Management of Secondary AML (sAML); New Directions in AML Care

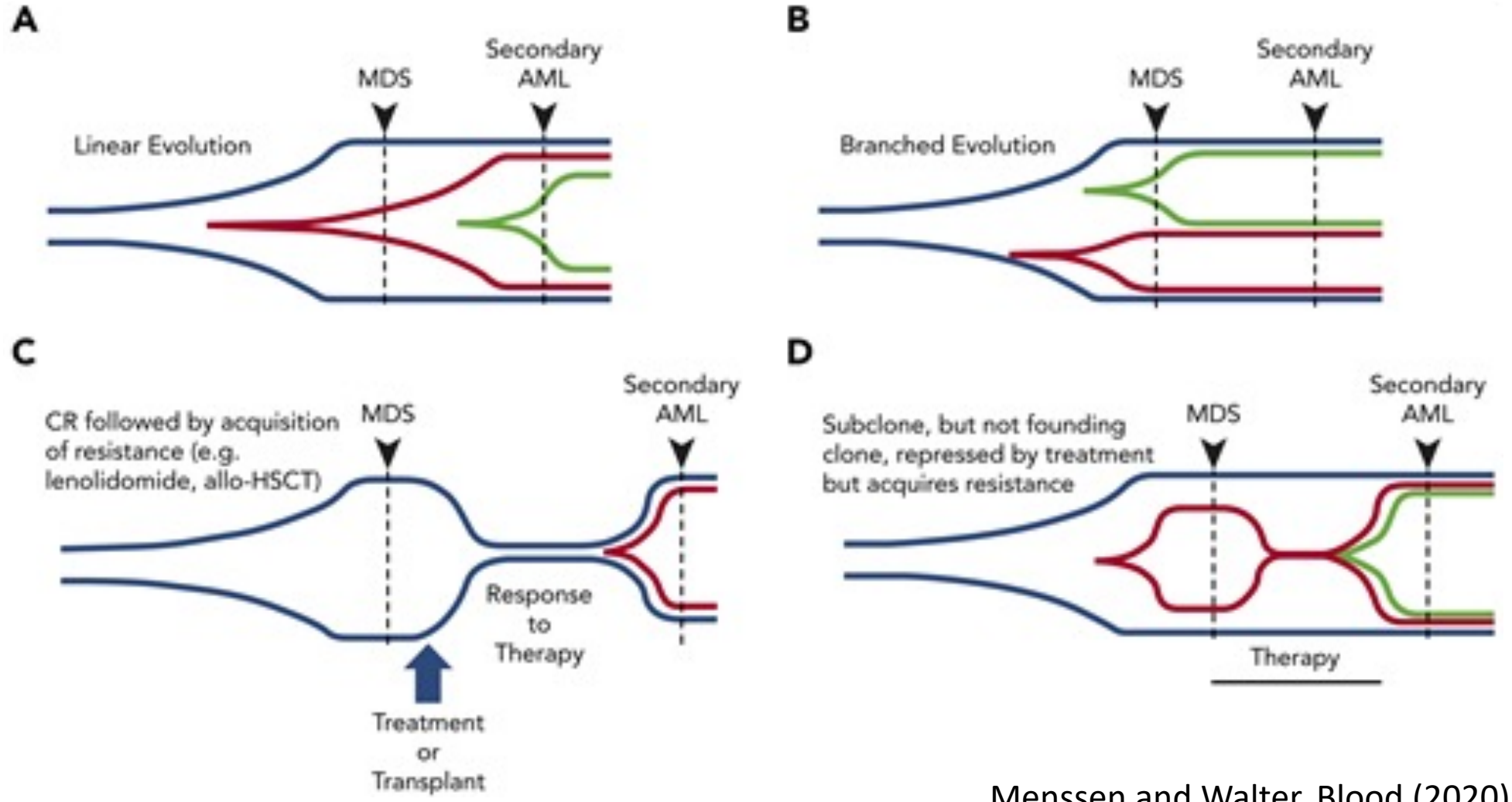
Geoffrey L Uy, MD

Secondary AML

- AML which occurs after antecedent MDS or MPN (sAML): 25-35%
- Complication of cytotoxic chemotherapy and/or radiation administered for unrelated disease (tAML): 10-20% of AML
  - Alkylator/ionizing radiation: 5-10 yr latency, loss of chromosome 5/7, TP53
  - DNA topoisomerase inhibitor related: 1-5 yr latency, rearrangements of 11q23/KMT2A
- Compared to *de novo* AML
  - Higher frequency of adverse-risk karyotype
  - More likely to be older, have poor PS and comorbidity

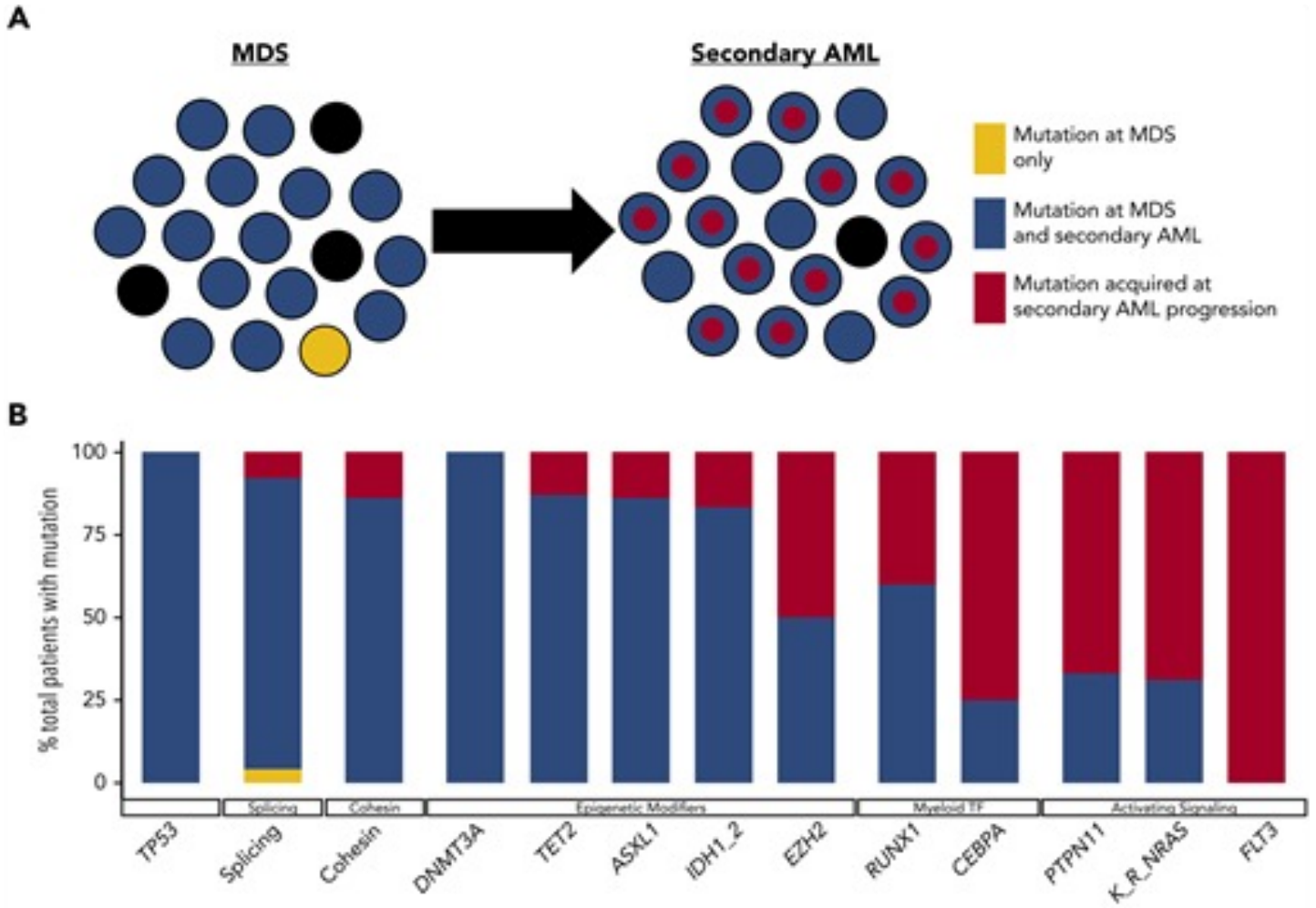
Granfeldt Østgård *et al*. JCO 2015**;** 33:3641-3649.

Patterns of clonal evolution during the progression of MDS to secondary AML



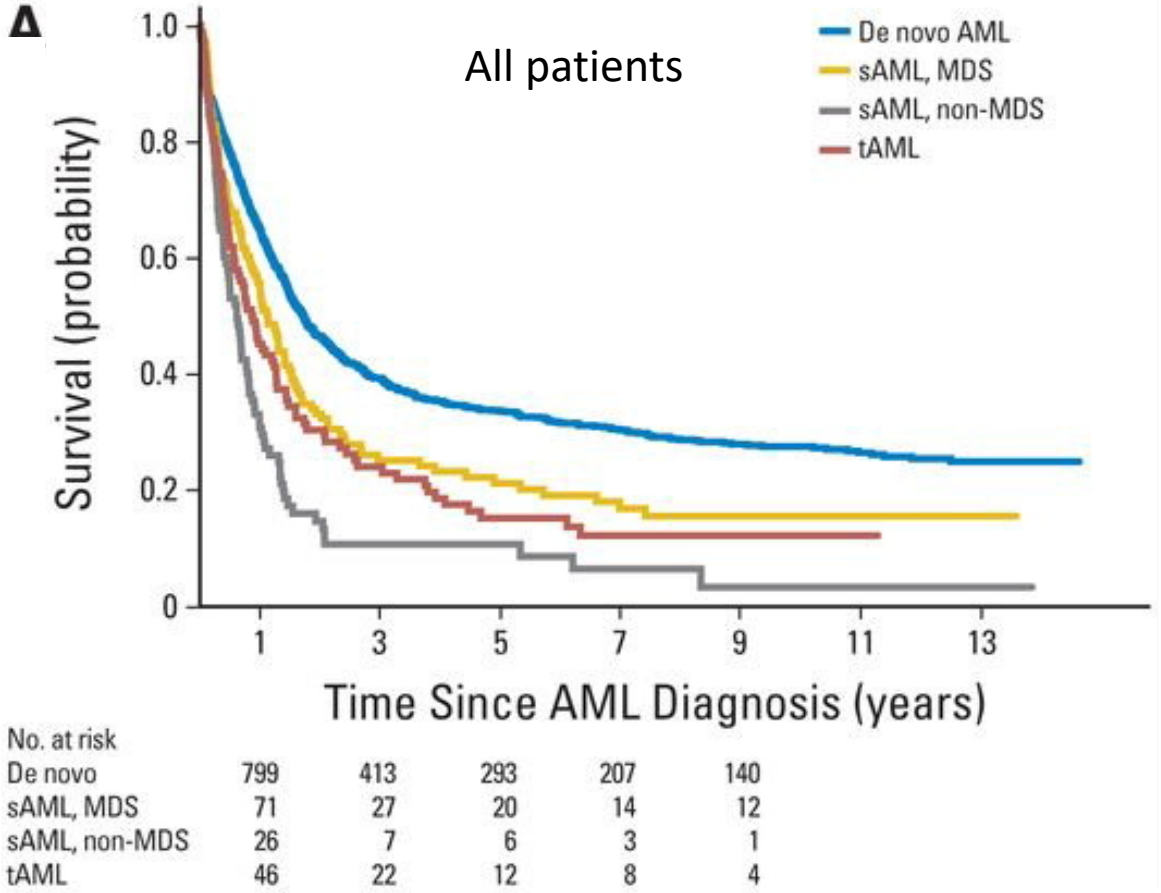
Menssen and Walter. Blood (2020) 136 (1): 50–60.

Clonal evolution during progression from MDS to secondary AML

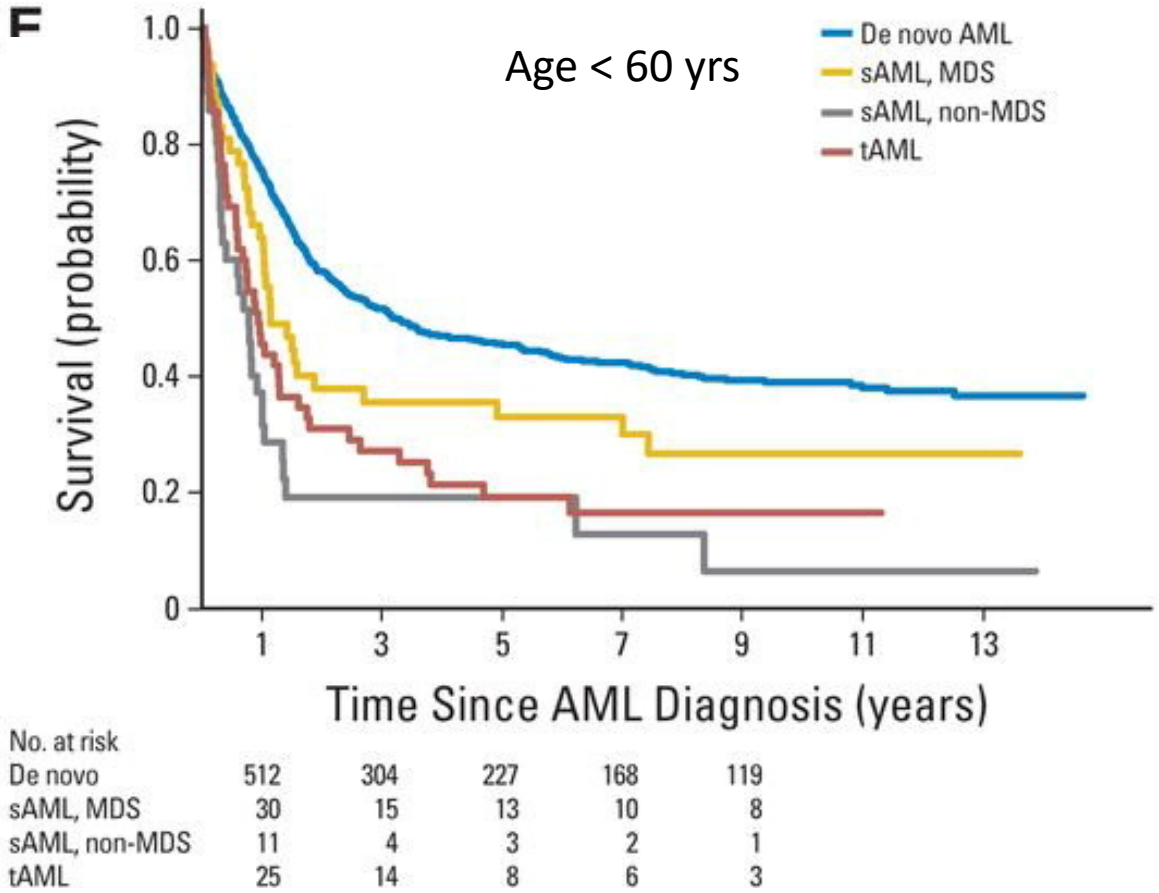


Menssen and Walter. Blood (2020) 136 (1): 50–60.

Outcome of AML receiving intensive therapy



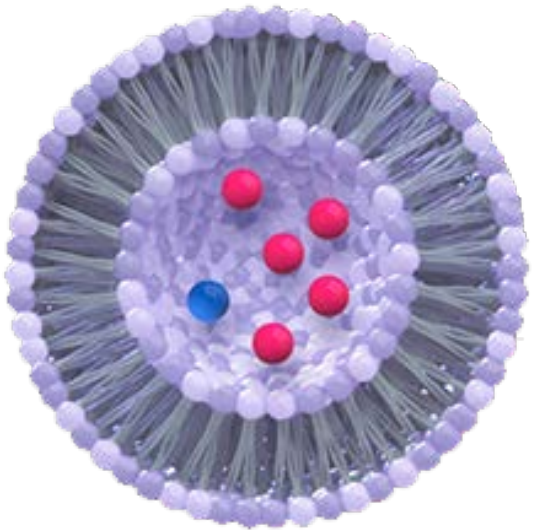
No. at risk					
De novo	799	413	293	207	140
sAML, MDS	71	27	20	14	12
sAML, non-MDS	26	7	6	3	1
tAML	46	22	12	8	4



No. at risk					
De novo	512	304	227	168	119
sAML, MDS	30	15	13	10	8
sAML, non-MDS	11	4	3	2	1
tAML	25	14	8	6	3

Granfeldt Østgård *et al*. JCO 2015; 33:3641-3649.

CPX-351 (Cytarabine:Daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia

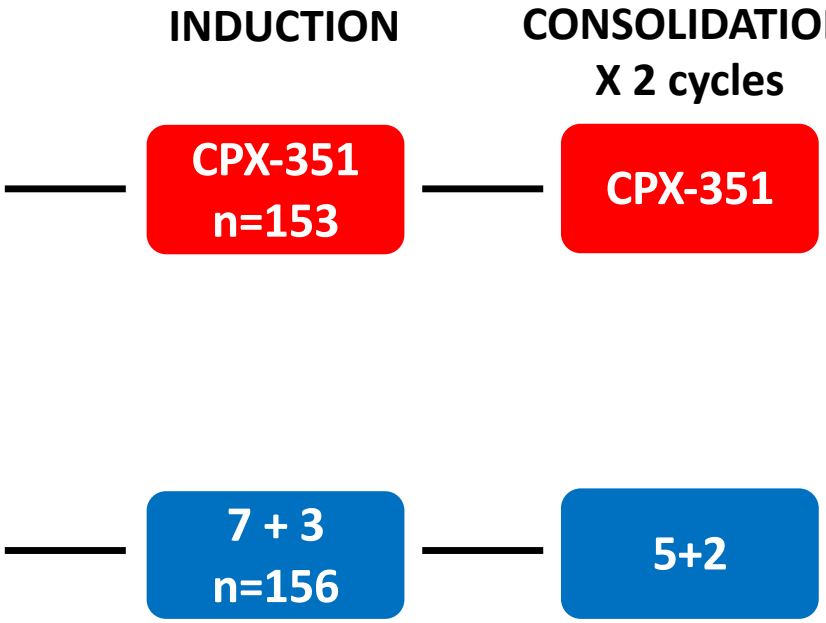


CPX-351

- Liposomal formulation of Daunorubicin:cytarabine 1:5 molar ratio
- Maintains drug exposure for 7 days
- Selective uptake by leukemic vs normal cells in bone marrow of leukemia-bearing mice

Key Eligibility

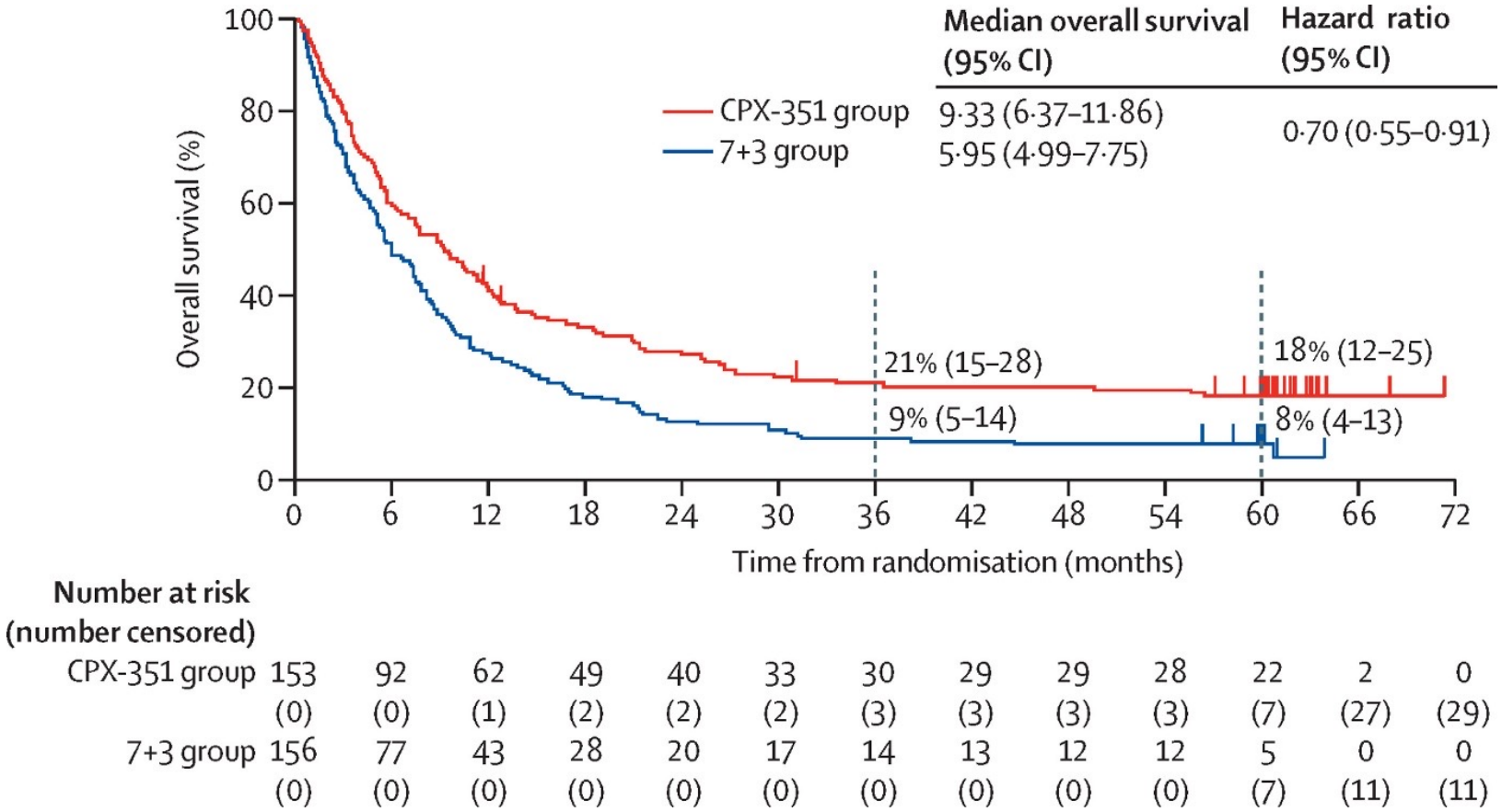
- Ages 60-75 years
- Untreated AML
- High-risk AML
  - Therapy-related AML
  - AML with history of MDS w/ and w/out prior HMA therapy
  - AML with history of CMML
  - *de novo* AML with MDS karyotype

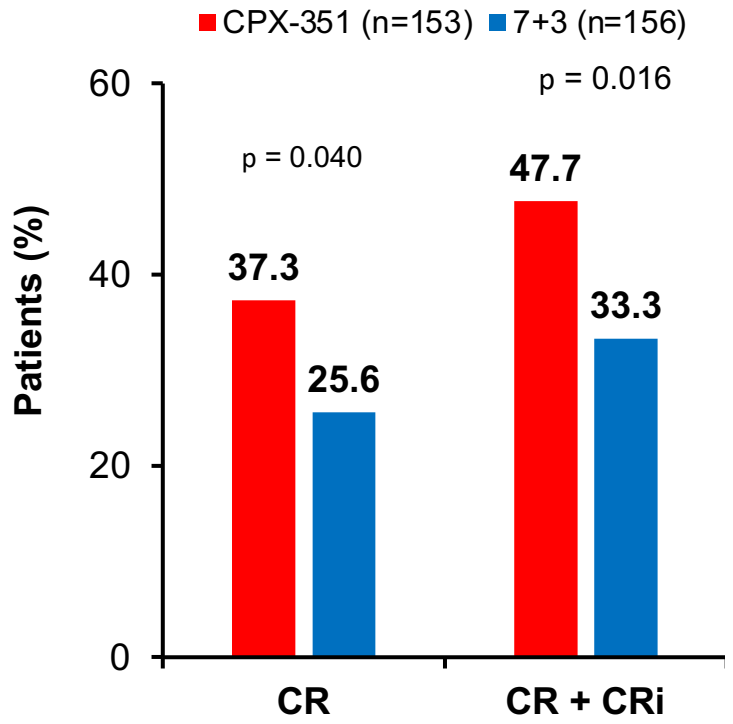


Primary Endpoint: Overall survival

Lancet et al., J Clin Oncol. 2018 Sep 10;36(26):2684-2692.

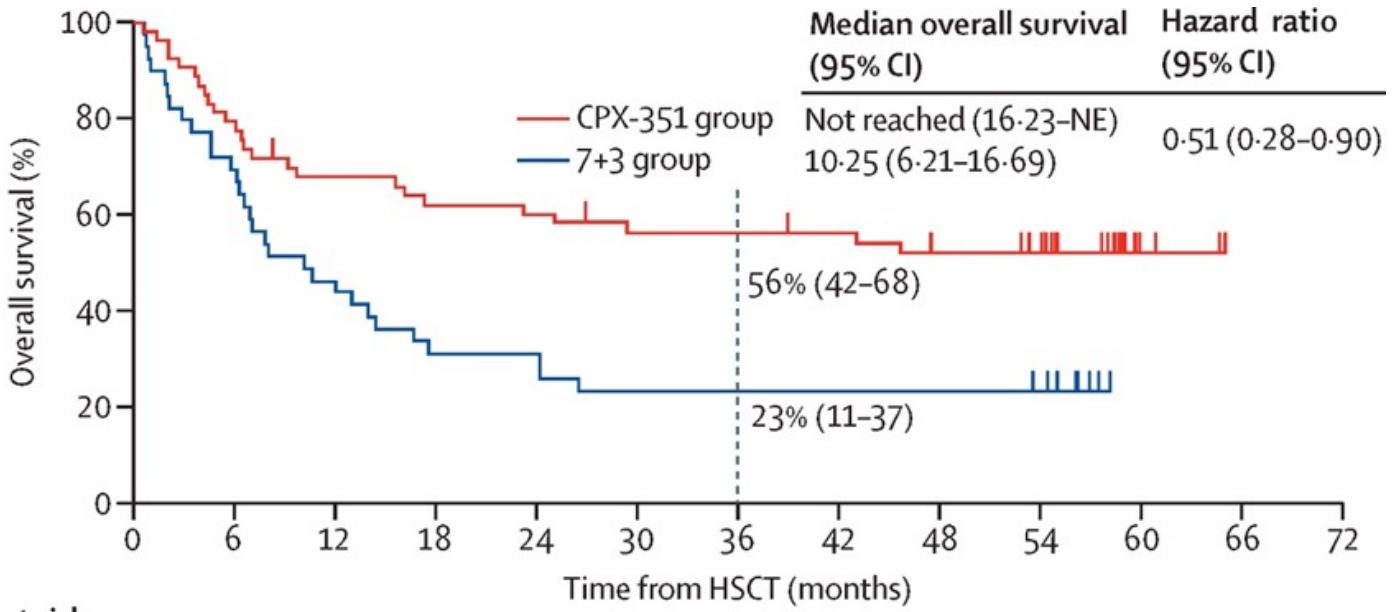
CPX-351-301 Study





Lancet et al., J Clin Oncol. 2018 Sep 10;36(26):2684-2692.
Lancet et al., Lancet Haematol. 2021 Jul;8(7):e481-e491.

Transplant Outcomes in CPX-351-301

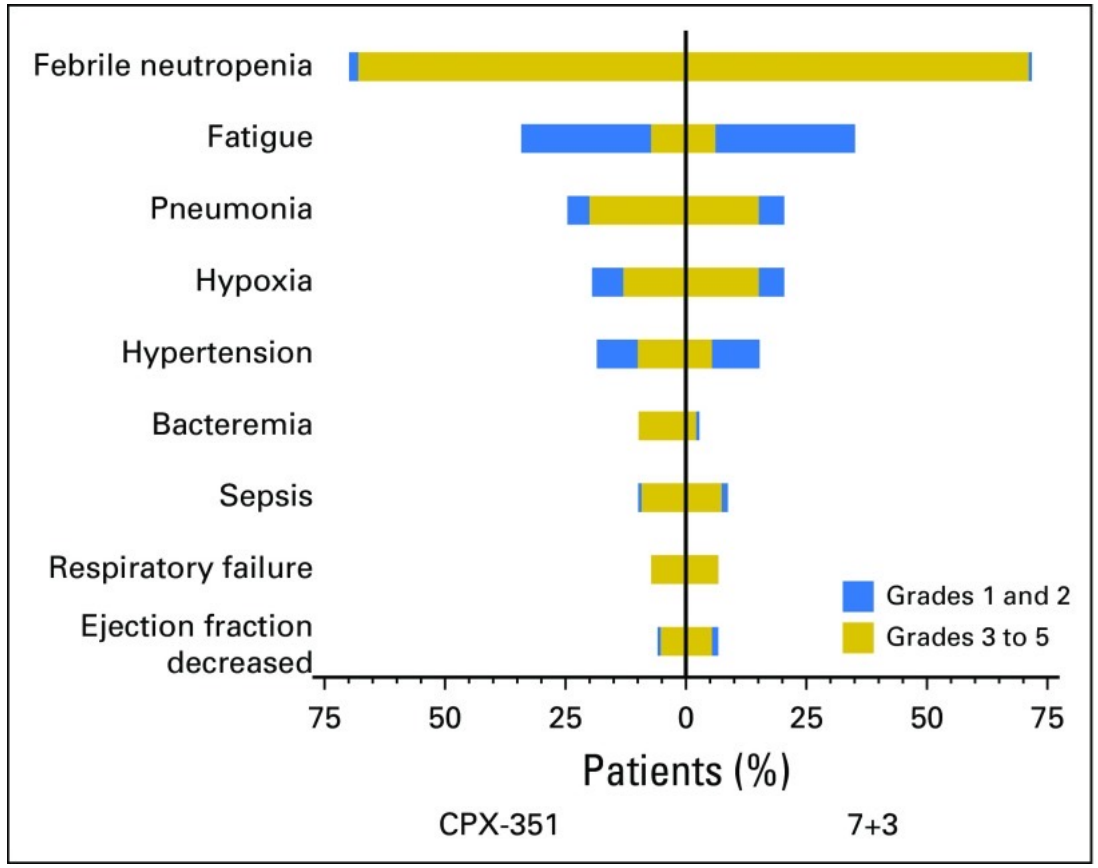


Number at risk (number censored)													
CPX-351 group	53 (0)	42 (0)	35 (1)	32 (1)	31 (1)	28 (2)	28 (2)	27 (3)	24 (4)	21 (7)	6 (22)	0 (28)	0 (28)
7+3 group	39 (0)	27 (0)	18 (0)	12 (0)	12 (0)	9 (0)	9 (0)	9 (0)	9 (0)	8 (1)	0 (9)	0 (9)	0 (9)

Characteristic (%)	CPX-351 (n=53)	7+3 (n=39)
60-69 yrs	37 (70)	33 (85%)
70-75 yrs	16 (30)	6 (15)
HCT in CR/CRi	39 (75)	24 (62)

Lancet et al., Lancet Haematol. 2021 Jul;8(7):e481-e491.

Adverse Events in CPX-351-301

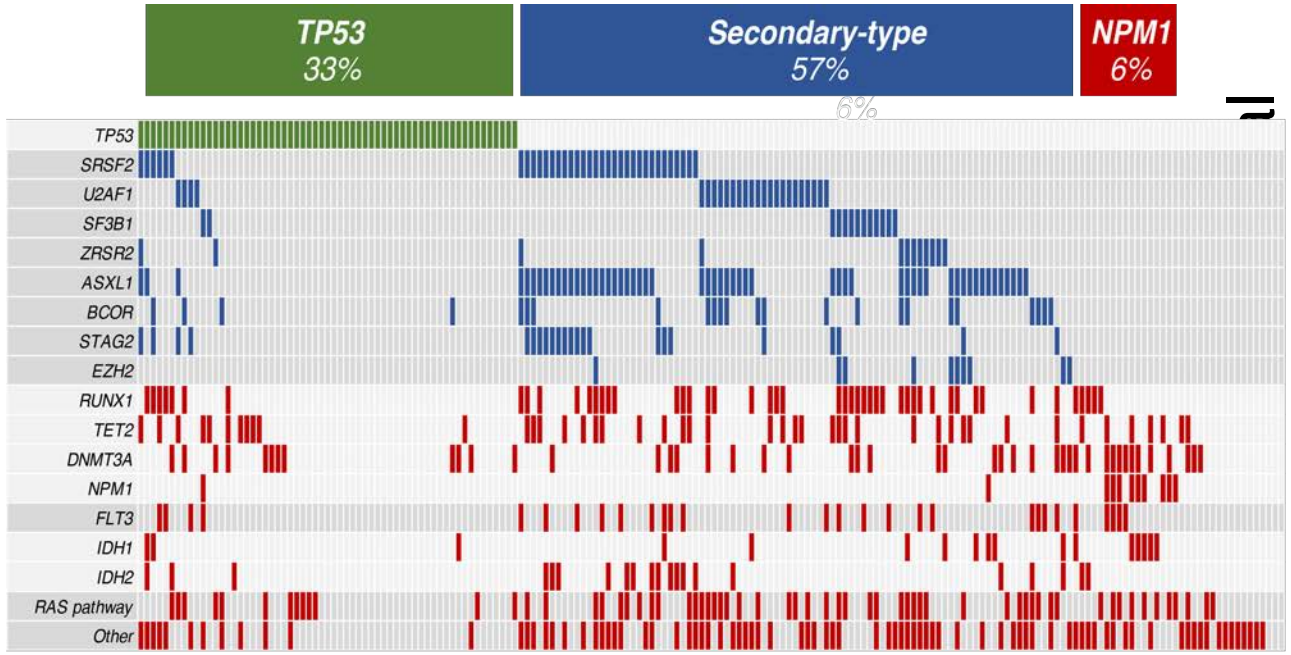


Hematologic Recovery	**CPX-351 (n=58)**	**7 + 3 (n=34)**
ANC ≥ 500/uL, median	35	29
Platelets ≥ 50,000/uL, median	36.5	29

Early Mortality	**CPX-351**	**7 + 3**
Mortality at 30 days	5.9%	10.6%
Mortality at 60 days	13.7%	21.2%

Lancet et al., J Clin Oncol. 2018 Sep 10;36(26):2684-2692.

Outcomes in CPX-351-301 by TP53 status



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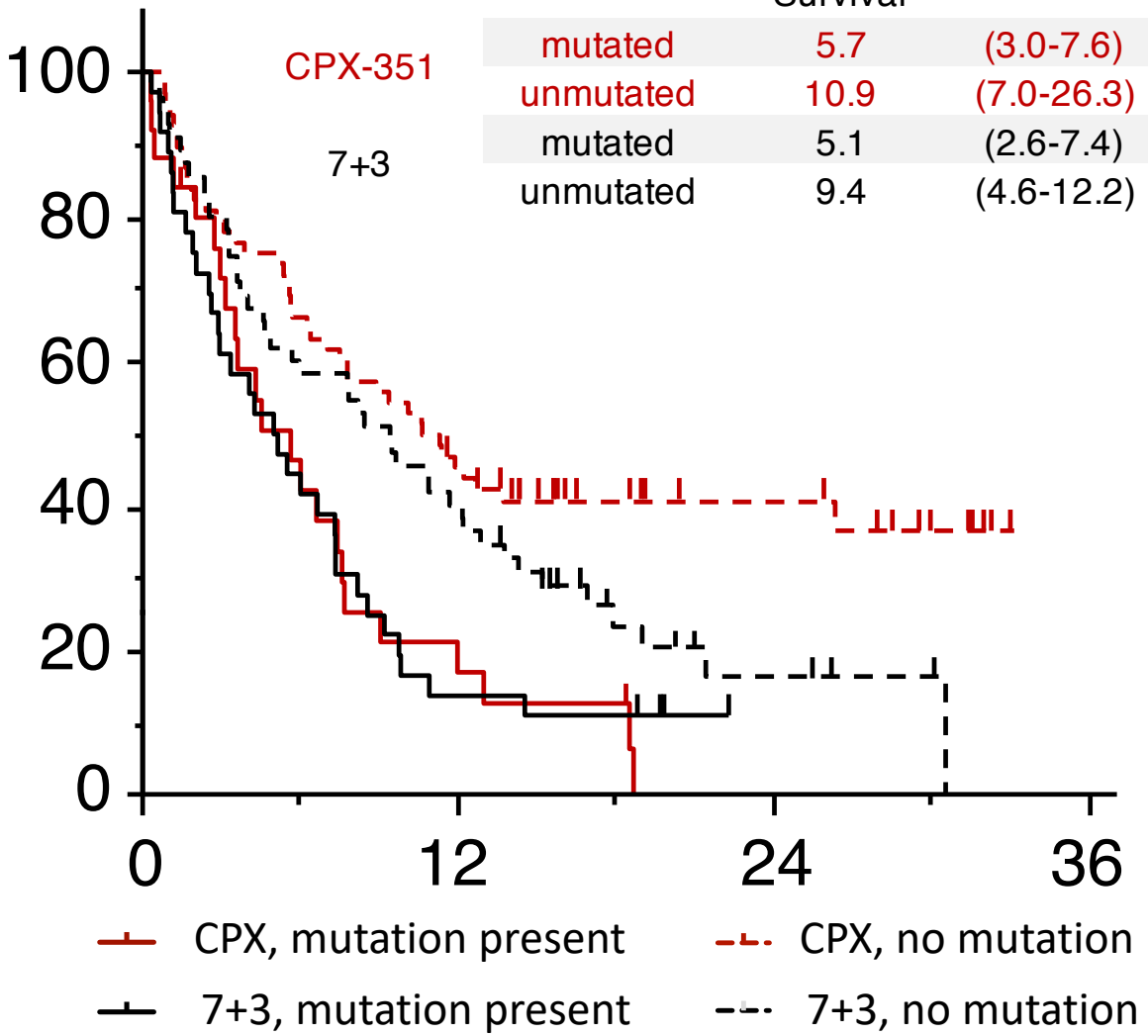
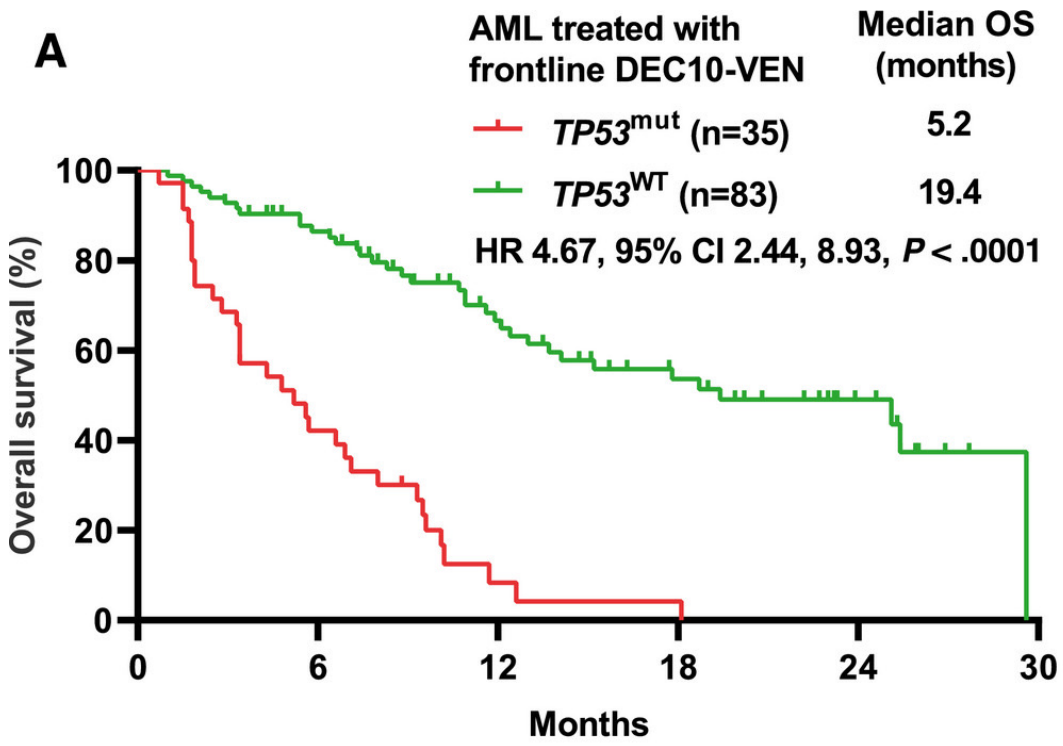
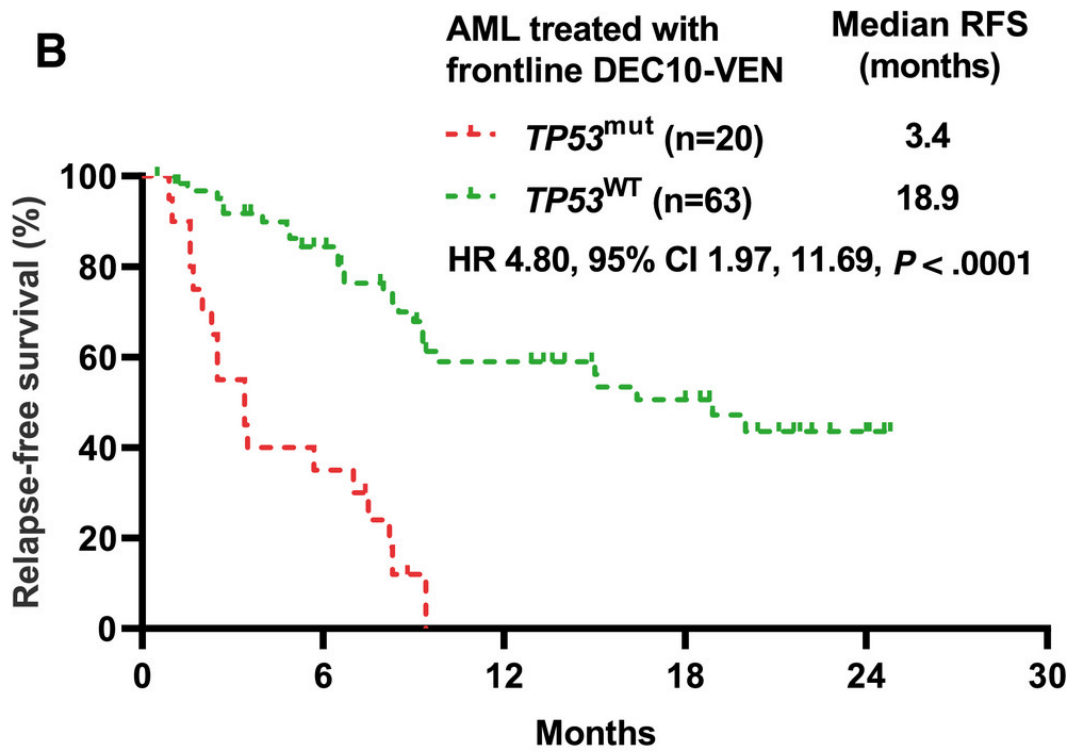


	Median Survival	(95% CI)
mutated	5.7	(3.0-7.6)
unmutated	10.9	(7.0-26.3)
mutated	5.1	(2.6-7.4)
unmutated	9.4	(4.6-12.2)

Lindsley, et al., ASH 2019

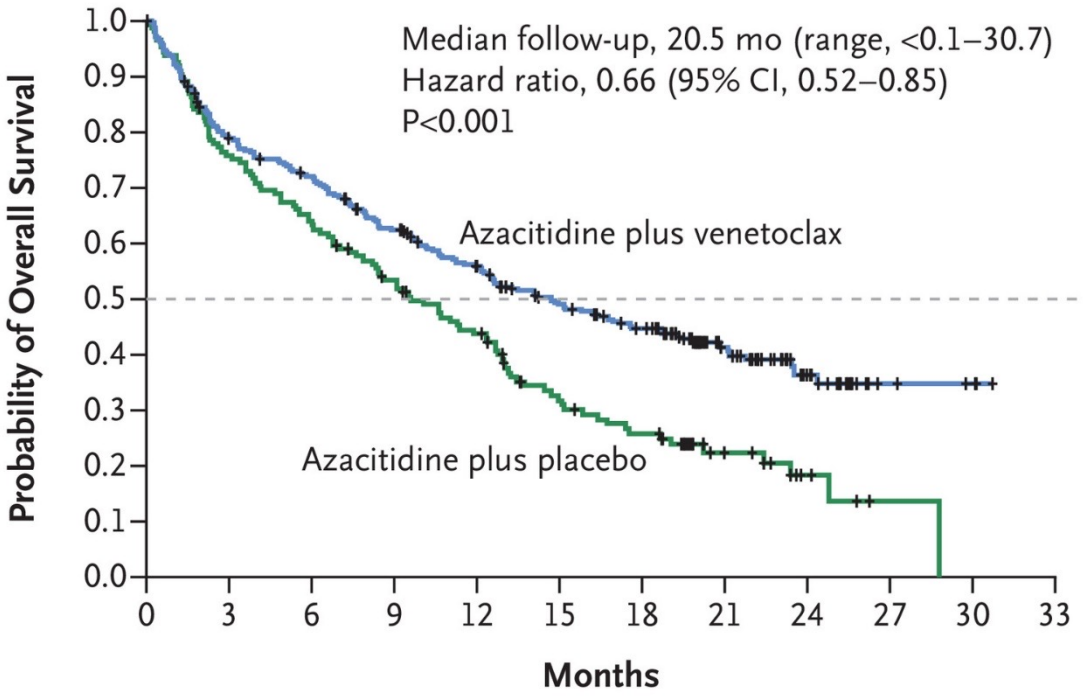
Decitabine + Venetoclax in TP53 AML

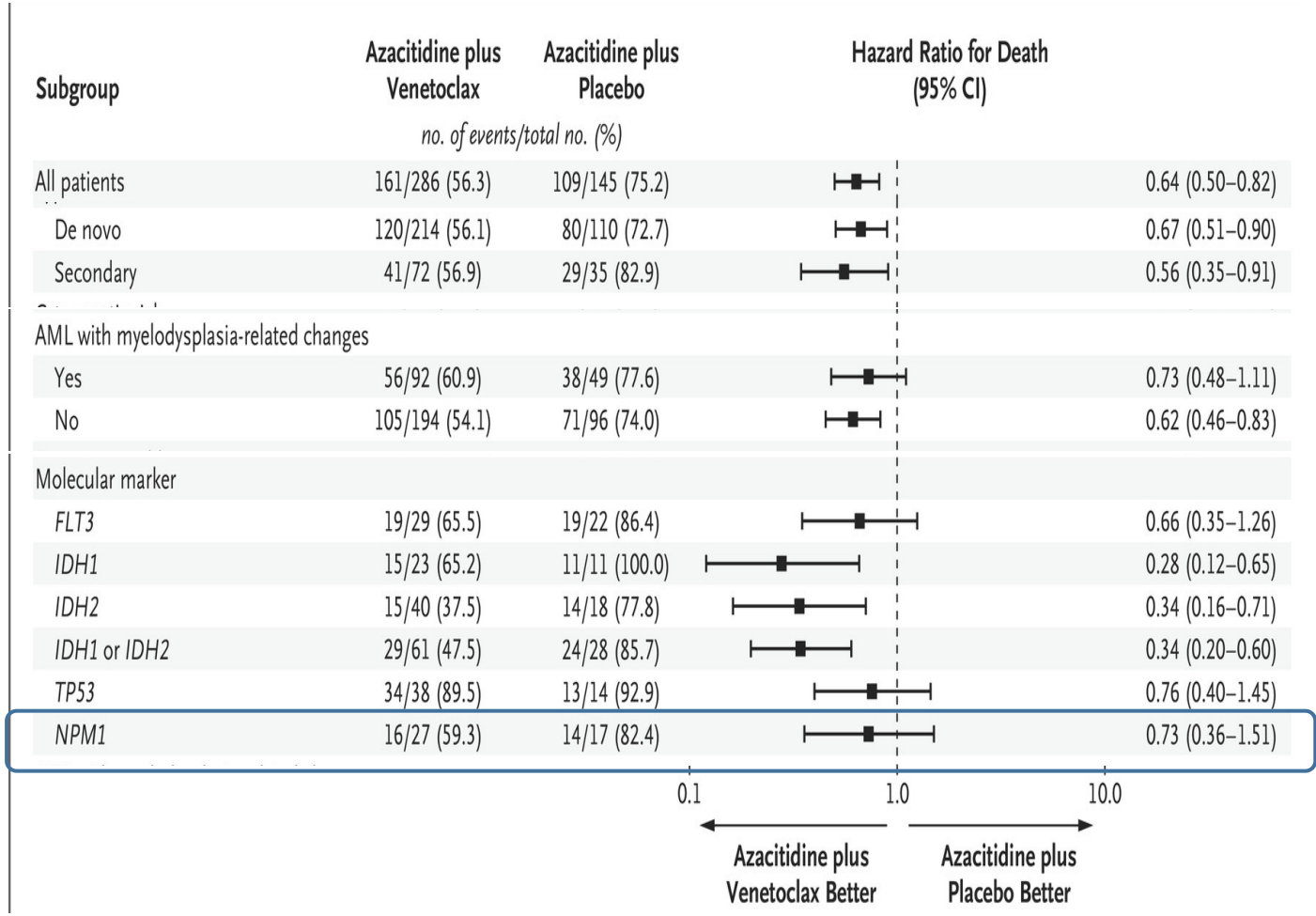




Kim et al., Cancer. 2021 Oct 15;127(20):3772-3781.

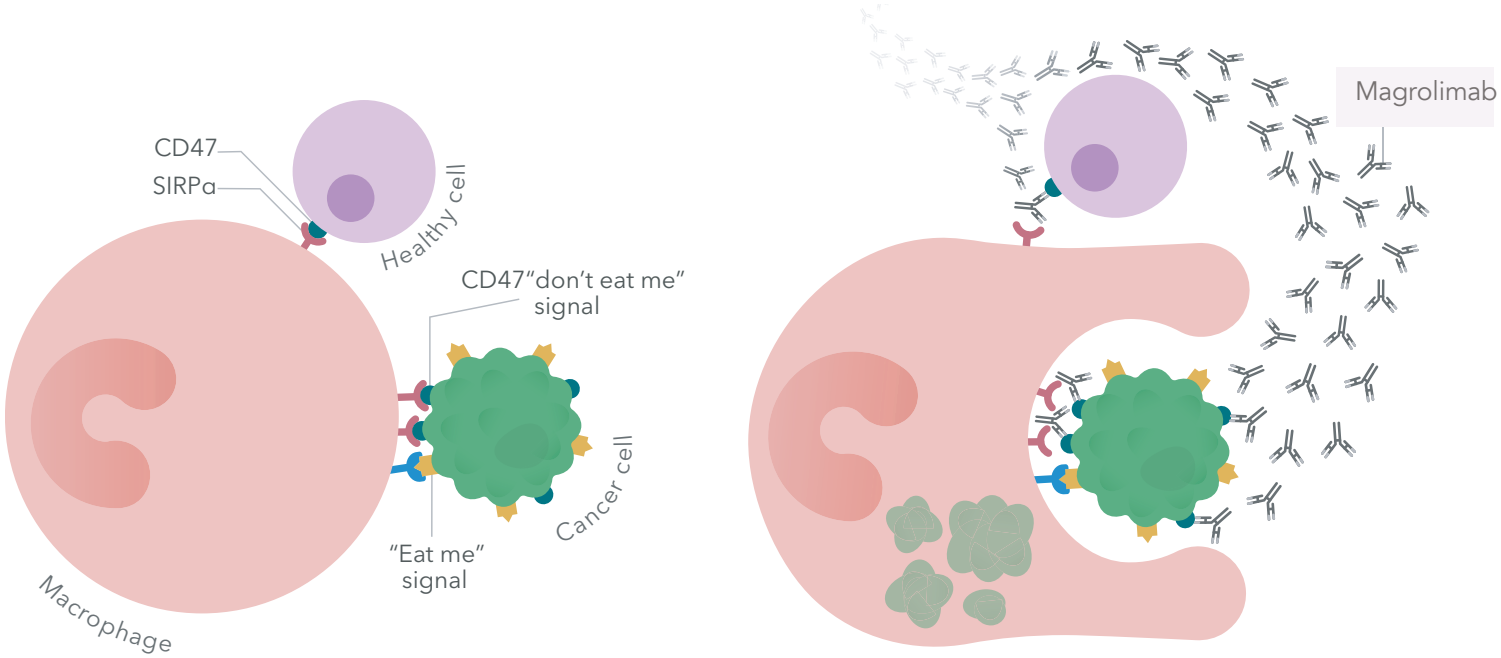
Azacitidine / Venetoclax in VIALE-A



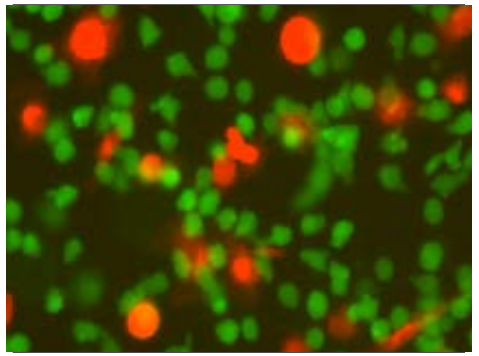


DiNardo et al, N Engl J Med 2020; 383:617-629

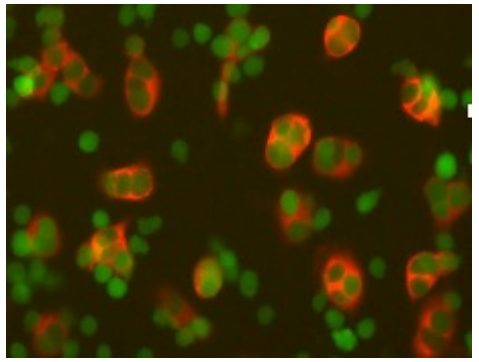
Magrolimab: Macrophage Immune Checkpoint Inhibitor Targeting CD47



Control mAb: No Phagocytosis



Anti-CD47 mAb: Phagocytosis



Macrophages
Cancer cells

- CD47 is a "do not eat me" signal that is overexpressed in multiple cancers, including acute myeloid leukemia, leading to macrophage immune evasion
- Magrolimab, an IgG4 anti-CD47 monoclonal antibody (mAb), eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dose

Sallman et al., ASH 2020

5F9005 Study: Magrolimab in Combination With AZA in AML and MDS

Untreated AML ineligible for induction chemotherapy or untreated MDS intermediate to very high risk by IPSS-R

Primary Objectives

1. Safety of magrolimab alone or with AZA
2. Efficacy of magrolimab + AZA in untreated AML/MDS

Secondary Objectives

1. Pharmacokinetics, pharmacodynamics, and immunogenicity of 5F9
2. Additional measures of efficacy (DOR, PFS, OS)

Exploratory Objective

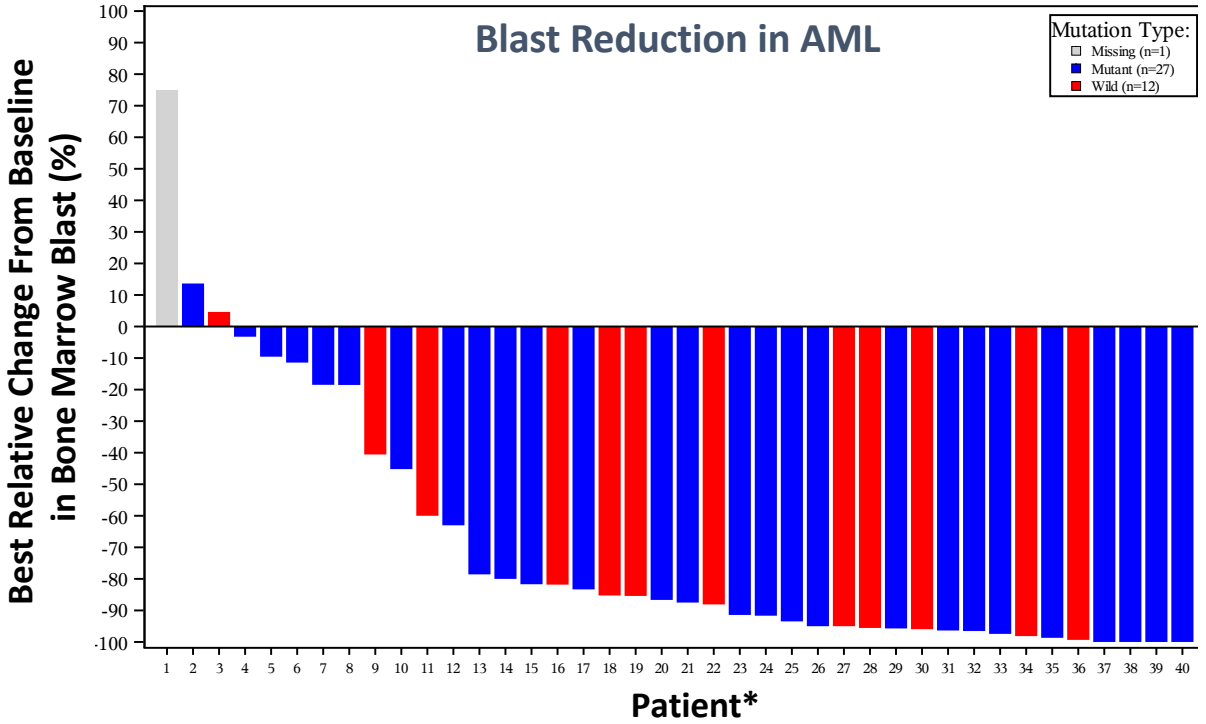
To assess CD47 receptor occupancy, markers of immune cell activity, and molecular profiling in AML/MDS

- A magrolimab priming dose (1 mg/kg) and dose ramp-up were utilized to mitigate on-target anemia
- Data from the AML expansion cohort are presented

- *Dose ramp-up from 1 mg/kg to 30 mg/kg by week 2, then 30 mg/kg maintenance dosing.
- IPSS-R: Revised International Prognostic Scoring System.

Magrolimab + AZA Induces High Response Rates in AML

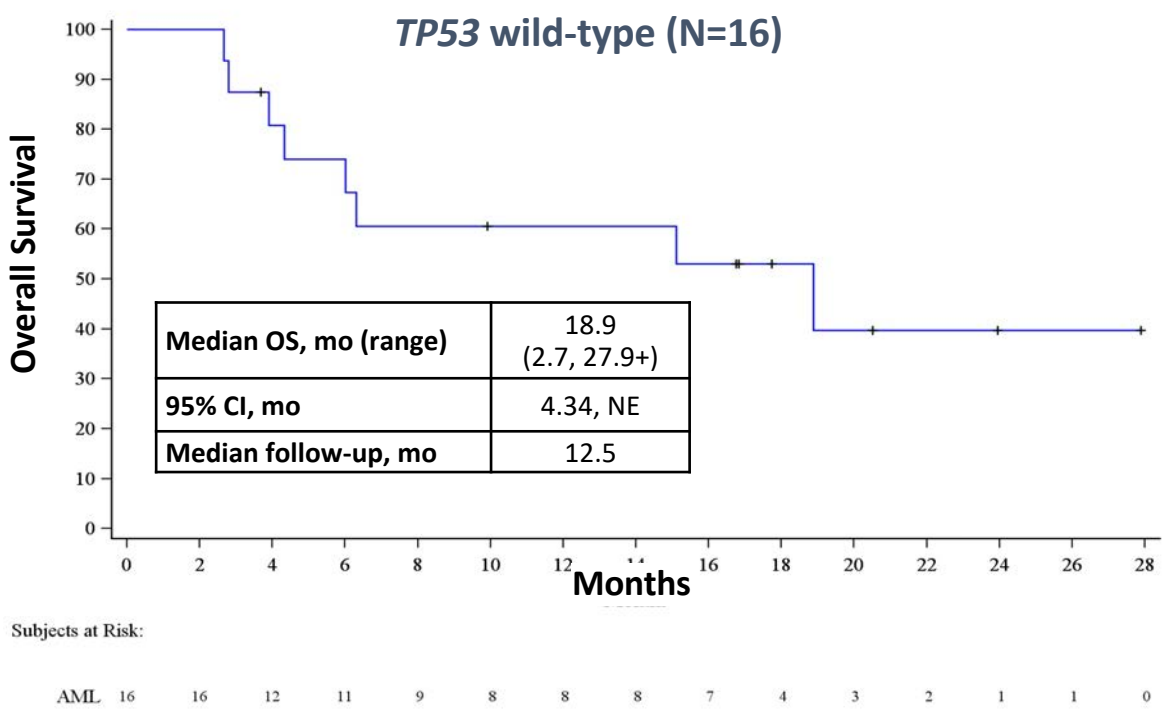
Best Overall Response	All AML (N=43)	*TP53*-mutant AML (29)
ORR	27 (63%)	20 (69%)
CR	18 (42%)	13 (45%)
CRi	5 (12%)	4 (14%)
PR	1 (2%)	1 (3%)
MLFS	3 (7%)	2 (7%)
SD	14 (33%)	8 (28%)
PD	2 (5%)	1 (3%)

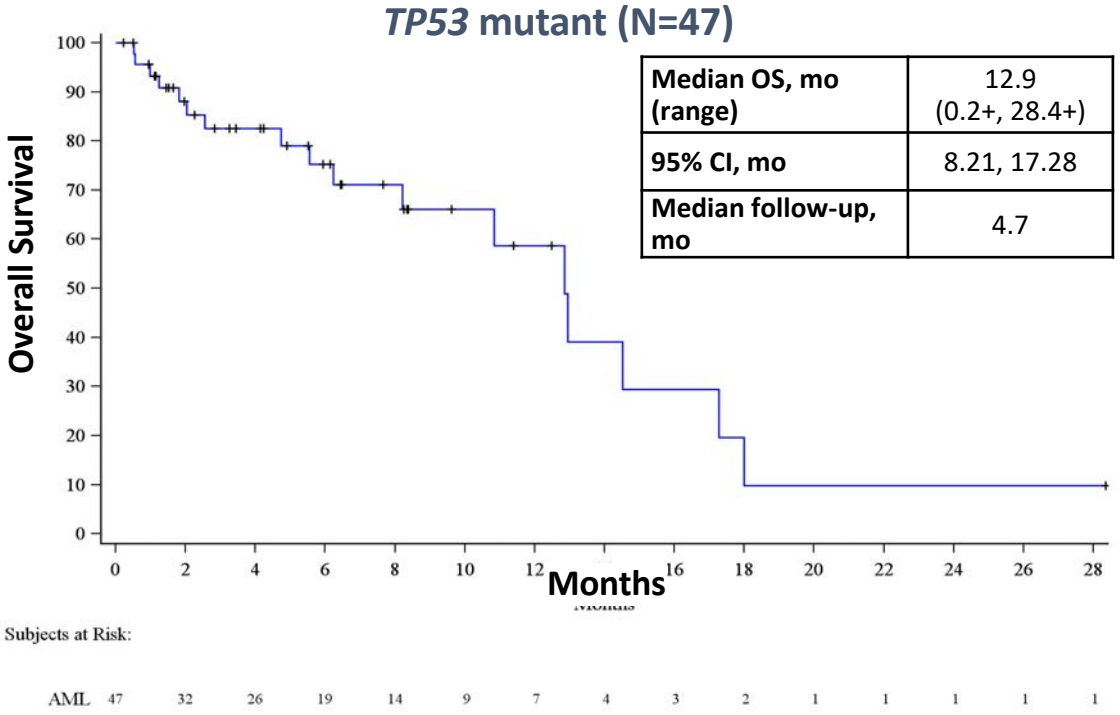


- Magrolimab + AZA induces a 63% ORR and 42% CR rate in AML, including similar responses in *TP53*-mutant patients
- Median time to response is 1.95 months (range 0.95 to 5.6 mo), more rapid than AZA monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab + AZA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



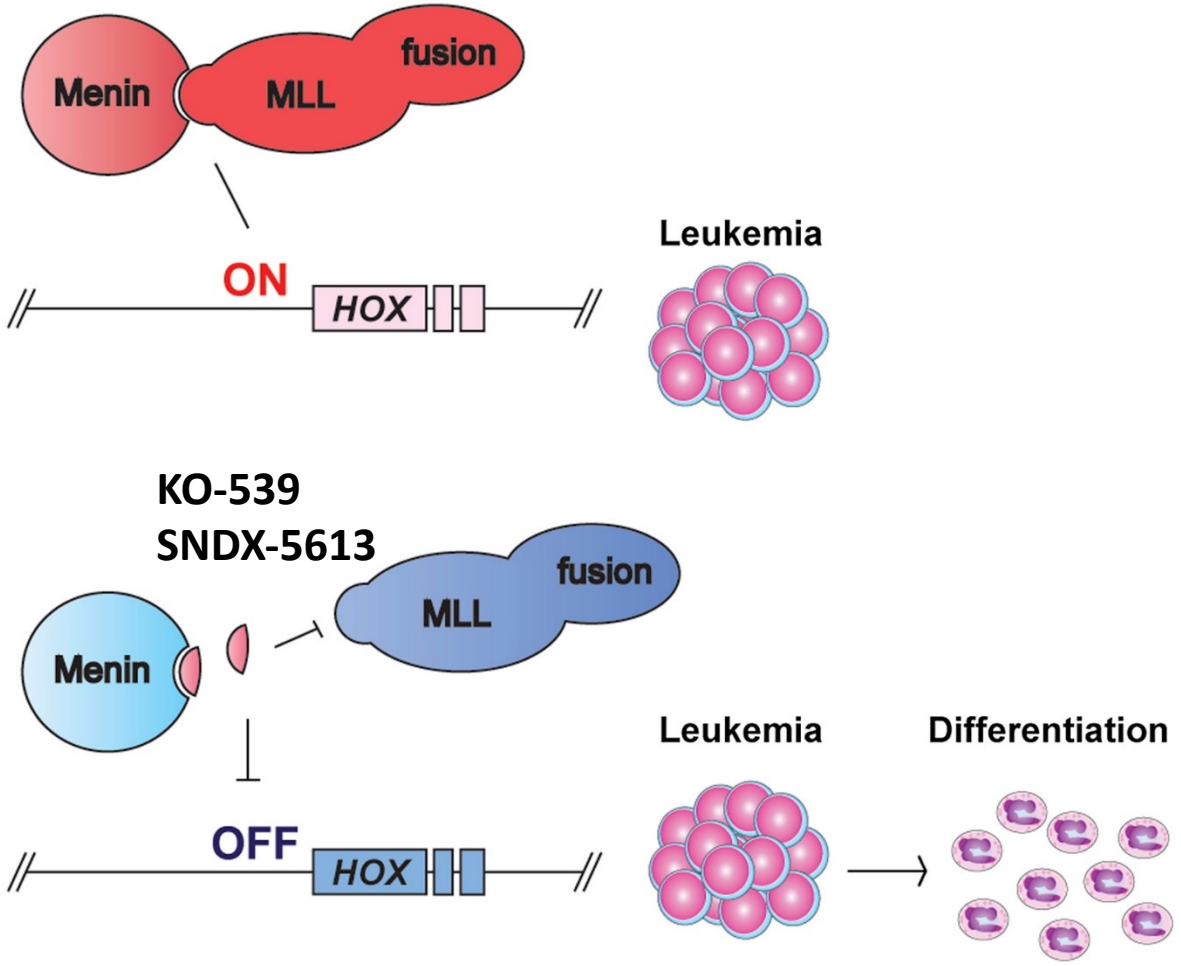


- The median OS is 18.9 months in *TP53* wild-type patients and 12.9 months in *TP53*-mutant patients
- This initial median OS data may compare favorably to venetoclax + hypomethylating agent combinations (14.7-17.5 mo in all-comers,[1,3] 5.2–7.2 mo in patients who are *TP53* mutant[2,3])
- Additional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

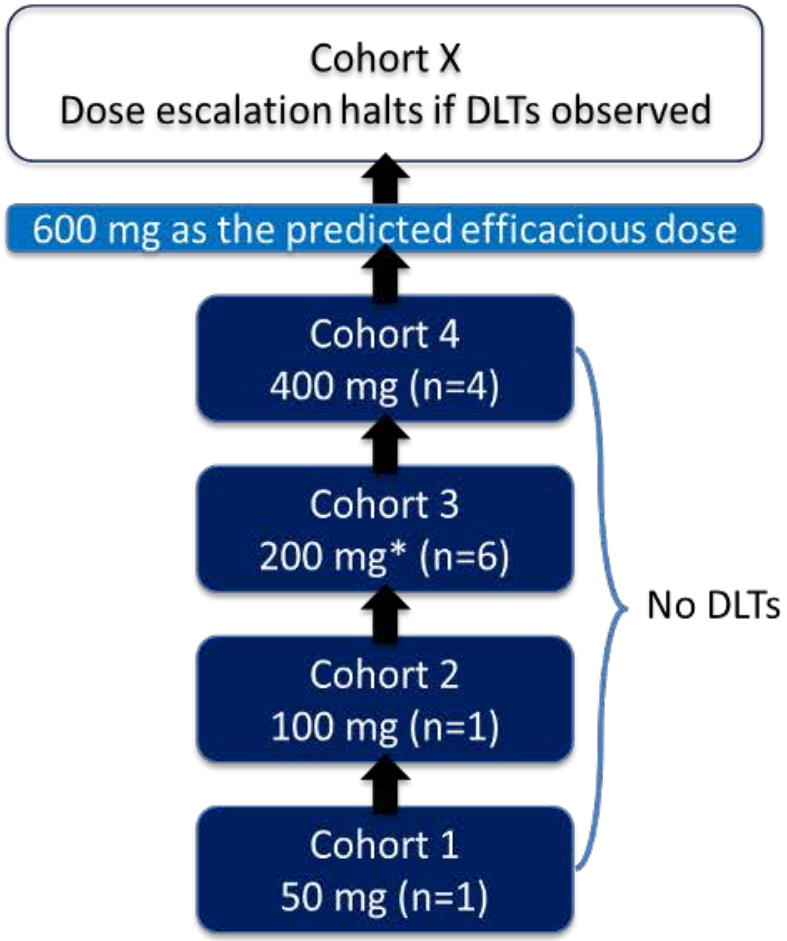
Menin Inhibitors for KMT2A (MLL) rearranged and NPM1^{mut} AML

- KMT2A (MLL)
  - histone methyltransferase that regulates gene expression via chromatin remodeling
  - >120 fusion partners have been described in acute leukemia
  - Associated with infantile leukemia, topoisomerase II inhibitors t-AML
- Menin: scaffold protein that interacts with cell signaling and gene regulators
- Orally available menin inhibitors currently in P1/2 studies
  - KO-539
  - SNDX-5613



Kuhn and Armstrong, Cancer Cell. 2015 Apr 13;27(4):431-3.

KO-539 Shows Encouraging Early Clinical Activity



*Expanded to characterize PK

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

Data as of 02 November 2020

Wang et al., ASH 2021

ASH Abstracts in AML

Title	Presenter	Time
Abstract 2316. Phase 1b Study of Lower-Dose CPX-351 Plus Venetoclax As First-Line Treatment for Patients with AML Who Are Unfit for Intensive Chemotherapy: Preliminary Safety and Efficacy Result	Geoffrey L. Uy	Sunday, December 12, 2021, 6:00 PM-8:00 PM
Abstract 1268. Preliminary Results By Age Group of Treatment with CPX-351 Plus Venetoclax in Adults with Newly Diagnosed AML: Subgroup Analysis of the V-FAST Phase 1b Master Trial	Vinod A. Pullarkat	Saturday, December 11, 2021, 5:30 PM-7:30 PM
Abstract 3426 A Phase 3, Randomized, Open-Label Study Evaluating the Safety and Efficacy of Magrolimab in Combination with Azacitidine in Previously Untreated Patients with TP53-Mutant Acute Myeloid Leukemia	Naval Daver	Monday, December 13, 2021, 6:00 PM-8:00 PM
Abstract 699. Safety and Efficacy of Menin Inhibition in Patients (Pts) with MLL-Rearranged and NPM1 Mutant Acute Leukemia: A Phase (Ph) 1, First-in-Human Study of SNDX-5613 (AUGMENT 101)	Eytan M. Stein	Monday, December 13, 2021: 3:15 PM
Abstract 540 A Pilot Study of CPX-351 for Transplant Eligible, Higher Risk Patients with Myelodysplastic Syndrome	Megan A. Jacoby	Sunday, December 12, 2021, 4:30 PM-6:00 PM