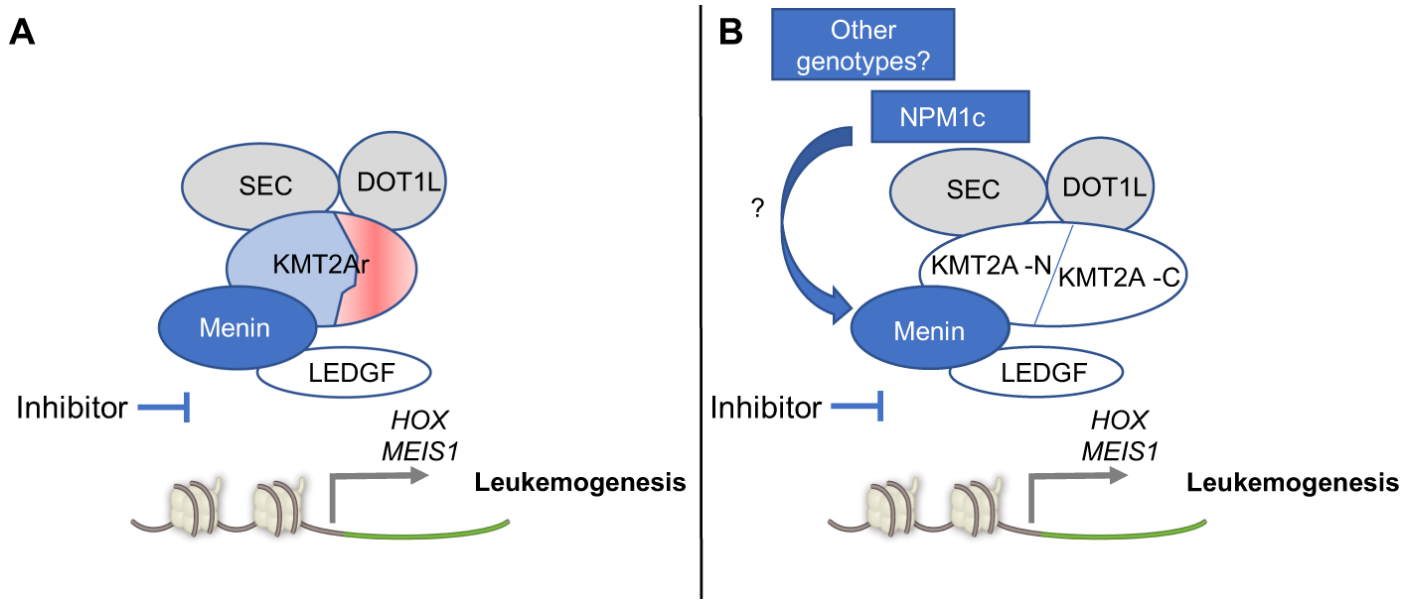
[1] Older AML and unfit basket = Pts. ≥ 60 years of age and unfit AML of any age
[2] Younger AML = 18-59 years of age

Courtesy NCI myeloMATCH

Leveraging the ETCTN

Menin inhibition in AML

Menin inhibitors for rKMT2A / mNPM1 AML



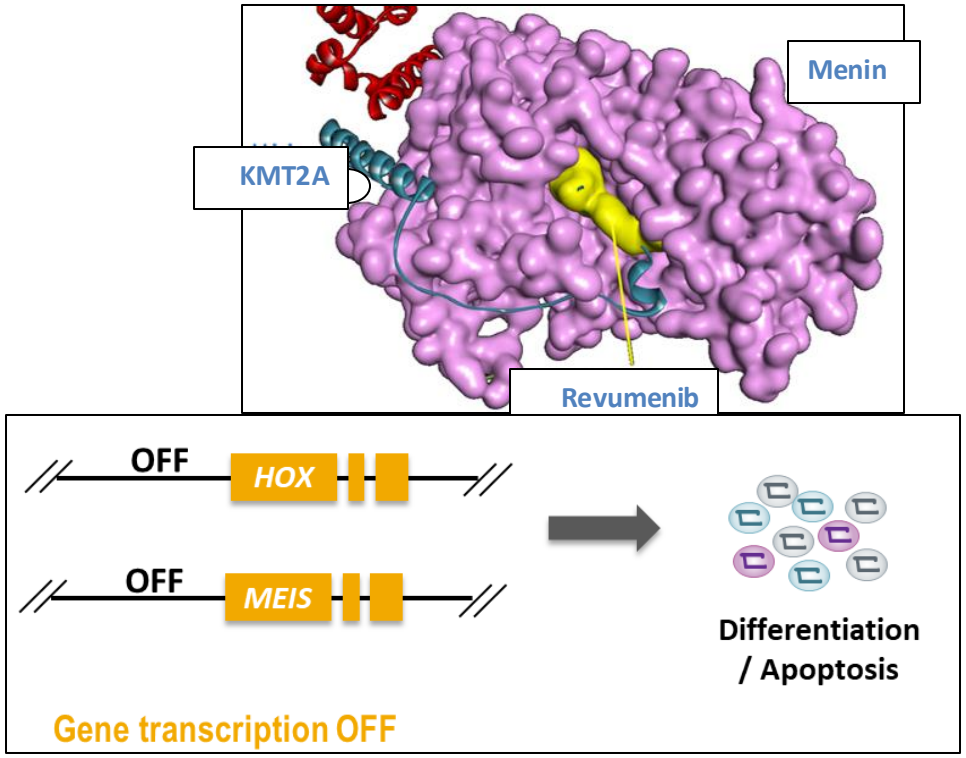
Menin inhibitors

SNDX-5613
KO-539
JNJ-75276617
DSP-5336
BMF-219

Issa G et al., Leukemia 2021

Revumenib (SNDX-5613)

- **Revumenib (SNDX-5613) is a potent, selective menin-KMT2A interaction inhibitor**
- **The menin-KMT2A interaction is a critical dependency in *KMT2Ar* (*MLL1r*) and *mNPM1* leukemias responsible for the leukemogenic gene expression**
  - ***KMT2Ar*: ~ 10% AML or ALL (~ 80% infant ALL)**
  - ***mNPM1*: ~ 30% AML**
- **Revumenib competitively binds a discrete, well-defined pocket within menin, where both wild-type KMT2A (MLL1) and KMT2A fusion proteins bind**

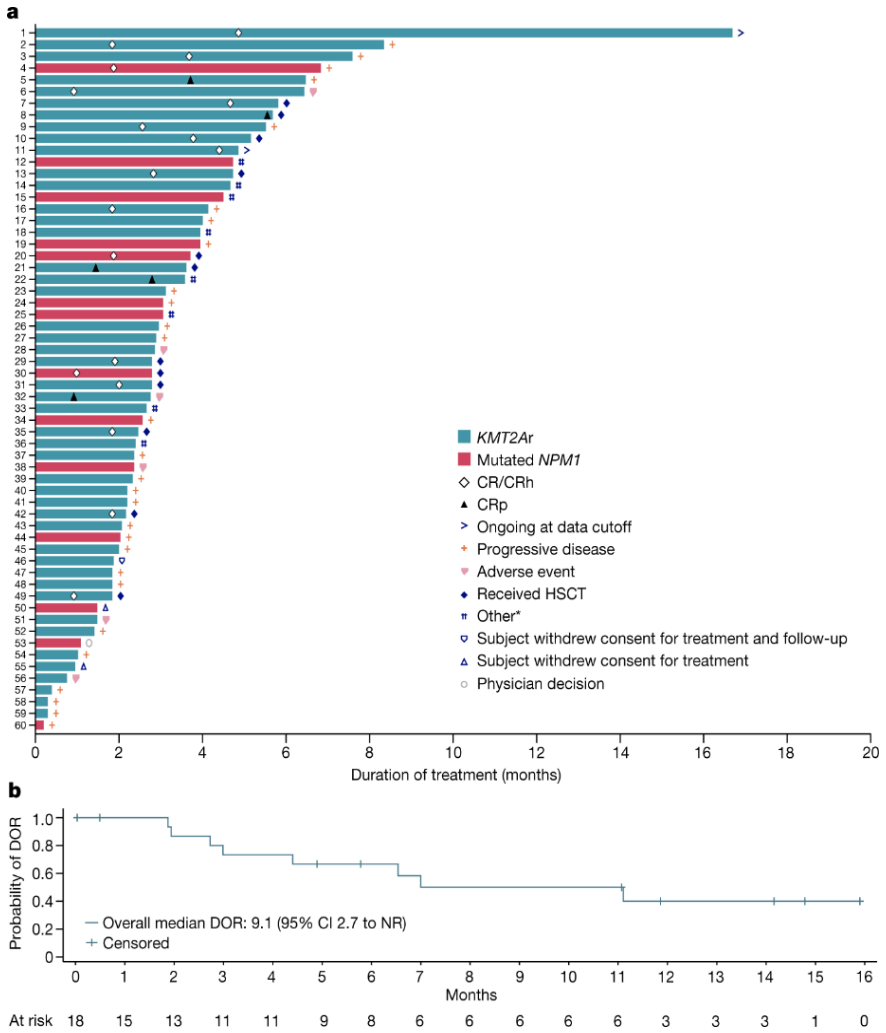


Issa GC, et al. *Leukemia*. 2021;35:2482–2495
Issa GC, et al. *Nature*. 2023;65:920-924

Revumenib (SNDX-5613)

Table 2 | Responses to treatment

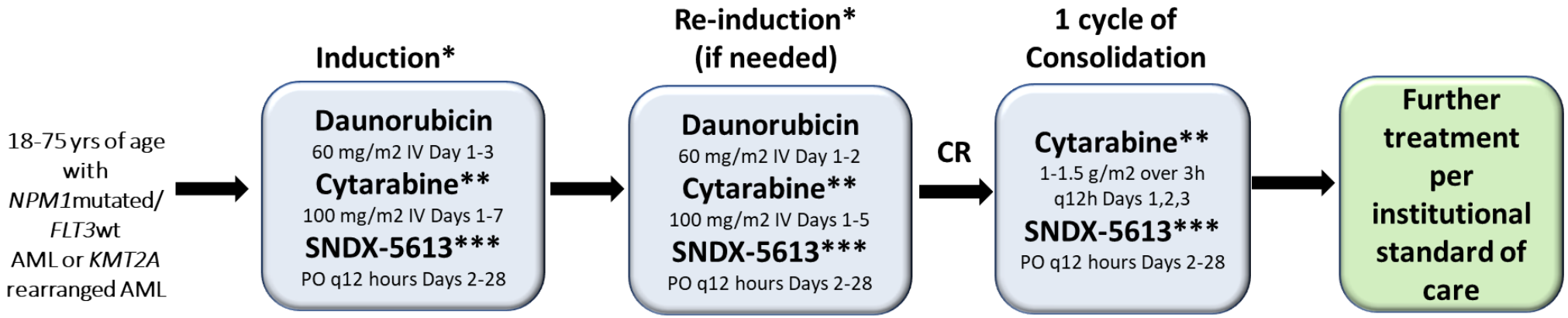
Response	Efficacy population (*n*=60)	*KMT2Ar* (*n*=46)	Mutated *NPM1* (*n*=14)
Overall response*	32 (53%)	27 (59%)	5 (36%)
Median time to first morphologic response (range), months	0.95 (0.9–3.7)	0.95 (0.9–3.7)	0.99 (1.0–1.9)
Best response*			
CR/CRh	18 (30%)	15 (33%)	3 (21%)
CR	12 (20%)	9 (20%)	3 (21%)
CRh	6 (10%)	6 (13%)	0
Median time to CR or CRh (range), months	1.9 (0.9–4.9)	2.0 (0.9–4.9)	1.9 (1.0–1.9)
CRi	0	0	0
CRp	5 (8%)	5 (11%)	0
MLFS	9 (15%)	7 (15%)	2 (14%)
Partial remission	0	0	0
No response	19 (32%)	12 (26%)	7 (50)
Progressive disease	7 (12%)	6 (13%)	1 (7%)
Missing	2 (3%)	1 (2%)	1 (7%)
MRD' neg. rate within CR/CRh	14/18 (78%)	11/15 (73%)	3/3 (100%)
Median time to MRD' neg. among patients with CR/CRh (range), months	1.9 (0.9–4.9)	1.9 (0.9–4.9)	1.9 (1.0–2.8)



Issa GC, et al. *Nature*. 2023;65:920-924

Study Schema: NCI 10596

Phase 1b Study of SNDX-5613 in combination with daunorubicin and cytarabine in Newly Diagnosed AML and NPM1mutated/FLT3 wildtype or MLL/KMT2A Rearranged Disease



*Reinduction allowed if midcycle marrow with significant morphological residual disease without a hypocellular marrow

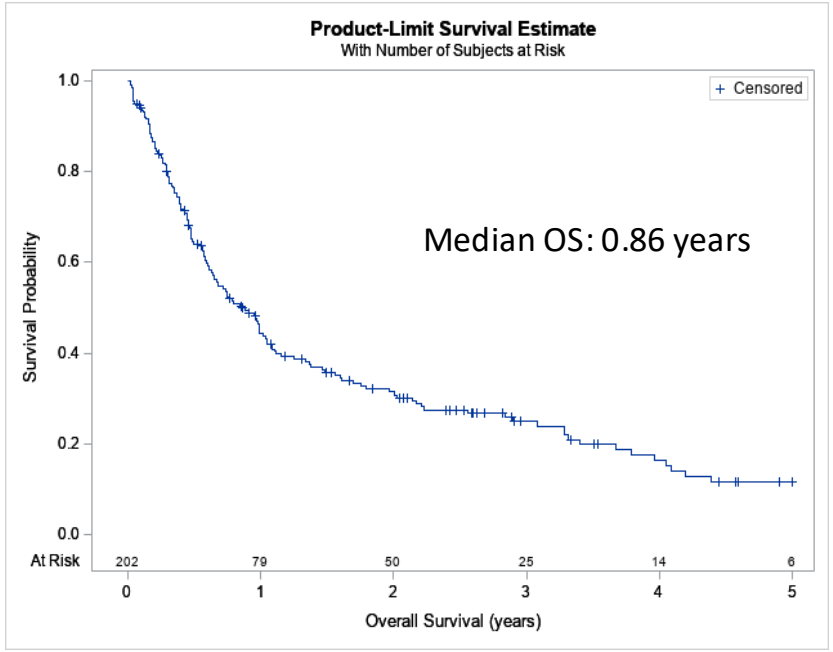
**Cytarabine is given as a continuous intravenous infusion (CIV) during induction and reinduction. During consolidation, cytarabine dosing will be given as 1 or 1.5g/m^2 based on age and creatinine clearance

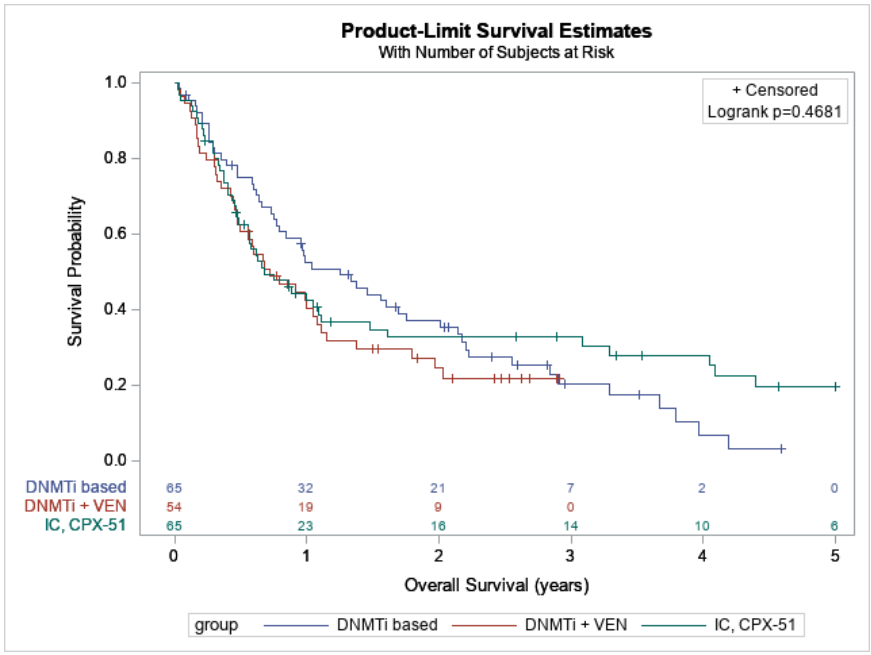
***SNDX-5613 will be given per dose assignment

PI: Alice Mims, OSU

LSD1 inhibition in Myeloproliferative Neoplasms –Accelerated Phase /Blast Phase

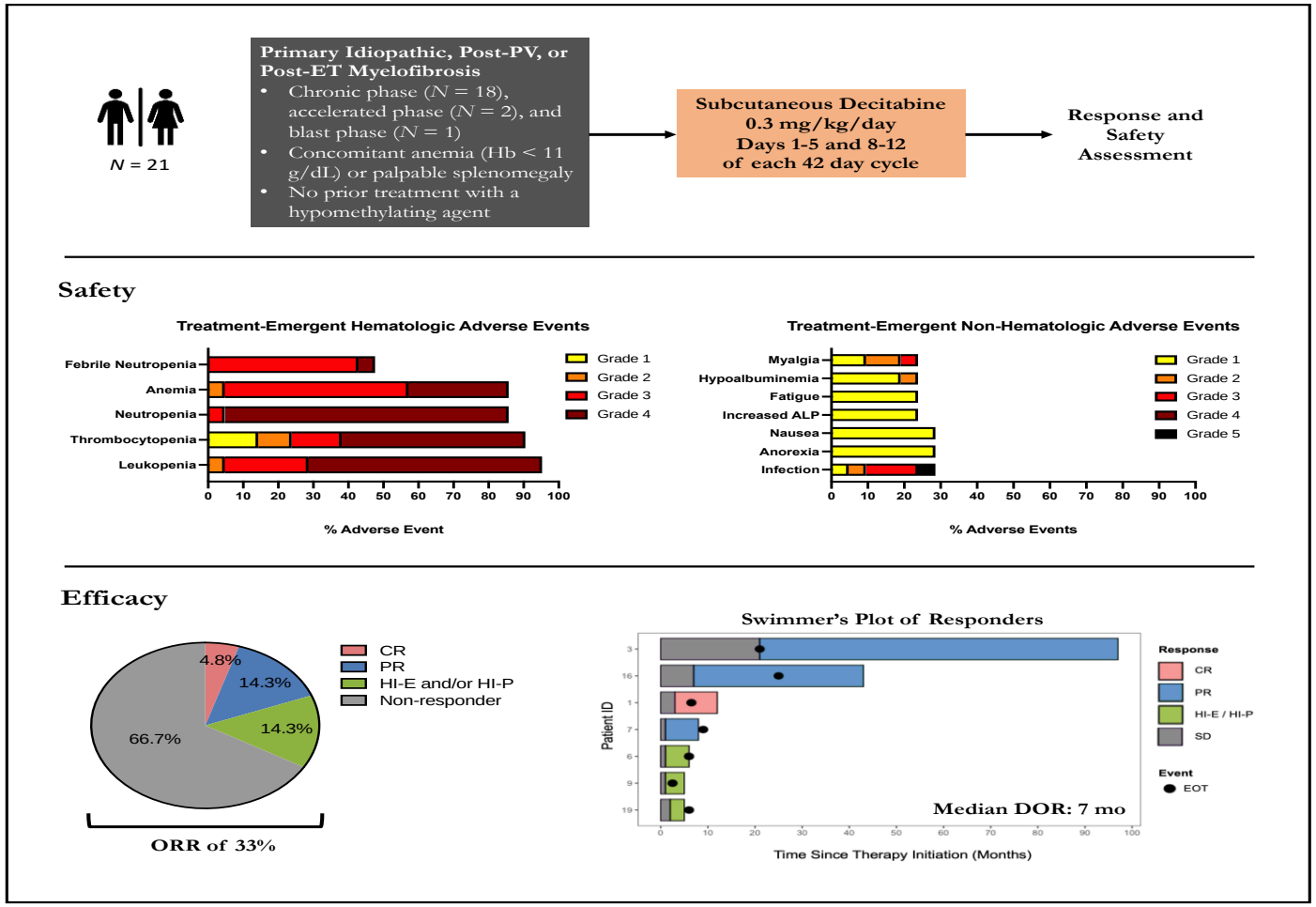
Ph neg MPN AP/BP Outcomes since 2017: University of Chicago led multicenter cohort (n=202)





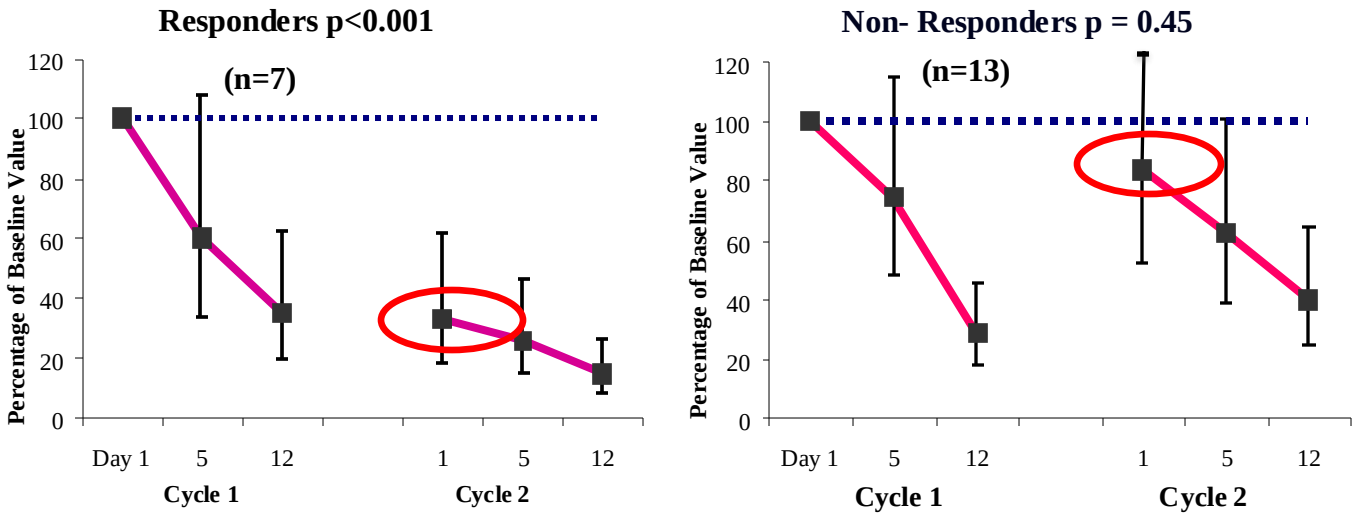
Patel A et al, Blood Advances, 2024

Phase II multicenter study of low dose subcutaneous decitabine in advanced myelofibrosis: NCI 6814



Lin et al, In Press, Blood Advances

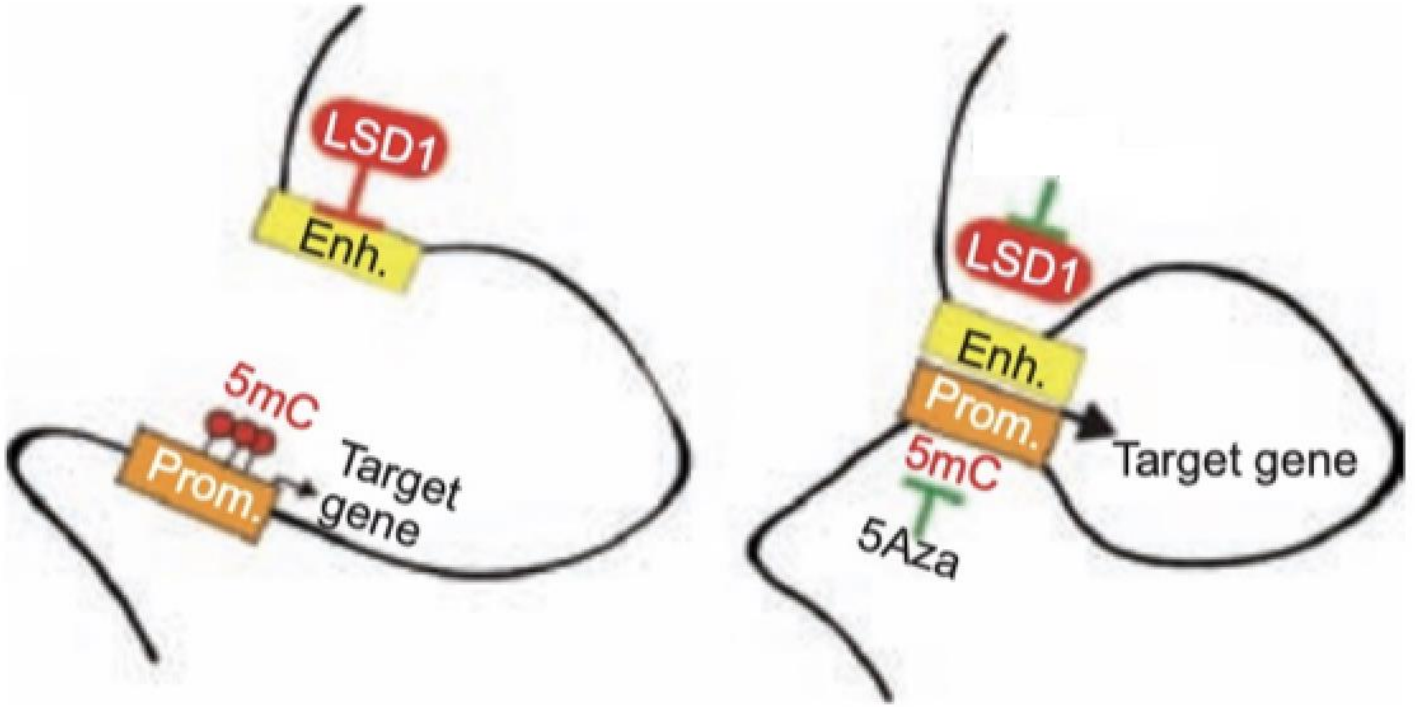
Decitabine in MF: Change in CD34+ progenitor cells- Responders Vs Non-Responders



Circulating CD34+ cells measured by flow cytometry at baseline, day 5 and day 12 of the first 2 cycles of therapy

Lin et al, In Press, Blood Advances

LSD1 inhibition synergizes with DNMTi in myeloid neoplasia



Adapted from Duy C et al. *Cancer Discovery*. 2019

Sugino N, Leukemia 2017
Maes T, Cancer Cell 2018
Salamero et al, Lancet 2024

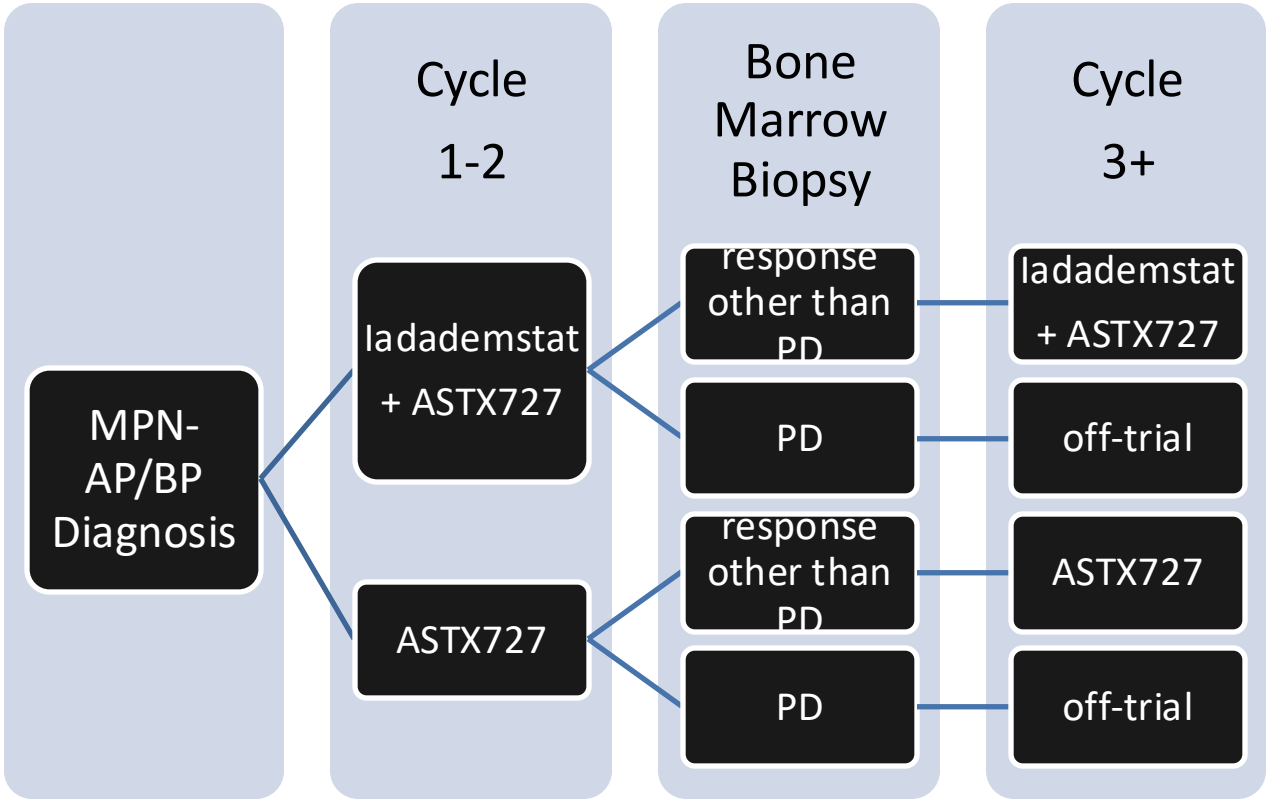
Randomized Phase II Study of ASTX727 (oral decitabine-cedazuridine) +/- iadademstat in MPN AP/BP: NCI 10675

Cycle = 28 days

Iadademstat
90μg/m^2/day (5 days on, 2 days off) per 28 day cycle

ASTX727
35-100mg
D1-5

Primary Endpoint
ALR-C or better by end of Cycle 2



PI: Dr. Anand Patel, University of Chicago

New Approaches in MDS

Stratification based on IPSS/IPSS-R

	Score	Risk Group	Median Survival in years
IPSS (N=816)	0	Low	5.7
	0.5-1.0	Intermediate-1	3.5
	1.5-2.0	Intermediate-2	1.2
	≥ 2.5	High	0.4

Score=>1.5 : Higher risk MDS

	Points	Risk Score	Median survival in years
IPSS-R (N=7,012)	≤ 1.5	Very Low	8.8
	> 1.5-3	Low	5.3
	>3-4.5	Intermediate	3.0
	>4.5-6	High	1.6
	>6	Very high	0.8

*Score=>3.5 : Higher risk MDS

Adapted from: Greenberg P, Blood 1997, 89:2079, Greenberg PL, Blood 2012, 30:820, *Pfeilstocker M, Blood 2016, 128:902-910

Selected Phase II/III Hypomethylating Agent Trials in MDS

Agent	*N	Overall Response Rate (CR/PR/HI)	Duration of response (months)	Overall Survival (months)	Author
Azacitidine	99	47%	13.1	20	Silverman
Azacitidine	179	49%	13.6	24.5	Fenaux
Decitabine	89	30%	10.3	14	Kantarjian
Decitabine	99	30%	10	19.4	Steensma
Azacitidine	75	46%	12	18	Prebet
Azacitidine	92	38%	10	15	Sekeres

Silverman , JCO,2002, 2006
Fenaux, Lancet Oncol, 2009
Kantarjian, Cancer, 2006
Steensma, JCO, 2009
Prebet, JCO, 2014
Sekeres, JCO, 2017

CR rate in the 10-20% range across studies;
*N=number on hypomethylating agent arm of trial

Changing landscape in MDS?

- **Desire to propel combinations forward that may deepen responses and improve outcomes?**

- **Possibility of FDA approval of one or more HMA-based (doublet) combinations at some point for HR-MDS?**

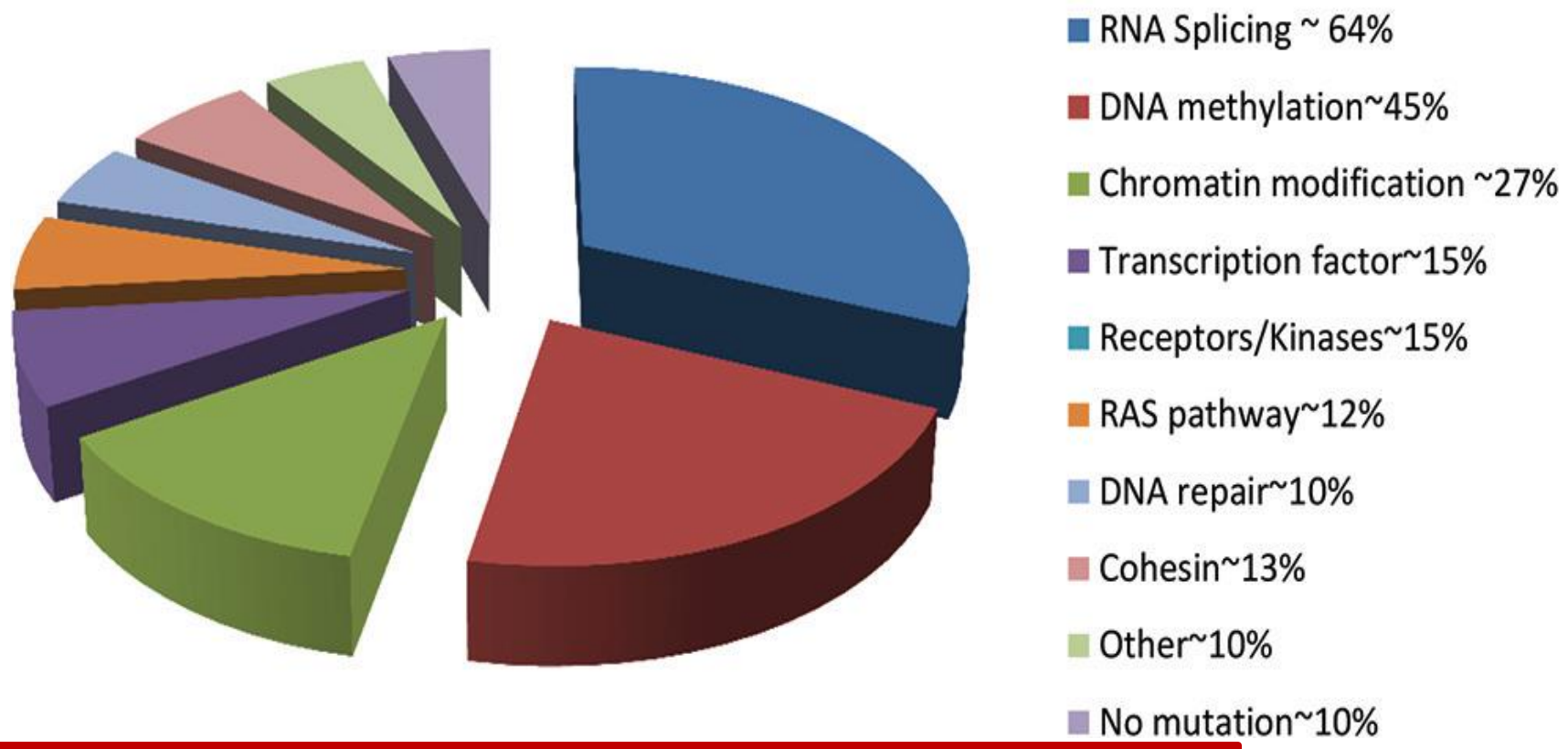
Selected Randomized Phase III Trials in frontline management of HR-MDS

Drug	NCT Identification	Patient characteristics	Intervention	Study outcomes
Venetoclax	NCT04401748 (VERONA) Estimated primary completion date: 02/2025	Newly-diagnosed HR-MDS Estimated enrollment: 500	Venetoclax + AZA vs. placebo + AZA	Primary Outcome: - Complete Remission (CR) based on IWG 2006 MDS criteria (Up to 36 Months) - Overall survival (OS) (Up to 5 years)
MBG453 (Sabatolimab)	NCT04266301 (STIMULUS-MDS2) Estimated primary completion date: 05/2027	Newly-diagnosed HR-MDS or CMML-2 Estimated enrollment: 500	MBG453+ AZA vs. placebo + AZA	Primary Outcome: - Overall Survival (Up to 5 years after last patient randomized)
Pevonedistat	NCT03268954 (PANTHER) Estimated Primary completion date: 07/2023	Newly-diagnosed HR-MDS, CMML, or Low-Blast AML Estimated enrollment: 502	Pevonedistat + AZA vs. AZA alone Open-label	Primary Outcome: - Event-Free Survival (From randomization until transformation to AML, or death due to any cause; up to 6 years)
Magrolimab	NCT04313881 (ENHANCE) Estimated primary completion date: 08/2022	Newly-diagnosed HR-MDS Estimated enrollment: 520	Magrolimab + AZA vs. AZA + placebo	Primary Outcomes: - Complete Remission (CR) based on IWG 2006 MDS criteria (Up to 24 Months) - Overall survival (OS) (Up to 5 years)
APR-246	NCT03745716 Actual primary completion date: 11/2020	Newly-diagnosed TP53-mutated HR-MDS Estimated enrollment: 154	APR-246 + AZA Vs. AZA alone Open-label	Primary Outcome: - Complete response rate (CR) with APR 246 + azacitidine vs. azacitidine only
SY-1425 (Tamibarotene)	NCT04797780 Estimated Primary completion date: 07/2023	Newly-diagnosed RARA-positive HR-MDS Estimated enrollment: 190	SY-1425 + AZA Vs. placebo + AZA	Primary outcome: - Complete response rate (CR) with SY-1425 + azacitidine vs. azacitidine only

DNMTi based combination therapy – lessons learned

- Combinations need to be tolerable and lend themselves to chronic dosing over extended periods of time
- Optimal schedules/sequence need to be carefully evaluated
- Development and incorporation of reliable predictive biomarkers
  - Move towards subset specific therapy

Mutations Occur in the Majority > 90% of Patients with MDS



RNA splicing:*SF3B1*, *SRSF2*, *U2AF1*, *U2AF2*, *ZRSR2*
DNA methylation: *TET2*, *DNMT3A*, *IDH1/2*
Chromatin modification: *ASXL1*, *EZH2*
Transcription factor: *TP53*, *EVI1*, *RUNX1*, *GATA2*
RAS/receptor kinase pathways:*NRAS*, *KRAS*, *CBL*, *JAK2*
*Chart is based on data from 944 MDS patients -**Haferlach et al, Leukemia 2014***

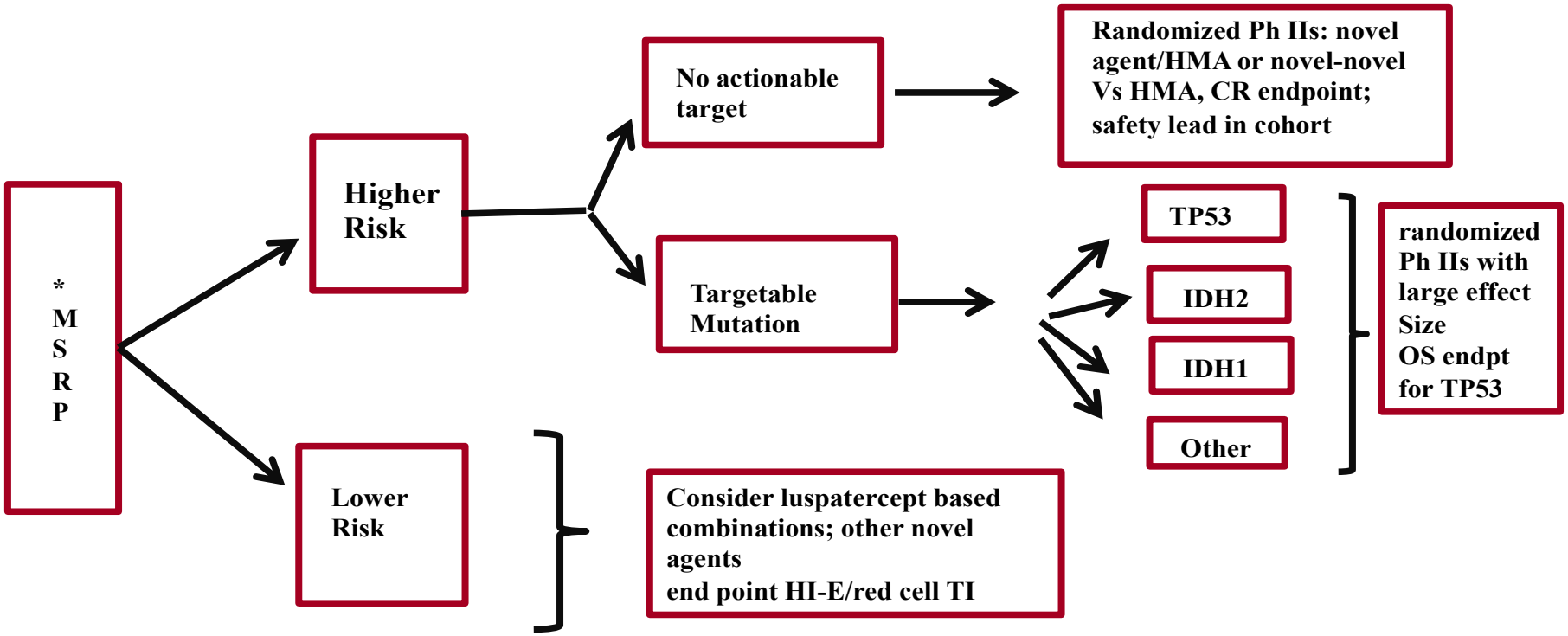
Odenike et al, ASCO Ed Book, 2015

IDH1 Inhibition in *IDH1*^{mut} MDS.

Author	Phase	Patient Population	Treatment	No. of Patients	CR Rate (%)	ORR (%)
Idiome Study Sebert et al, 2021	II	R/R HR-MDS	IVO	13	23	54
		HMA-naïve HR-MDS	IVO x 3 cycles; then IVO + Aza if no response	11	73	91
		LR-MDS failed prior ESA	IVO	2	50	50
Dinardo et al, 2022	I	R/R MDS	IVO	18	38.9	83
Watts et al, 2022	I	HMA-naïve and R/R HR-MDS	Oluta or Oluta + AZA	Oluta: 6 Oluta+AZA: 7	Oluta: 17 Oluta+AZA: 57	Oluta: 33 Oluta+AZA: 86

Sebert et al. ASH 2021; Dinardo et al. ASH 2022; Watts et al. Lancet Haematol 2022.

MDS Working Group Overview



*MSRP=myeloMATCH Screening and Reassessment Protocol

Looking to the future…targeted therapies in high risk myeloid neoplasms

- **Subset specific therapy is here to stay**
  - **has been validated in AML**

- **In MDS and high risk MPNs**
  - **90% harbor gene mutations**
  - **efforts need to be made to identify subsets that may benefit from specific approaches**

- **Accelerating clinical trial development by conducting focused early phase trials, and moving tolerable combinations more rapidly into the frontline setting.**