Oncology Today with Dr Neil Love — Novel Agents and Strategies in Acute Myeloid Leukemia

A CME/MOC-Accredited Virtual Event

Thursday, November 17, 2022
5:00 PM – 6:00 PM ET

Faculty

Daniel A Pollyea, MD, MS

Moderator

Neil Love, MD

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Faculty

Daniel A Pollyea, MD, MS
Professor of Medicine
Clinical Director of Leukemia Services
Robert H Allen, MD Chair in Hematology Research
Division of Hematology
University of Colorado School of Medicine
Aurora, Colorado

Live Moderator
Neil Love, MD
Research To Practice

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Novel Agents and Strategies in AML

DR EYTAN STEIN
MEMORIAL SLOAN KETTERING CANCER CENTER

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BCMA-Directed Therapy in Multiple Myeloma — Expert Opinions and Patient Perspectives

Part 2 of a 2-Part CME/MOC-Accredited Virtual Series

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Part 1 of a 2-Part CME Satellite Symposium Series Held in Conjunction with the 2022 San Antonio Breast Cancer Symposium®

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Chief, Leukemia Service

Director, Program for Drug Development in Leukemia
Memorial Sloan Kettering Cancer Center

New York, New York

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CME and MOC credit information will be emailed to each participant within 5 business days.

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ASH 2022; other key papers

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Memorial Sloan Kettering
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Novel Agents and Strategies in Acute Myeloid Leukemia

Eytan M. Stein, MD

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Memorial Sloan Kettering Cancer Center

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AML 2014 to 2022

Dr Eytan Stein (New York, New York)

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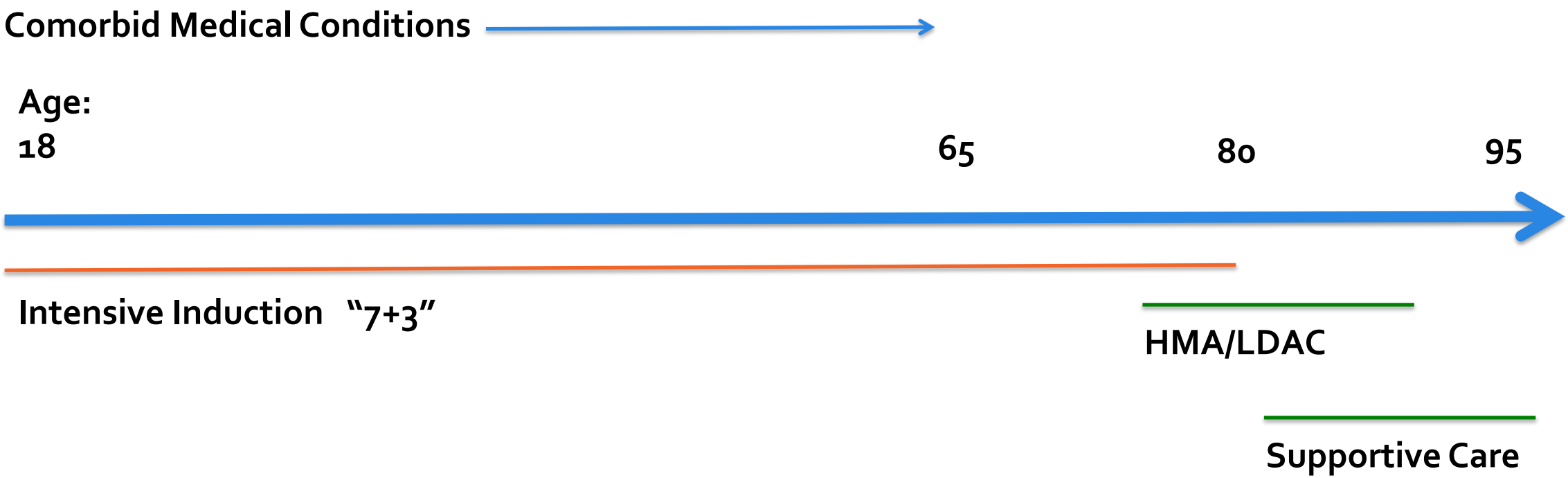
Historical Paradigms for Treating Newly Diagnosed AML



Defining AML versus MDS

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Case 1: 82-year-old man presenting with cytopenias and AML

Dr Stein

A Typical AML Patient

- 82 year old man with newly diagnosed AML associated with trisomy 8 and a DNMT3A mutation

- He has a history of coronary artery disease, hypertension, hyperlipidemia, and diabetes well controlled on oral anti-hypoglycemics

- On baseline labs, white blood count is 2.1, Hgb is 7.9, platelets are 43. Absolute neutrophil count is 0.7 and he has 10% circulating myeloblasts

Case 1: 82-year-old man presenting with cytopenias and AML — Follow-up

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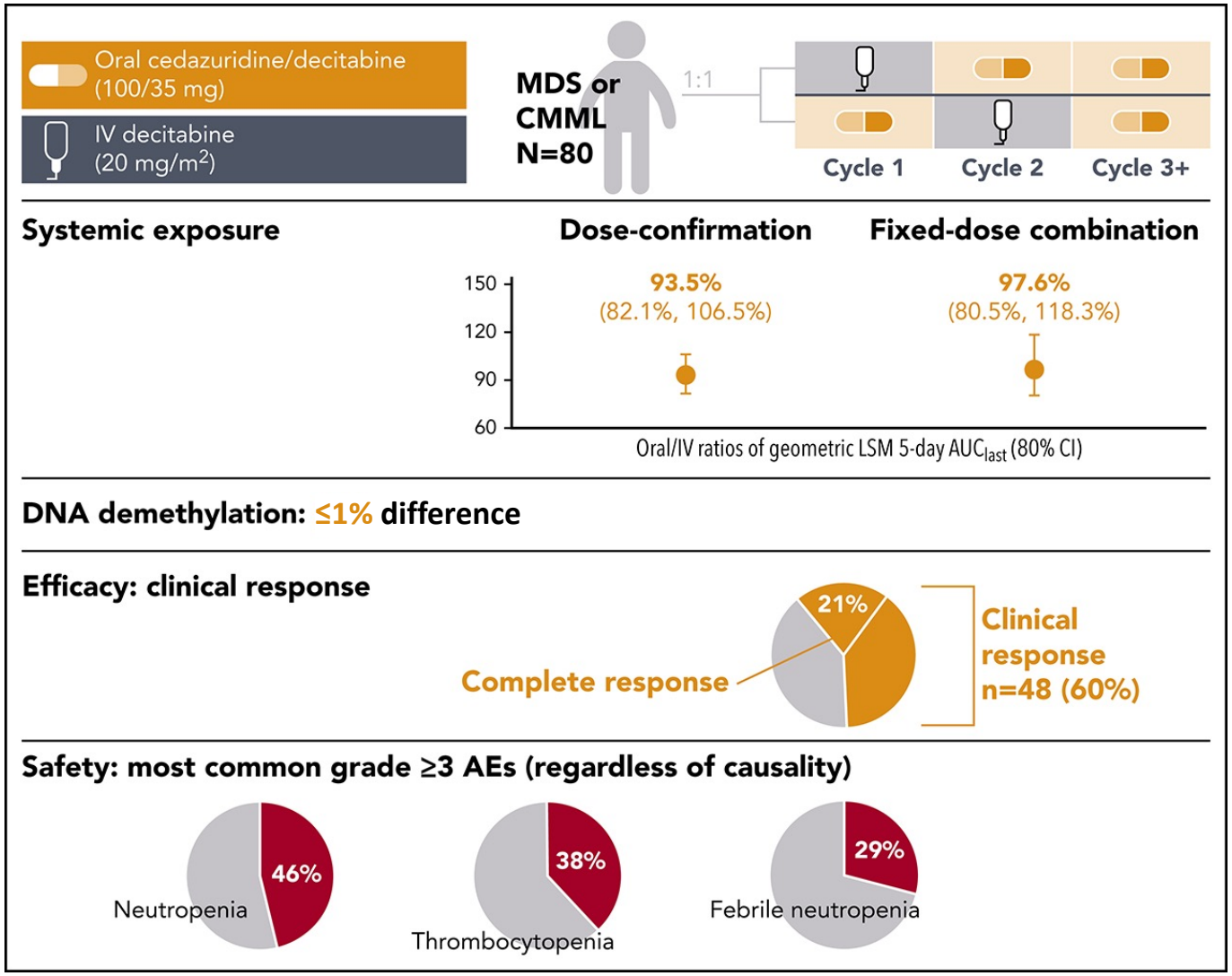
Oral decitabine/cedazuridine

Dr Stein

Oral Decitabine with Cedazuridine



Garcia-Manero G, et. al, Blood 2020

Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Crossover Phase 3 Study of an Oral Hypomethylating Agent, ASTX727 (DEC-C), Compared to IV Decitabine

Geissler K et al.

EHA 2022;Abstract P573.

ASCERTAIN (ASTX727-02) AML Cohort: A Phase III Trial of Oral Decitabine/Cedazuridine for Patients with AML Who Are Not Candidates for Standard Induction Therapy

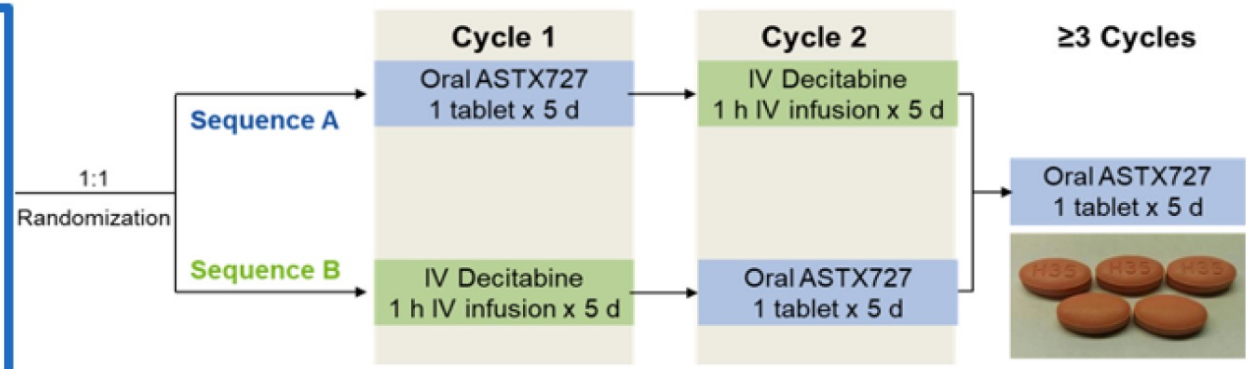
Decitabine Labeled Indications

US: int/high-risk MDS, CMML, AML 20-30% Blast

EU: AML not candidates for induction chemotherapy

N=200 (130+70)

Ascertain MDS, CMML, and AML



130 MDS/CMML patients (118 evaluable) were enrolled for the primary PK endpoint of the study. Approximately 70 AML patients were planned to be enrolled into an additional part of the study to obtain PK and efficacy data in this population.

Major entry criteria

- Candidates for IV decitabine
- ECOG PS 0-1
- Life expectancy of >3 months
- Adequate organ function
- One prior cycle of HMA is allowed

Primary endpoint

- Total 5-day decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

Secondary endpoints

- Efficacy: Response rate; duration of response; transfusion independence; event-free survival, and overall survival
- Safety of ASTX727
- Maximum LINE-1 demethylation

Geissler K et al. EHA 2022;Abstract P573.

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ASCERTAIN (ASTX727-02) AML Cohort Primary Endpoint: 5-Day Decitabine AUC Equivalence

Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC		Oral ASTX727		Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
		N	Geo. LSM	N	Geo. LSM		
Primary Analysis	Paired[1]	69	907.39	69	904.13	99.64 (91.23, 108.8)	31.55

[1]Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~100% with 90% CI of ~91-109%
- All sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

Geissler K et al. EHA 2022;Abstract P573.

ASCERTAIN (ASTX727-02) AML Cohort: Preliminary Efficacy Response

Response category	All Treated Subjects (N=87) n (%)	95% CI
Complete response (CR)	19 (21.8)	(13.7, 32.0)
CR with incomplete blood count recovery (CRi)	5 (5.7)	(1.9, 12.9)
CR with incomplete platelet recovery (CRp)	2 (2.3)	(0.3, 8.1)
Partial response (PR)	4 (4.6)	(1.3, 11.4)
Stable disease	33 (37.9)	(27.7, 49.0)
Not Evaluable (NE)*	26 (29.9)	(20.5, 40.6)
Composite Response (CR + CRi + PR)	28 (32.2)	(22.6, 43.1)

* Subjects who did not have a valid post-treatment efficacy assessment (ie, no post-treatment BM/PB sample or the quality of BM/PB sample was not adequate for an assessment of efficacy) were classified as NE for response classification.

- Median CR duration was 5.8 months
- Median time to best response was 3.4 months
- 38% of the 37 subjects who were RBC transfusion dependent at baseline were RBC transfusion independent for any consecutive ≥56-day period post-baseline

Geissler K et al. EHA 2022;Abstract P573.

ASCERTAIN (ASTX727-02) AML Cohort: Treatment-Emergent Adverse Events in >5% of Patients

Preferred Term	Phase 3 Total (N=87, n[%])	Phase 3 Total Grade 3 or higher
Thrombocytopenia	22 (25.3)	20 (23.0)
Neutropenia	14 (16.1)	14 (16.1)
Anemia	14 (16.1)	12 (13.8)
Febrile neutropenia	10 (11.5)	10 (11.5)
Nausea	9 (10.3)	0
Constipation	6 (6.9)	0
Asthenia	6 (6.9)	4 (4.6)
Decreased Appetite	6 (6.9)	0
Diarrhea	5 (5.7)	0

*Events attributed to oral decitabine/cedazuridine

- Safety profile consistent with that of decitabine
- Most grade 3 or higher events related to myelosuppression
- GI system adverse events following ASTX727 were generally grade 1-2

Geissler K et al. EHA 2022;Abstract P573.

Management of cytopenias with HMA/venetoclax: Drug-drug interactions

Dr Stein

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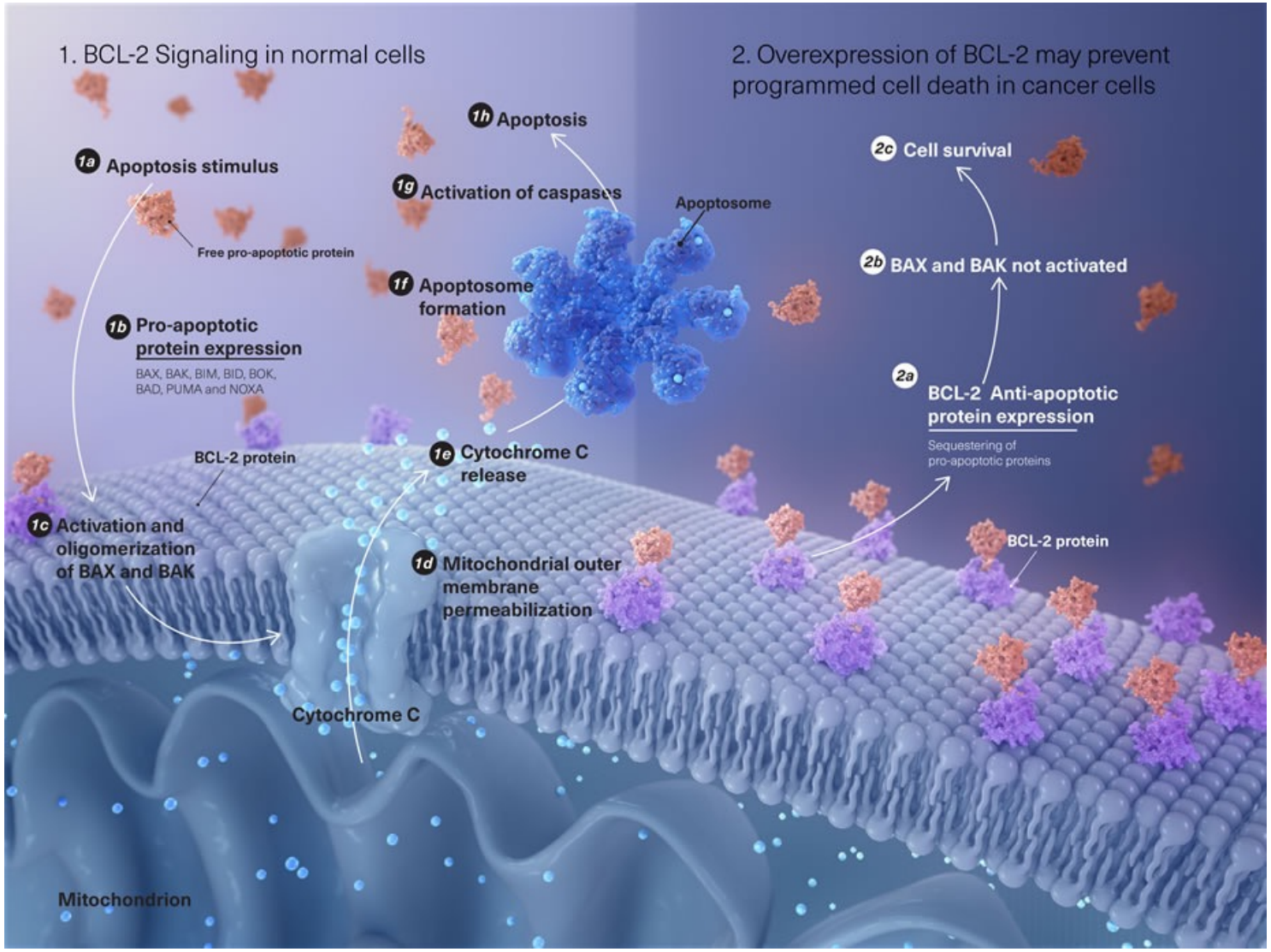
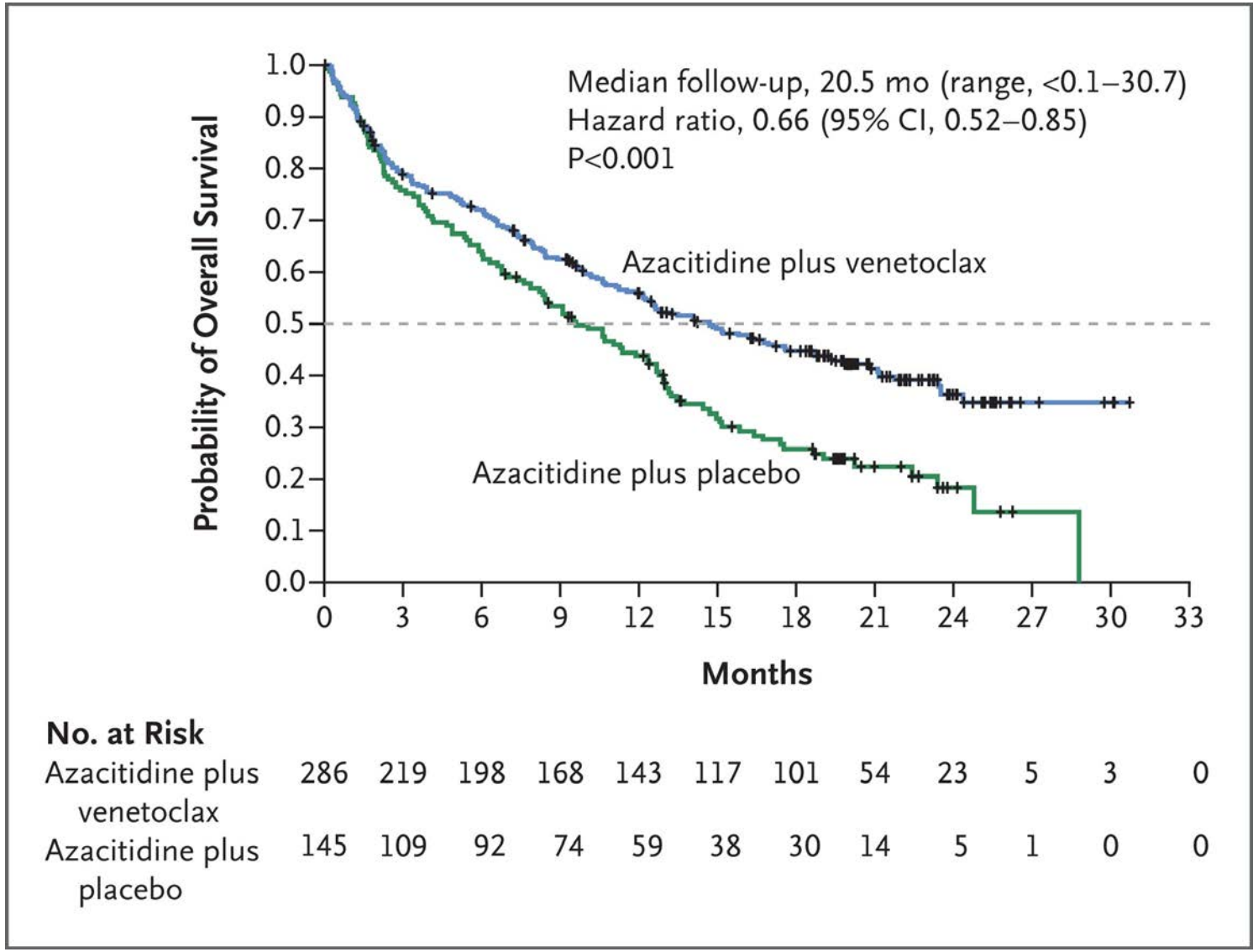
BCL-2 Inhibition in AML



Venetoclax and Aza versus Aza, Overall Survival

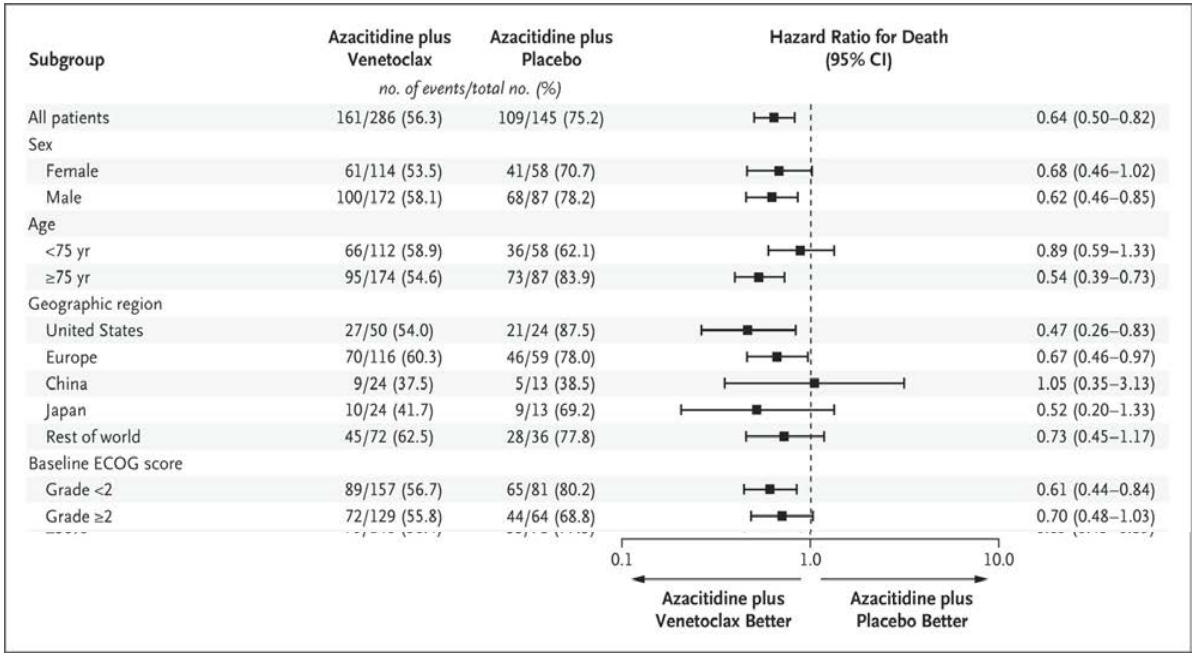


No. at Risk

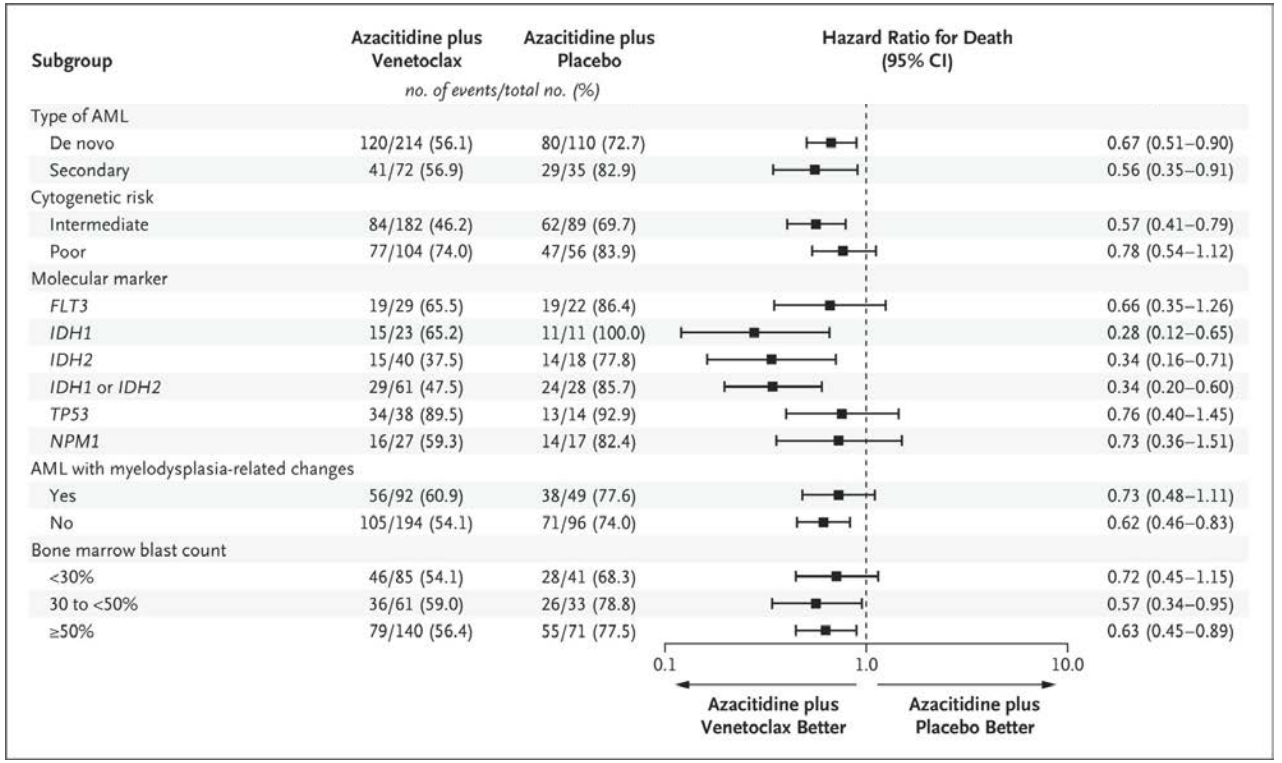
Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0

Dinardo CD, et. al, NEJM 2021

Venetoclax and Aza versus Aza, Overall Survival, Subsets



Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
All patients	161/286 (56.3)	109/145 (75.2)	0.64 (0.50–0.82)
Sex			
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			
<75 yr	66/112 (58.9)	36/58 (62.1)	0.89 (0.59–1.33)
≥75 yr	95/174 (54.6)	73/87 (83.9)	0.54 (0.39–0.73)
Geographic region			
United States	27/50 (54.0)	21/24 (87.5)	0.47 (0.26–0.83)
Europe	70/116 (60.3)	46/59 (78.0)	0.67 (0.46–0.97)
China	9/24 (37.5)	5/13 (38.5)	1.05 (0.35–3.13)
Japan	10/24 (41.7)	9/13 (69.2)	0.52 (0.20–1.33)
Rest of world	45/72 (62.5)	28/36 (77.8)	0.73 (0.45–1.17)
Baseline ECOG score			
Grade <2	89/157 (56.7)	65/81 (80.2)	0.61 (0.44–0.84)
Grade ≥2	72/129 (55.8)	44/64 (68.8)	0.70 (0.48–1.03)

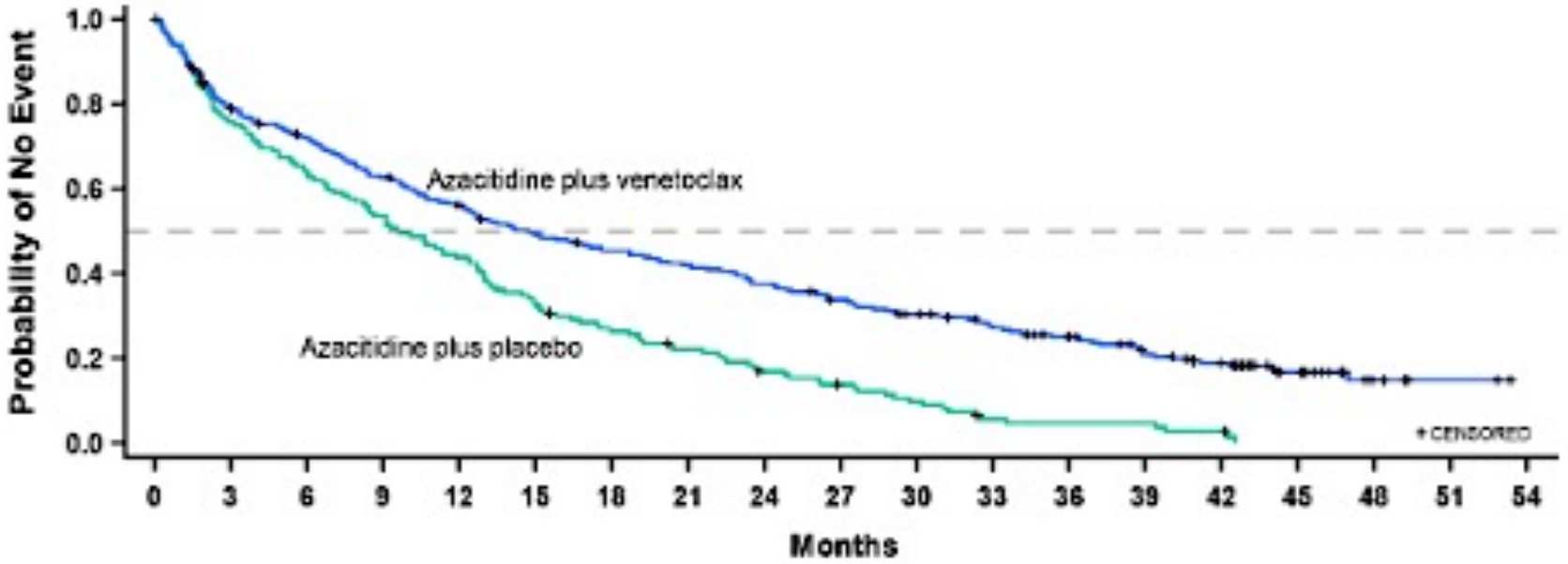


Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51–0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35–0.91)
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	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)	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)
AML with myelodysplasia-related changes			
Yes	56/92 (60.9)	38/49 (77.6)	0.73 (0.48–1.11)
No	105/194 (54.1)	71/96 (74.0)	0.62 (0.46–0.83)
Bone marrow blast count			
<30%	46/85 (54.1)	28/41 (68.3)	0.72 (0.45–1.15)
30 to <50%	36/61 (59.0)	26/33 (78.8)	0.57 (0.34–0.95)
≥50%	79/140 (56.4)	55/71 (77.5)	0.63 (0.45–0.89)

Dinardo CD, et. al, NEJM 2021

Long Term Survival of Patients Treated on VIALE-A Trial

Figure 1. Overall Survival



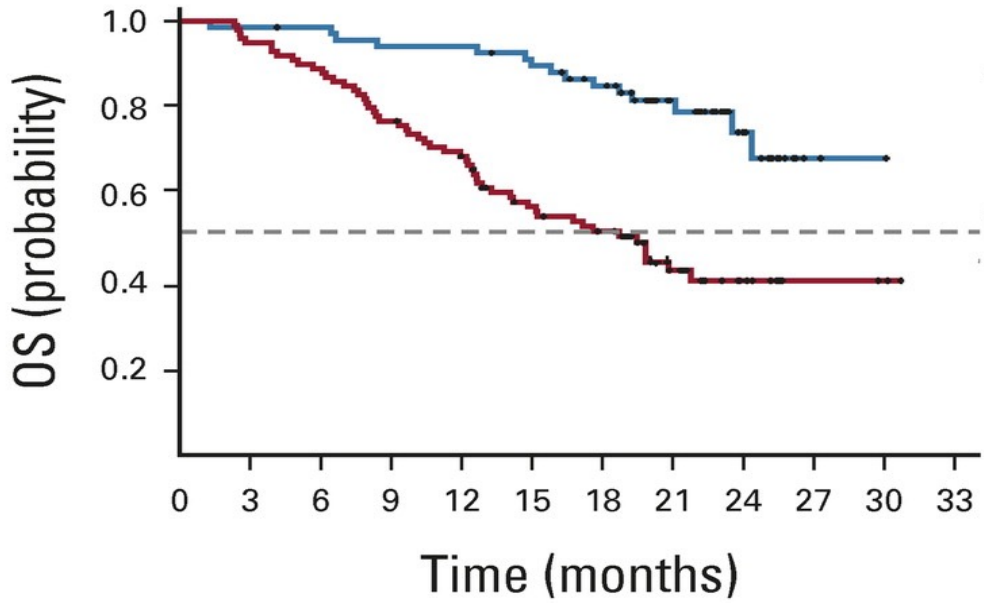
Patients at Risk

Azacitidine plus placebo	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0			
Azacitidine plus venetoclax	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0

Pratz et al, ASH 2022

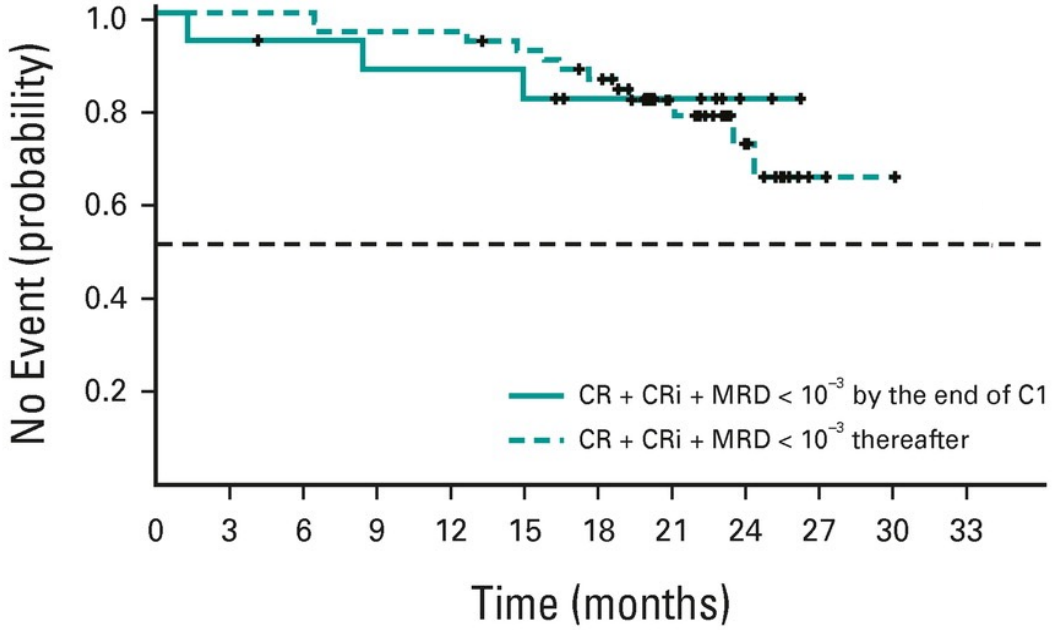
VIALE-A Trial – Measurable Residual Disease – practical implications – transplant?

A



No. at risk:

CR + CRi + MRD < 10^{-3}	67	66	65	62	62	58	52	30	13	2	1	0
CR + CRi + MRD ≥ 10^{-3}	97	92	86	74	64	49	42	21	10	3	2	0



No. at risk:

CR + CRi + MRD < 10^{-3} by the end of C1	17	16	15	14	14	13	11	6	2	0	0	0
CR + CRi + MRD < 10^{-3} thereafter	50	50	50	48	48	45	41	24	11	2	1	0

Pratz K et. al, JCO 2022

HMA/venetoclax for younger patients

Dr Stein

Proposed Randomized Clinical Study

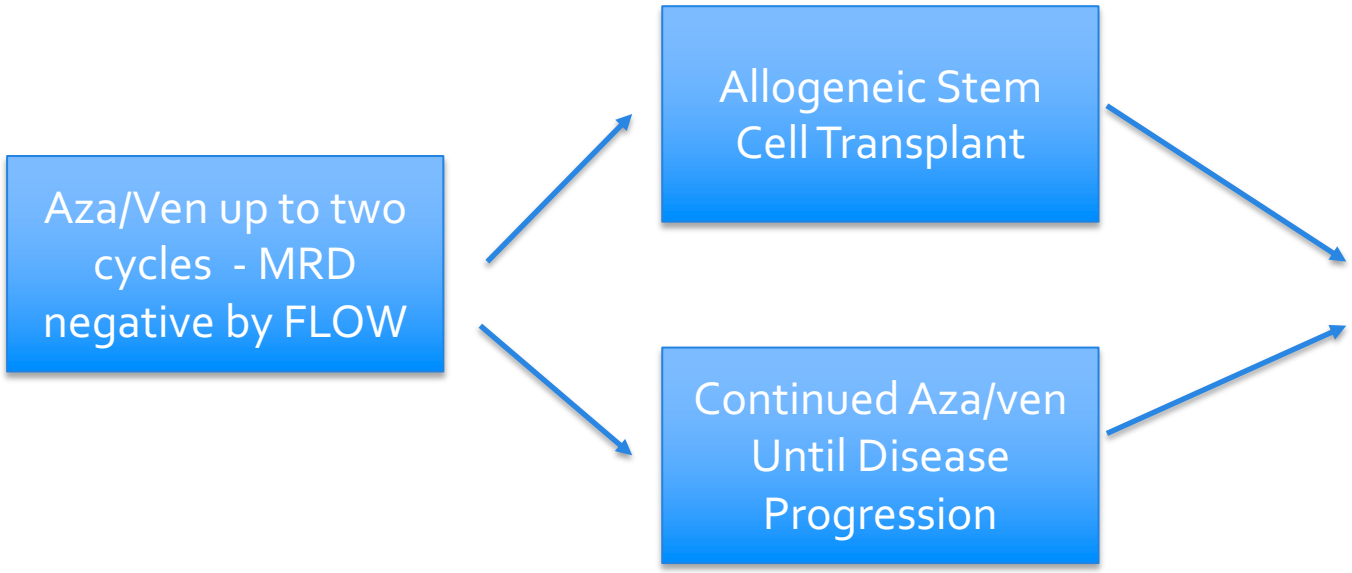
Inclusion:

Pts who receive Aza/Ven

Age 65 or older

Pts achieve an MRD negative CR with aza/ven

Intermediate or high risk AML



Primary Outcome:
Relapse-Free Survival

Secondary Outcome:
Overall Survival
Patient reported quality of life
Economic costs in each arm

Venetoclax in Younger Patients – FLAG-IDA-VEN

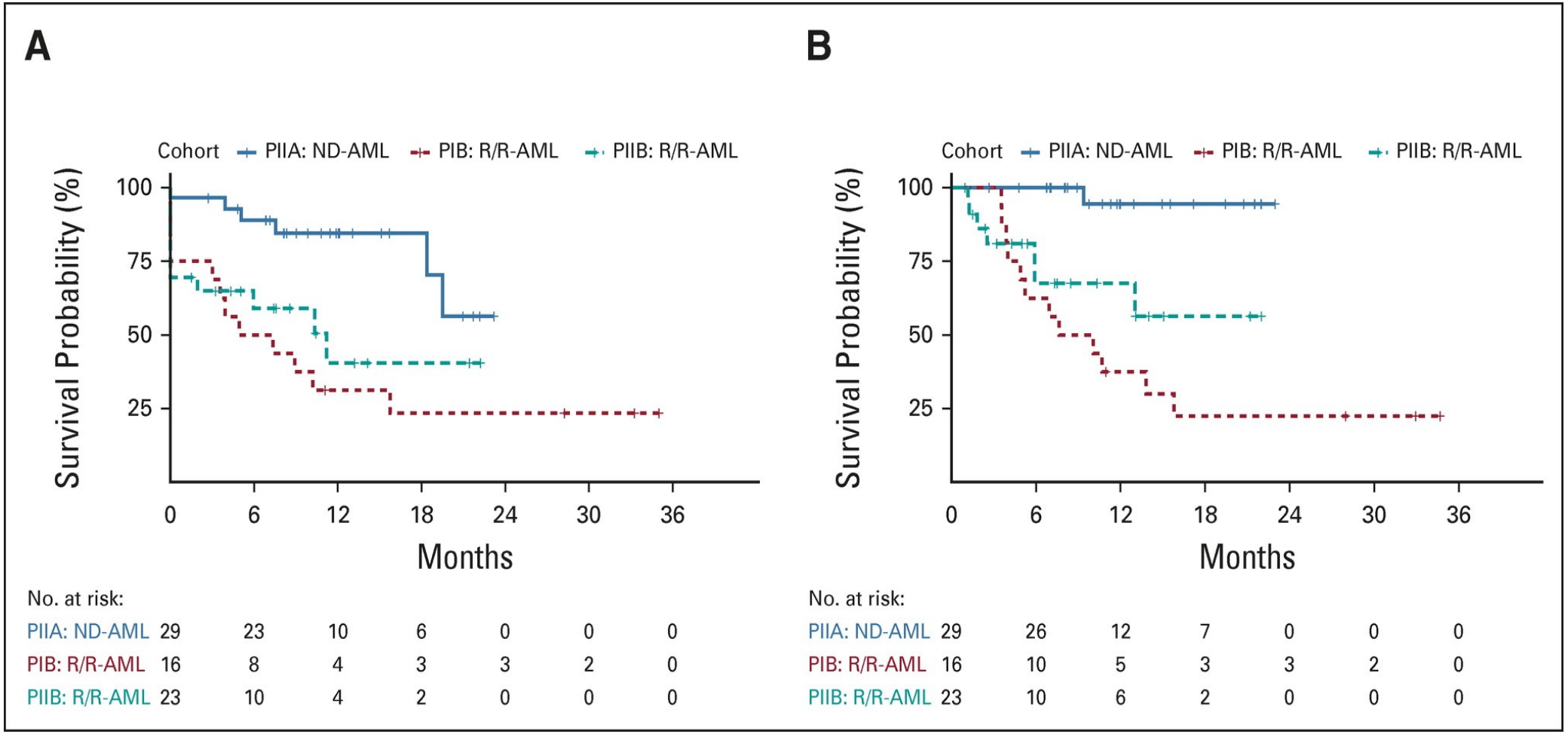


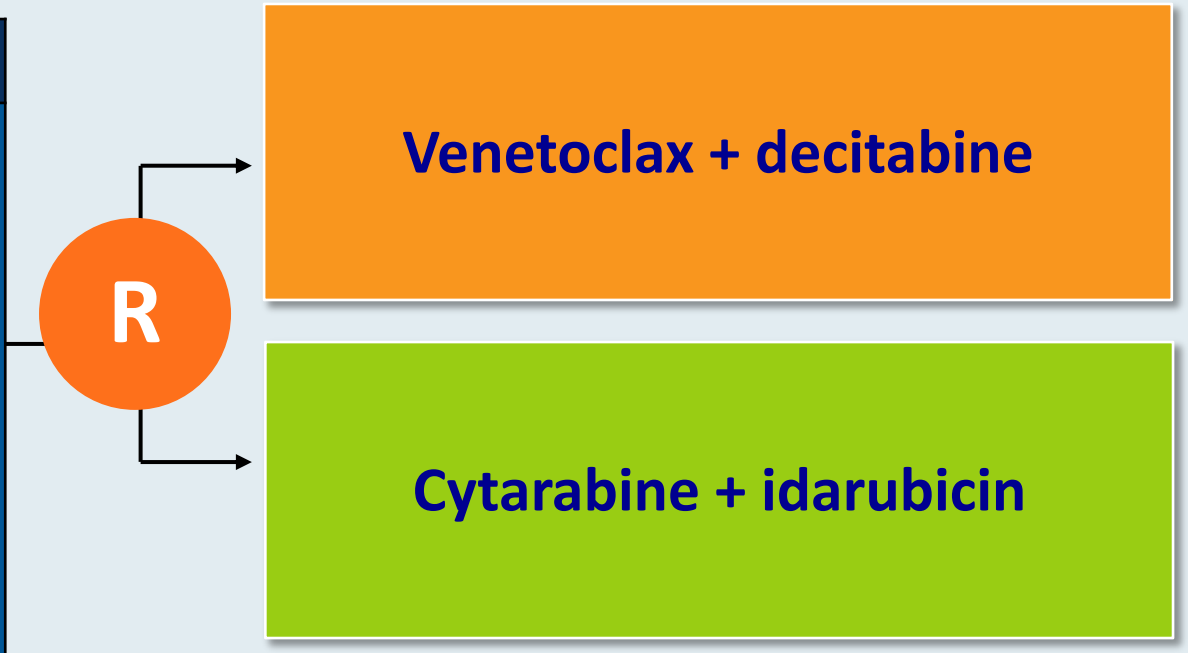
FIG 3. (A) EFS and (B) OS by cohort. EFS, event-free survival; ND-AML, newly diagnosed acute myeloid leukemia; OS, overall survival; R/R-AML, relapsed or refractory acute myeloid leukemia.

Ongoing Phase III Trial of Venetoclax with Decitabine versus Conventional 7 + 3 Induction Chemotherapy for Younger Patients with AML

Target accrual: 188

Eligibility

- Newly diagnosed
- No prior AML therapy (except hydroxyurea and Ara-C <1.0 g/d)
- Age 59 ≥ age (years) ≥ 18
- Adequate liver and renal function
- ECOG PS 0-2



Primary endpoint: Overall response rate

Secondary endpoints: Incidence of severe infection, duration of myelosuppression, event-free survival, overall survival, rate of MRD (minimal residual disease)

www.clinicaltrials.gov. NCT NCT05177731. Accessed November 2022.

Translational biology of AML: New agents and treatment strategies

Dr Stein

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Management of Acute Myeloid Leukemia

Introduction

- AML 2014 to 2022
- Defining AML versus MDS

Case 1: 82-year-old man presenting with cytopenias and AML

- Oral decitabine/cedazuridine
- Management of cytopenias with HMA/venetoclax: Drug-drug interactions
- HMA/venetoclax for younger patients
- Translational biology of AML: New agents and treatment strategies

Case 2: 75-year-old man with p53-mutated AML and complex karyotype

- Anti-CD47 antibody magrolimab

Case 3: 61-year-old woman with MLL-rearranged AML; s/p 7 + 3, FLAG-IDA and aza/ven

- Clinical implications of NPM1 mutation in AML

ASH 2022; other key papers

Case 2: 75-year-old man with p53-mutated AML and complex karyotype

Dr Stein

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Typical Patient #2

- 75 year old man with a history of prostate cancer, s/p definitive radiation therapy presents with fatigue and frequent epistaxis

- On baseline labs, white blood count is 3, Hgb is 7.9, platelets are 12. Absolute neutrophil count is 0.4

- Bone marrow biopsy shows AML with 25% myeloblasts, a complex karyotype and a p53 mutation

Anti-CD47 antibody magrolimab

Dr Stein

RTP RESEARCH TO PRACTICE

Magrolimab – Mechanism of Action

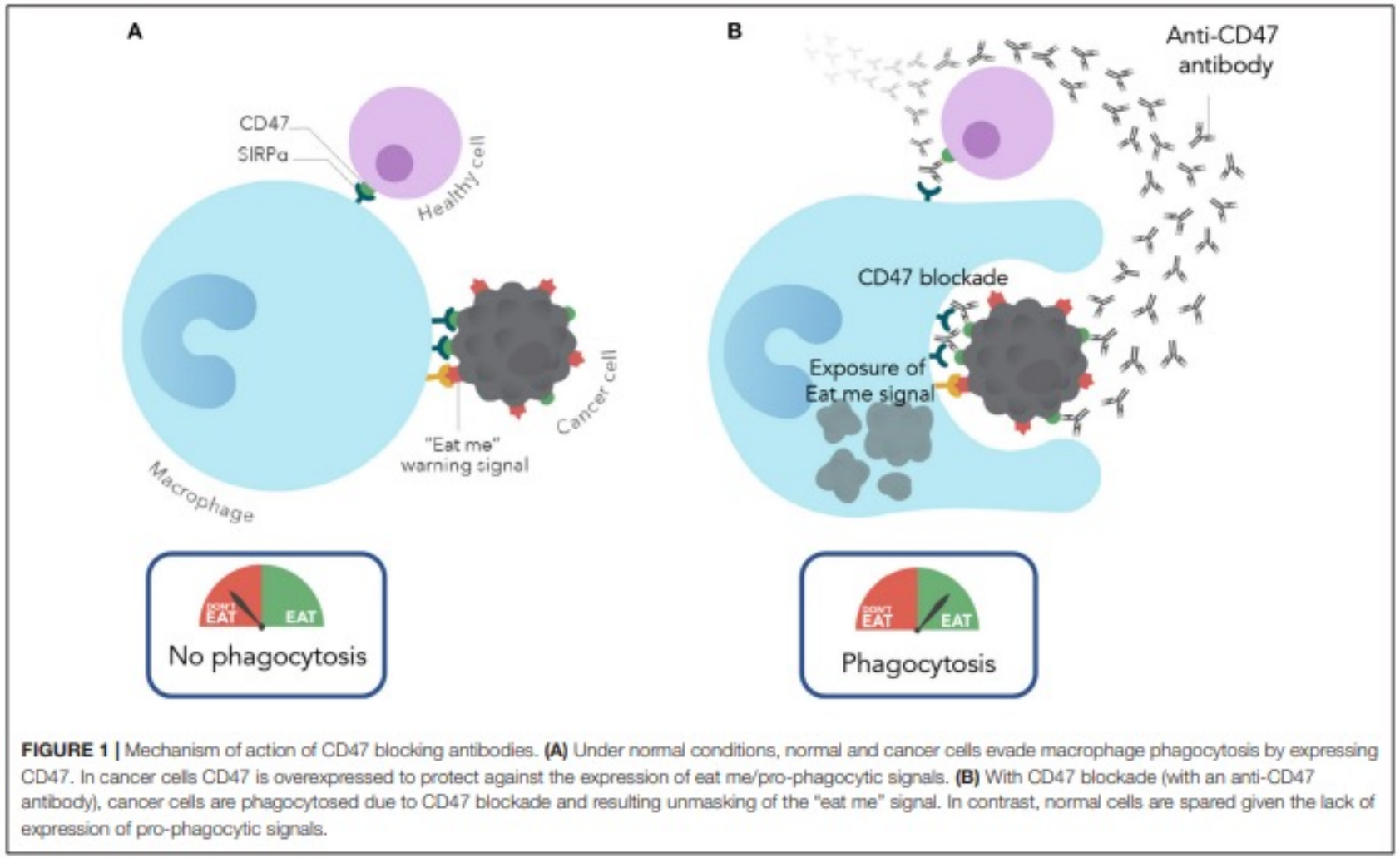


FIGURE 1 | Mechanism of action of CD47 blocking antibodies. **(A)** Under normal conditions, normal and cancer cells evade macrophage phagocytosis by expressing CD47. In cancer cells CD47 is overexpressed to protect against the expression of eat me/pro-phagocytic signals. **(B)** With CD47 blockade (with an anti-CD47 antibody), cancer cells are phagocytosed due to CD47 blockade and resulting unmasking of the "eat me" signal. In contrast, normal cells are spared given the lack of expression of pro-phagocytic signals.

Chao et.al Frontiers in Oncology, 2019

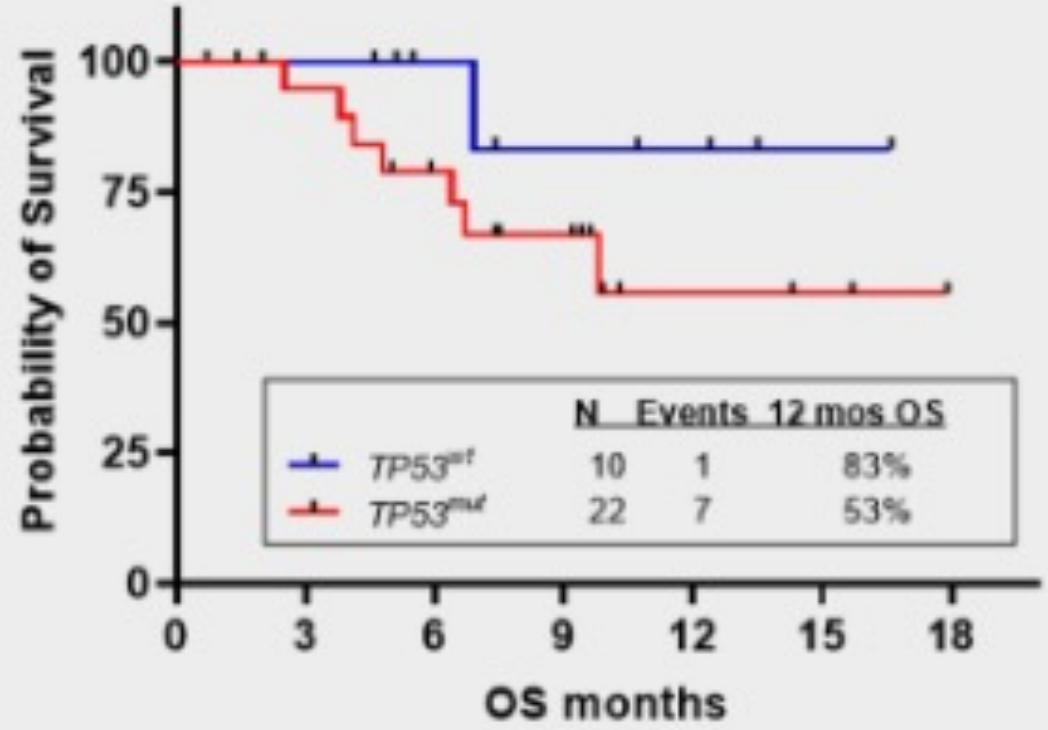
Magrolimab/Aza/Ven – Newly Diagnosed and R/R AML

Table 1: Baseline characteristics and response (N=41)

Parameters		Frontline		Untreated secondary AML	
		TP53^{mut} (N=22)	*TP53*^{WT} (N=10)	*TP53*^{mut} (N=5)	*TP53*^{WT} (N=4)
		N (%), Median [range]			
Age (yrs)		65 [33-81]	76 [67-80]	75 [61-84]	72 [69-82]
Age >65 years		11 (50)	10 (100)	5 (80)	4 (100)
Gender	Females	10 (45)	3 (30)	1 (20)	1 (25)
ECOG PS	0	2 (10)	0 (0)	0 (0)	0 (0)
	1-2	20 (90)	10 (100)	5 (100)	4 (100)
Therapy related AML		10 (45)	0 (0)	2 (40)	3 (75)
ELN 2017 risk stratification	Intermediate	0 (0)	3 (30)	0 (0)	0 (0)
	Adverse	22 (100)	7 (70)	5 (100)	4 (100)
CTG per ELN 2017	Intermediate	4 (18)	7 (70)	1 (20)	1 (25)
	- Diploid	3	5	1	0
	- Others	1	2	0	1
	Adverse	18 (82)	3 (30)	4 (80)	3 (75)
	- CK	17	1	4	1
	- -5/5q- or -7/7q-	1	2	0	1
	- 11q abnormality	0	0	0	1
Mutations	IDH1/IDH2	4 (18)	3 (27)	0 (0)	0 (0)
	FLT3 ITD/TKD	1 (5)	0 (0)	0 (0)	0 (0)
	NPM1	0 (0)	0 (0)	0 (0)	0 (0)
	ASXL1	2 (9)	5 (45)	0 (0)	0 (0)
	RUNX1	2 (9)	3 (27)	0 (0)	0 (0)
		Response and outcomes			
Overall response	ORR	15 (68)	10 (100)	5 (100)	3 (75)
	CR	9 (41)	6 (60)	2 (40)	2 (50)
	CRi	5 (22)	3 (30)	1 (20)	1 (25)
	CR + CRi	**14 (63)**	**9 (90)**	**3 (60)**	**3 (75)**
	MLFS/PR	1 (5)	1 (10)	2 40)	0 (0)
Time to first response (days)		24 [20-81]	20 [20-29]	20 [19-105]	27 [20-45]
Time to best response (days)		49 [20-130]	34 [20-63]	48 [20-105]	27 [20-88]
Time to ANC ≥ 500/cu mm (days)		36 [16- 88]	33 [26-62]	34 [30-36]	42 [36-59]
Time to platelet ≥ 100 x 10^9/L (days)		31 [15-55]	33 [19-74]	28 [22-49]	43 [0-46]
Mortality:					
- **4 week**		0 (0)	0 (0)	0 (0)	0 (0)
- **8 week**		0 (0)	0 (0)	0 (0)	0 (0)

Magrolimab/Aza/Ven – Newly Diagnosed and R/R AML

Fig. 1: Kaplan Meier estimates of OS in frontline patients based on their *TP53* mutation status



Median survival not reached for both groups

Davar N, et. al. ASH 2022

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ASH 2022; other key papers

Case 3: 61-year-old woman with MLL-rearranged AML; s/p 7 + 3, FLAG-IDA and aza/ven

Dr Stein

Typical Patient #3

- 61 year old woman with a history of breast cancer, treated with surgery, radiation and dose-dense AC-T
- On baseline labs, white blood count is 10, Hgb is 6.8, platelets are 11. 80% circulating myeloblasts
- Bone marrow biopsy shows AML with sheets of blasts and a 6;11 translocation (MLL rearrangement)
- She is treated and refractory to 7 + 3, FLAG-IDA and aza-venetoclax

Clinical implications of NPM1 mutation in AML

Dr Stein

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Menin and NPM1 Mutant Acute Myeloid Leukemia

Targeting Chromatin Regulators Inhibits Leukemogenic Gene Expression in *NPM1* Mutant Leukemia

Michael W.M. Kühn[1,2], Evelyn Song[1], Zhaohui Feng[1], Amit Sinha[1], Chun-Wei Chen[1], Aniruddha J. Deshpande[1], Monica Cusan[1], Noushin Farnoud[1], Annalisa Mupo[3], Carolyn Grove[4,5], Richard Koche[1], James E. Bradner[6], Elisa de Stanchina[7], George S. Vassiliou[3], Takayuki Hoshii[1], and Scott A. Armstrong[1,8]

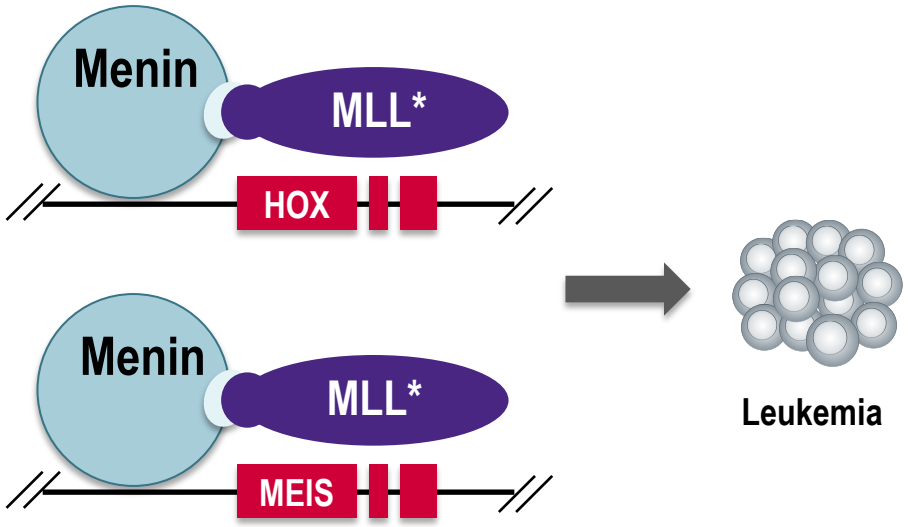
CANCER

Therapeutic targeting of preleukemia cells in a mouse model of *NPM1* mutant acute myeloid leukemia

Hannah J. Uckelmann[1,2], Stephanie M. Kim[1,2], Eric M. Wong[1,2], Charles Hatton[1,2], Hugh Giovinazzo[1,2], Jayant Y. Gadrey[1,2], Andrei V. Krivtsov[1,2], Frank G. Rücker[3], Konstanze Döhner[3], Gerard M. McGeehan[4], Ross L. Levine[5], Lars Bullinger[6], George S. Vassiliou[7,8], Scott A. Armstrong[1,2]*

Menin Inhibitors turn off leukemic transcriptional programs by binding to Menin and displacing MLL complexes

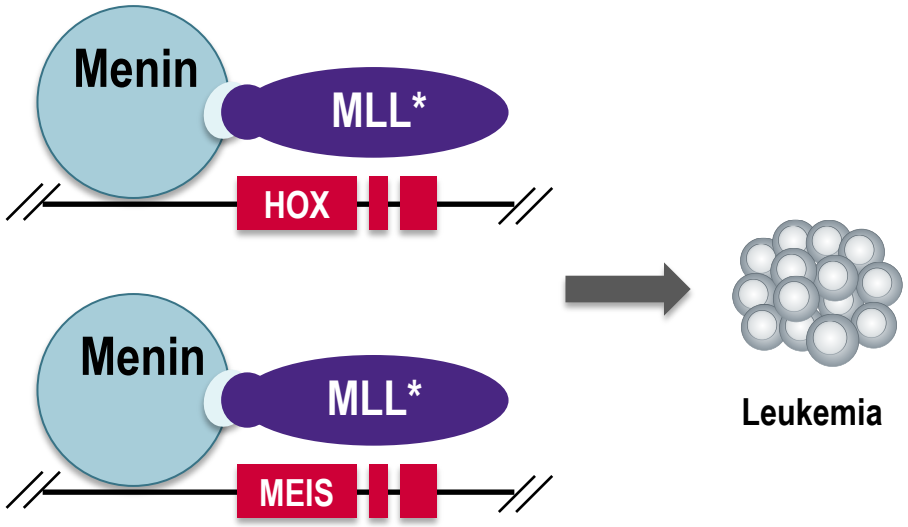
MLLr Acute Leukemias



Gene transcription ON

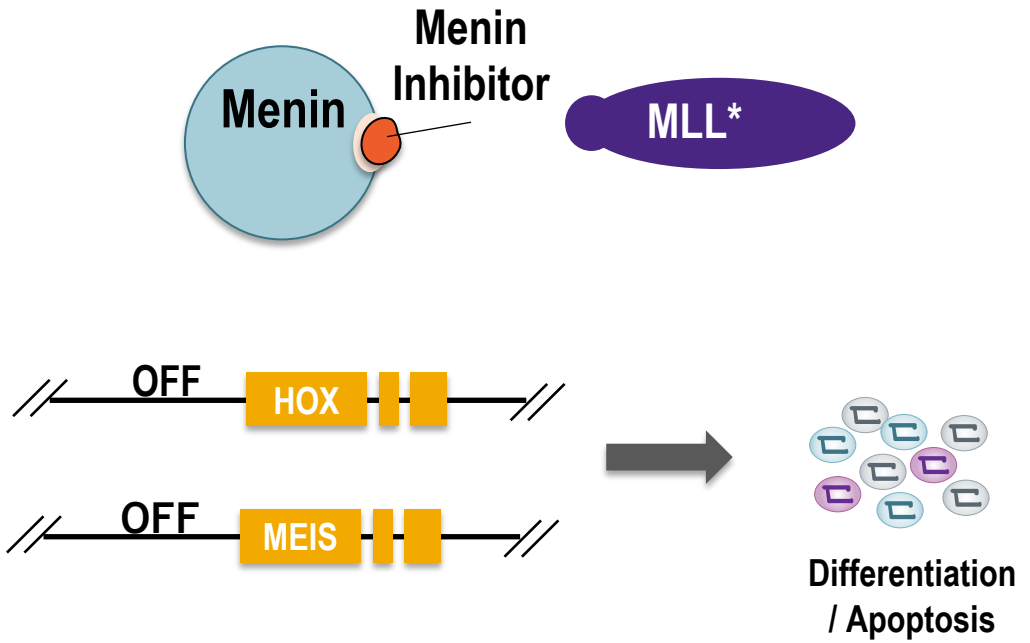
Menin Inhibitors turn off leukemic transcriptional programs by binding to Menin and displacing MLL complexes

MLLr Acute Leukemias



Gene transcription ON

Menin Inhibitor



Gene transcription OFF

Revumenib

Table 1. Response of Pts with *KMT2Ar* or *mNPM1*

Best Response	Efficacy Population (N=60)
Response	
Overall response rate[1], n, (%)	32 (53%)
CR/CRh	18 (30%)
CR	12 (20%)
CRh	6 (10%)
CRp	5 (8%)
MLFS	9 (15%)
MRD^{neg}	
CRc MRD^{neg} Rate[2]	18/60 (30%)
within CR/CRh MRD^{neg} n, (%)	14/18 (78%)
within CR/CRh/CRp MRD^{neg} n, (%)	18/23 (78%)
KMT2Ar	
Overall response rate[1], n, (%)	27/46 (59%)
CR/CRh	15/46 (33%)
mNPM1	
Overall response rate[1], n, (%)	5/14 (36%)
CR/CRh	3/14 (21%)

[1]Overall Response Rate = CR+CRh+CRp+MLFS; [2]CR+CRh+CRp; MRD status assessed locally by PCR or MCF

Issa G, et. al, ASH 2022

Ziftomenib

Table 1: Preliminary Efficacy Data for the Phase 1b Portion of KOMET-001

	200 mg (N=12)	600 mg (N = 12)
CR/CRh Rate, n (%)[1]	0	3 (25.0)
95% CI[2]	(0.0, 26.5)	(5.5, 57.2)
Complete Remission Rate, n (%)	0	2 (16.7)
95% CI[2]	(0.0, 26.5)	(2.1, 48.4)
CRc Rate, n(%)[3]	0	4 (33.3)
95% CI[2]	(0.0, 26.5)	(9.9, 65.1)
MRD Negativity Rate, n (%)	0	3 (75.0)
95% CI[2]	(NA, NA)	(19.4, 99.4)
Overall Response Rate, n (%)[4]	0	5 (41.7)
95% CI[2]	(0.0, 26.5)	(15.2, 72.3)
MRD Negativity Rate, n(%)	0	3 (60.0)
95% CI[2]	(NA, NA)	(14.7, 94.7)

Abbreviations: CI = confidence interval; CR = complete remission; CRc = composite complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; CRp = complete remission with incomplete platelet recovery; MLFS = morphologic leukemia-free state; MRD = measurable residual disease; n/N = number of patients; NA = not applicable; ORR = overall response rate; PR = partial response.

[1] CR/CRh response rate is defined as the proportion of patients achieving a best overall response of CR or CRh.

[2] Clopper-Pearson 95% confidence intervals are calculated based on binomial distribution.

[3] CRc response rate is defined as the proportion of patients achieving a best overall response of CRi (including CRp), CRh, or CR.

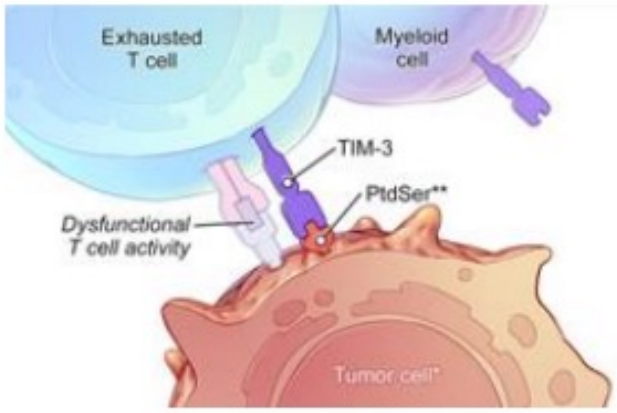
[4] ORR is defined as the proportion of patients achieving a best overall response of MLFS, PR, CRi (including CRp), CRh, or CR.

Erba H, et. al. ASH 2022

Sabatolimab (MBG453) – Mechanism of Action

Rationale for targeting TIM-3 in hematology: targeting immune and myeloid cells

MBG453 simultaneously targets immune and myeloid leukemic cells



* Or antigen-presenting cell (APC)
** Other TIM-3 ligands include: Galectin-9, HMGB1, and CEACAM1

- TIM-3 is an inhibitory receptor[1] expressed on[2,3,4]:
  - T cells and innate immune cells (myeloid & dendritic cells)
  - Leukemic stem cells (LSCs) but not normal hematopoetic stem cells
- Expression of TIM-3 correlates with severity and progression in MDS and AML[2,5]
- Anti-leukemic effect of TIM-3 blockade in MDS/AML models[2,3]
- In vitro data shows that targeting TIM-3 with inhibitory antibody MBG453[3,6,7]:
  - Re-awaken immunity to restore an anti-leukemic immune response
  - Selectively target the LSC and blasts

For references see slides 179-180

Sabatolimab with Hypomethylating Agents

	ND AML[a]		HR-MDS[a]		CMML[a,b]	
Parameter	+ Dec n=22	+ Aza n=26	+ Dec n=19	+ Aza n=20	+ Dec n=5	+ Aza n=7
Duration of sabatolimab exposure, median (range) mo	6.8 (0.7-28.3)	3.5 (0.3-15.2)	8.0 (0.7-33.6)	2.8 (0.8-14.3)	8.4 (5.6-12.6)	5.0 (1.6-15.8)
Efficacy evaluable pts[c], n	17	17	18	17	5	6
ORR[d], n (%)	8 (47.1)	6 (35.3)	11 (61.1)	11 (64.7)	3 (60)	4 (66.7)
CR	6 (35.3	2 (11.8)	6 (33.3)	2 (11.8)	0	2 (33.3)
CRi	1 (5.9)	2 (11.8)	NA	NA	NA	NA
mCR	NA	NA	3 (16.7)	5 (29.4)	1 (20)	2 (33.3)
mCR with HI	NA	NA	3 (16.7)	2 (11.8)	0	1 (16.7)
PR	1 (5.9)	2 (11.8)	0	0	1 (20)	0
SD with HI	NA	NA	2 (11.1)	4 (23.5)	1 (20)	0

[a] The + Dec and + Aza combination arms were initiated in August 2017 and February 2019, respectively.
[b] Response assessment for pts with CMML used IWG criteria (Cheson 2006).
[c] The first efficacy assessment was conducted at 2 months after the start of study treatment.
[d] ORR for pts with MDS was defined as CR + mCR + PR + SD with HI; ORR for pts with ND AML was defined as CR + CRi + PR.
CR, complete remission; CRi, CR with incomplete blood count recovery; mCR, marrow CR; PR, partial remission; SD, stable disease.

Brunner A, et. al ASH 2020

Results of a Phase 1b/2 Study of Entospletinib Monotherapy and In Combination With Induction Chemotherapy In Newly Diagnosed Patients With Acute Myeloid Leukemia

Alison R. Walker[1], John C Byrd[1], Bhavana Bhatnagar[1],Alice Mims[1],Tara Lin[2], Howland E. Croswell[3], Danjie Zhang[4], Arati V. Rao[4], Mark D Minden[5], William Blum[6]

[1]The Ohio State University, Columbus, Ohio, USA; [2]University of Kansas Medical Center, Kansas City, Kansas, USA; [3]Bon Secours St. Francis Health System, Greenville, South Carolina, USA, [4]Gilead Sciences, Inc., Foster City, California, USA; [5]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [6]Winship Cancer Institute of Emory University, Atlanta, Georgia, USA

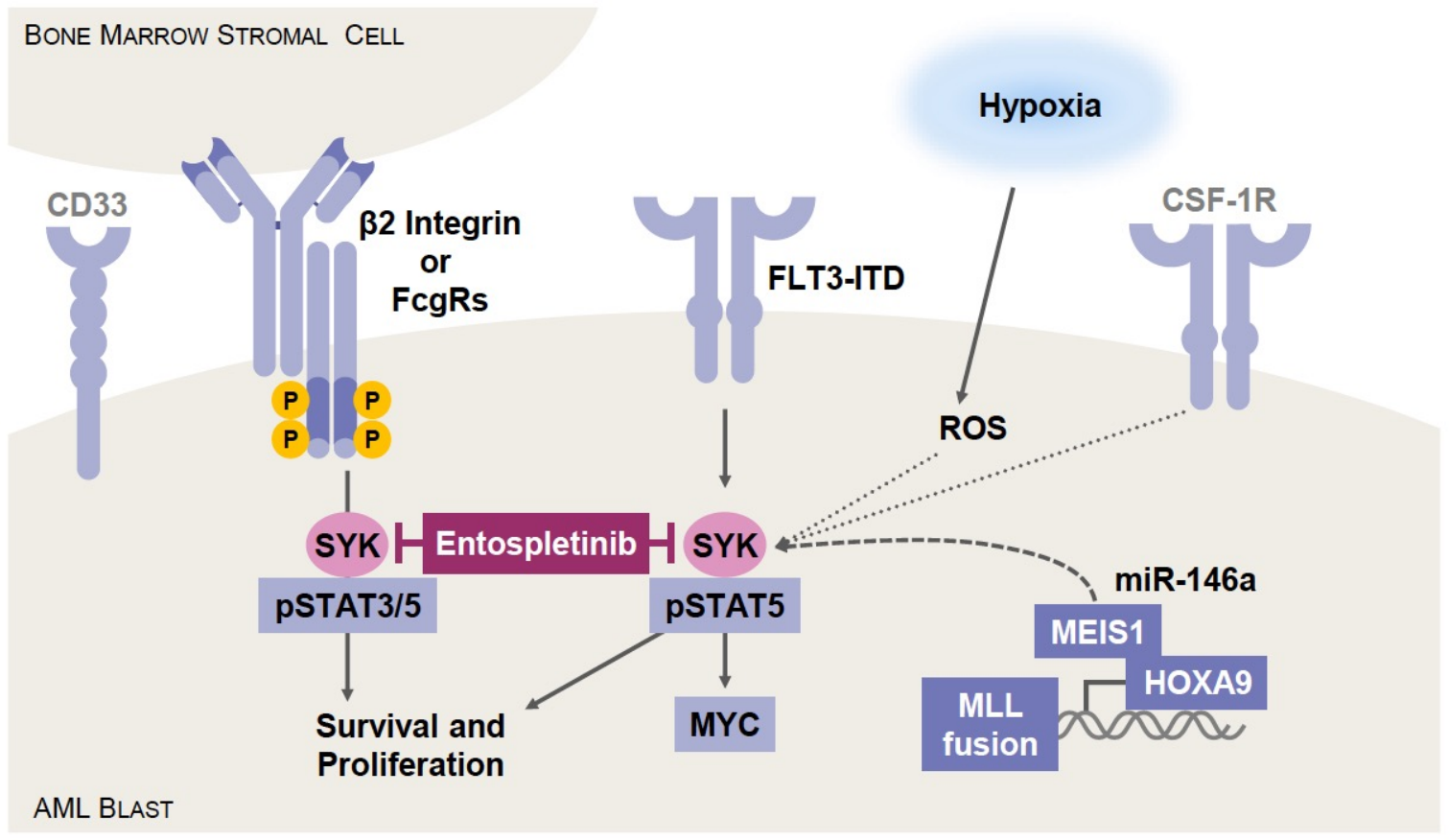
EHA 2018;Abstract S118.

Entospletinib in Combination with Induction Chemotherapy in Previously Untreated Acute Myeloid Leukemia: Response and Predictive Significance of *HOXA9* and *MEIS1* Expression

Alison R. Walker[1], John C. Byrd[1], James S. Blachly[1], Bhavana Bhatnagar[1], Alice S. Mims[1], Shelley Orwick[1], Tara L. Lin[2], Howland E. Crosswell[3], Danjie Zhang[4], Mark D. Minden[5], Veerendra Munugalavadla[4], Lauren Long[1], Jinfeng Liu[4], Yang Pan[4], Thomas Oellerich[6,7], Hubert Serve[6,7], Arati V. Rao[4], and William G. Blum[8]

***Clin Cancer Res* 2020;26(22):5852-59.**

Investigation of SYK as a Critical Signaling Node in AML



- Spleen tyrosine kinase (SYK) is a non-receptor tyrosine kinase primarily expressed in hematopoietic cells
- Constitutive activation of SYK in AML has been reported; targeted inhibition of SYK-induced differentiation in vitro demonstrated anti-leukemia activity in AML mouse models
- SYK promotes leukemogenesis by directly phosphorylating the FLT3 receptor, and inducing MEIS1 in conjunction with HOXA9 to form a regulatory loop in KMT2A (mixed lineage leukemia [MLL]) rearranged leukemia

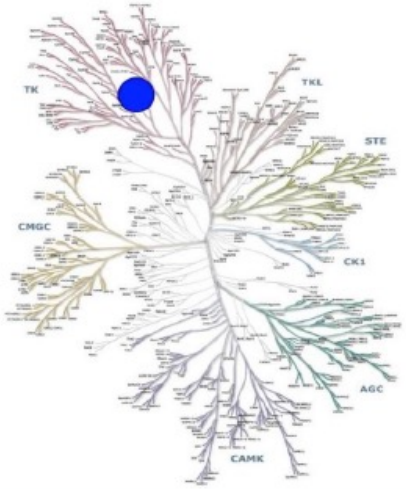
Walker AR et al. *Clin Cancer Res* 2020;26(22):5852-59. Walker AR et al. EHA 2018;Abstract S118.

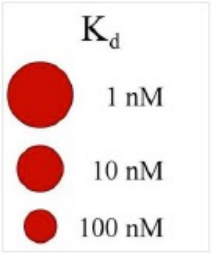
Entospletinib (ENTO): Mechanism of Action

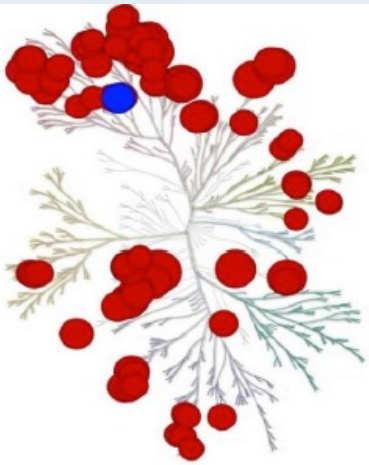
ENTO: Syk-selective

Syk K_d = 7.6 nM

No other kinases with K_d <100nM







R406: non-selective

Syk K_d = 15 nM

24 kinases with K_d <15 nM

54 additional kinases with K_d <100 nM

- **ENTO exposures approach a plateau above 600 mg BID**
- **Biliary excretion is the major route of elimination**
- **Absorption is highly pH dependent: drug-drug interaction with PPIs- they decrease the absorption of ENTO by ~60%**
- **ENTO is an inhibitor of UGT1A1**
- **Clinical interactions with CYP inhibitors: CYP1A2, CYP2B6,CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A**

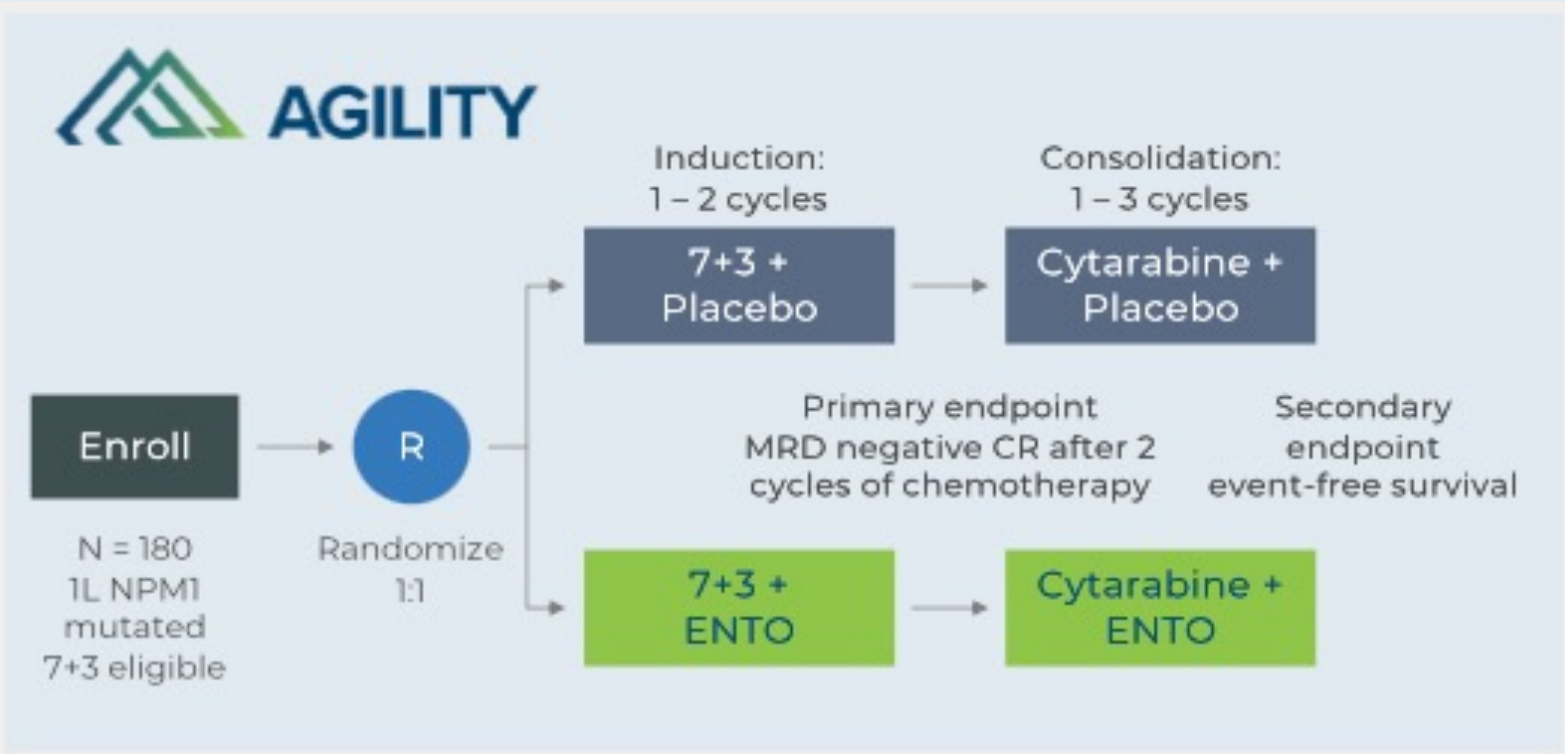
Walker AR et al. *Clin Cancer Res* 2020;26(22):5852-59. Walker AR et al. EHA 2018;Abstract S118.

Phase Ib/II Study of ENTO Monotherapy Lead-In and in Combination with Induction Chemotherapy: Author Conclusions

- **No benefit as monotherapy: only 1 out of 53 patients responded to monotherapy**
- **CR rate 70% in untreated fit AML patients treated with ENTO+7+3**
- **Overall ENTO is well tolerated and 30-day induction mortality 0%**
- **Higher response rates with SYK inhibition in AML patients with high *HOXA9/MEIS1* expression**
- **Potential role in subsets of AML: *KMT2A/MLL* and *NPM1*. Further development ongoing with the Leukemia Lymphoma Society and the BEAT-AML program**

Walker AR et al. EHA 2018;Abstract S118.

AGILITY: An Ongoing Phase III Study Evaluating the Addition of Entospletinib to Intensive Induction and Consolidation Chemotherapy for Newly Diagnosed NPM1-Mutated AML



- NPM1 mutation drives HOXA9/MEIS1 expression
- Novel use of MRD negative CR as primary endpoint has potential to support accelerated approval
- Key secondary endpoint of EFS supports conversion for full approval

www.clinicialtrials.gov (NCT05020665); Accessed November 2022; Byrd JC et al. EHA 2022;Abstract P525.

RTP RESEARCH TO PRACTICE

Discontinuation of the Phase III AGILITY Study Evaluating the Addition of Entospletinib to Intensive Induction and Consolidation Chemotherapy for Newly Diagnosed NPM1-Mutated AML

Press Release – November 9, 2022

"The biotech [company] will discontinue the Phase 3 trial of its spleen tyrosine kinase (SYK) inhibitor entospletinib for the treatment of newly diagnosed patients with NPM1-mutated AML. The company stressed the decision had been made due to enrollment difficulties rather than reports of any adverse events or lack of efficacy.

The study, which kicked off in November 2021 and was due to run into 2026, aimed to enroll 180 participants across sites in the US, Canada, Brazil, South Korea, Israel and various countries in Europe, according to ClinicalTrials.gov.

"The company projected significant delays due to several factors, including the operational challenges the company faced in enrolling a genetically defined subset of patients in a front-line setting, the residual and ongoing impacts of the COVID-19 pandemic, and the inability to activate planned clinical trial sites in Russia and Ukraine," [the company] said in a statement released ahead of its third-quarter earnings.

It doesn't mean [the company] has given up on trying to treat AML by inhibiting SYK. One of the two assets being prioritizing in the company's revamped strategy is the SYK inhibitor lanraplenib, which is currently being assessed in combination with gilteritinib in a Phase 1b/2 trial for relapsed/refractory AML."

https://www.fiercebiotech.com/biotech/time-runs-out-kronos-phase-3-aml-drug-biotech-blames-enrolment-struggles-ending-trial

RTP RESEARCH TO PRACTICE

Phase Ib/II Study Evaluating Lanraplenib in Combination with Gilteritinib Administers First Dose to a Patient with AML with a FLT3 Mutation

Press Release – August 22, 2022

"The first patient in a phase 1b/2 clinical trial received treatment with lanraplenib plus gilteritinib, according to a press release from the targeted therapy's manufacturer.

Lanraplenib, a spleen tyrosine kinase inhibitor, is being developed for the treatment of patients with relapsed/refractory FLT3-mutated acute myeloid leukemia. This genetic mutation is found in approximately one-third of patients with acute myeloid leukemia, according to the release.

'The initiation of this study is an important first step as we advance lanraplenib for patients with certain genetically defined types of (acute myeloid leukemia),' said Dr Jorge DiMartino, chief medical officer and executive vice president of clinical development, in the release. 'Our long-term vision is to develop lanraplenib as a cornerstone of targeted regimens for these patients, allowing us to potentially reach as many as two-thirds of patients with (acute myeloid leukemia). Today's announcement represents important progress toward that goal.'"

https://www.curetoday.com/view/first-patient-receives-investigational-cancer-drug-combination-for-relapsed-refractory-acute-myeloid-leukemia

RTP RESEARCH TO PRACTICE

FDA Grants Priority Review to Quizartinib for Newly Diagnosed AML with a FLT3-ITD Mutation

Press Release – October 24, 2022

"Based on findings from the QuANTUM-First trial (NCT02668653), the FDA has granted priority review to quizartinib in combination with standard cytarabine and anthracycline induction followed by consolidation cytarabine and continuation of quizartinib monotherapy after consolidation in patients with newly diagnosed FLT3-ITD–positive acute myeloid leukemia (AML).

The decision was based on data presented at the 2022 European Hematology Association (EHA) Congress. In the QuANTUM-First trial, the quizartinib regimen demonstrated a statistically significant and clinically meaningful benefit to overall survival (OS) among patients with newly diagnosed FLT3-ITD–positive AML compared with chemotherapy alone. The prescription drug use fee act date has been set for April 24, 2023.

'There is a need for new targeted therapy options for patients with [AML] and the results of the QuANTUM-First trial showed that quizartinib in combination with standard chemotherapy has potential to change the current standard of care for newly diagnosed patients with the historically difficult-to-treat FLT3-ITD subtype,' Ken Takeshita, MD, global head and R&D, said in the press release. 'The FDA's prioritization of this application reflects the importance of the data, and we will continue to work with the FDA and other global regulatory authorities to support the review of quizartinib for the treatment of patients with newly diagnosed FLT3-ITD–positive [AML].'"

https://www.cancernetwork.com/view/fda-grants-priority-review-to-quizartinib-for-newly-diagnosed-flt3-itd-aml

RTP RESEARCH TO PRACTICE

SYK Inhibitors, Entospletinib and Lanraplenib, Show Potent Anti-Leukemic Activity in Combination with Targeted Agents

Carvajal LA et al.

ASH 2022;Abstract 2639 (Poster).

Sunday, December 11, 2022

6:00 PM – 8 PM EST

Poster 3356

Preclinical Activity of Selective SYK Inhibitors, Entospletinib and Lanraplenib, Alone or Combined With Targeted Agents in Ex Vivo AML Models With Diverse Mutational Backgrounds

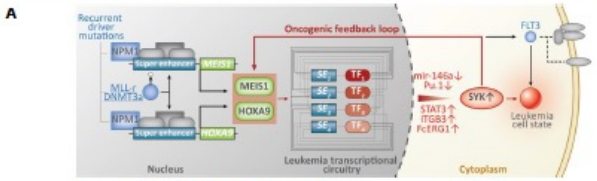
Melinda A. L. Day,[1] Philipp Sergeev,[2] Caroline A. Heckman,[2] Anna Schinzel,[1] Nikolaus D. Obholzer,[1] Charles Y. Lin,[1] Pavan Kumar,[1] Jorge DiMartino,[1] Douglas C. Saffran[1]

[1]Kronos Bio, Inc., San Mateo, CA, USA; [2]Institute for Molecular Medicine Finland, Helsinki Institute of Life Science, iCAN Digital Precision Cancer Medicine Flagship, University of Helsinki, Helsinki, Finland

Abstract

Spleen tyrosine kinase (SYK) is a nonreceptor tyrosine kinase that mediates integrin and Fc receptor signaling in myeloid cells and has been implicated as an oncogenic driver in acute myeloid leukemia (AML). The oral SYK inhibitor entospletinib (ENTO) has demonstrated clinical activity in *HOXA9/MEIS1*-driven AML and is currently being investigated in a phase 3 trial, AGILITY (NCT05020665). Lanraplenib (LANRA) is a next-generation oral SYK inhibitor with potency, selectivity, and pharmacokinetic (PK) properties comparable to ENTO. Here we present data comparing the activity of ENTO and LANRA in ex vivo models of patient-derived AML cells, both as a single-agent and in combination with other AML therapies. ENTO and LANRA showed comparable effects on cell viability with no significant differences between the compounds when compared across 44 models representing different mutational backgrounds. Matrix combination assays were performed by combining ENTO or LANRA with either cytarabine (AraC; *NPM1* mut), gilteritinib (*FLT3* mut), or trametinib (*RAS* mut). Increased cell death in an additive manner was observed in all combinations tested, with results for ENTO and LANRA being similar, indicating the utility of both compounds in combinatorial treatment paradigms.

Spleen Tyrosine Kinase as an Oncogenic Driver in Acute Myeloid Leukemia[1,2]



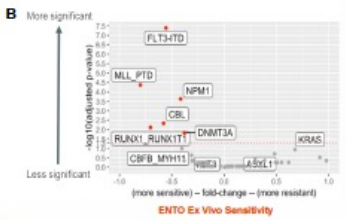


Figure 1: SYK is a critical node in *HOXA9/MEIS1* high AML. (A) *HOXA9/MEIS1* overexpression promotes leukemogenesis and is associated with high-risk AML. *MEIS1* increases SYK protein expression and activity, which then acts in a positive feedback loop by further promoting *MEIS1* expression thereby supporting leukemic cell survival and proliferation.[1,2] Inhibiting SYK disrupts the feedback loop and promotes apoptosis. **(B)** Ex vivo ENTO-treated AML samples were analyzed for mutations associated with sensitivity. Nucleophosmin-1 mutated (*NPM1c*) patients were among those sensitive to ENTO. (Figure 1B courtesy of Brian Drucker, MD of Oregon Health and Sciences University).

LANRA Pharmacokinetic Properties Compare Favorably With ENTO

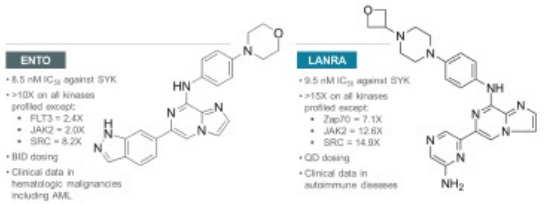


Figure 2: LANRA PK properties compare favorably with ENTO. LANRA is a next-generation oral SYK inhibitor with similar potency and selectivity as ENTO. LANRA has shown PK properties in human subjects that allow for once daily (QD) dosing as compared to twice daily (BID) dosing for ENTO. This poster compares the activity of LANRA to ENTO, both as a single agent and in combination with other AML therapies to support the clinical development of LANRA in AML.

Disclosures

MALD reports current employment by Kronos Bio, Inc. previous employment by Cyteir Therapeutics, and equity in Kronos Bio, Inc. and Cyteir Therapeutics. **PS** has no financial relationships to disclose. **CAH** reports consulting fees from Oncopeptides, and research funding from Kronos Bio, Inc., Oncopeptides, Novartis, Orion Pharma, and Celgene/BMS. **AS** reports current employment by and equity in Kronos Bio, Inc. **NDO** reports current employment by and equity, stock, and options in Kronos Bio, Inc. **CYL** reports current employment by Kronos Bio, Inc. **PK, JD, and DCS** report current employment by and equity in Kronos Bio, Inc.

ENTO and LANRA Show Comparable Activity in *NPM1*- and *FLT3*-Mutated Peripheral Blood Derived Leukemic Blasts

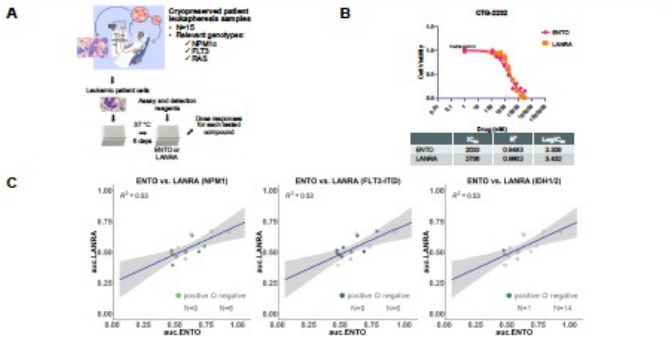
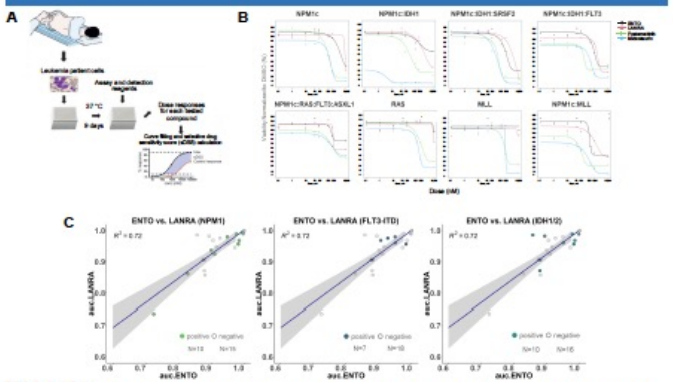


Figure 3: ENTO and LANRA display comparable antileukemic activity in *NPM1*- and/or *FLT3*-mutated AML blasts derived from peripheral blood. (A) Outline of the experiment. Blood was collected from patients, AML blasts isolated and cryopreserved. The cells were then thawed, placed in culture, and treated with varying concentrations ENTO or LANRA for 6 days. Cell viability was measured using CellTiter Glo. **(B)** Example cell viability curve for a *NPM1c* model, CTG-2232. Dose response curve with ENTO is in red and LANRA is in orange. **(C)** Comparison of ENTO and LANRA area under the curve (AUC) values across the 15 models showed a linear relationship indicating good correlation in response between the two inhibitors. (Work performed by Champions Oncology).

ENTO and LANRA Show Comparable Activity in *NPM1*- and *FLT3*-Mutated Bone Marrow Derived Leukemic Blasts



DMSO, dimethyl sulfoxide.

Figure 4: ENTO and LANRA display comparable antileukemic activity in *NPM1*- and/or *FLT3*-mutated AML blasts from bone marrow. (A) Cryopreserved AML cells from patient bone marrow samples were placed in culture and treated with increasing concentrations of ENTO, LANRA, fostamatinib or midostaurin for 9 days. Cell viability was measured with a flow cytometric assay using Annexin V and 7-aminoactinomycin D (7-AAD) staining. **(B)** Example cell viability curves in patient samples representing different mutational backgrounds. **(C)** Comparison of ENTO and LANRA AUC values across 29 models showed a linear relationship indicating good correlation in response between the two inhibitors.

References

1. Mohr S, et al. *Cancer Cell*. 2017;31(4):549-562.e11. 2. Tyner JW, et al. *Nature*. 2018;562(7728):526-531. 3. Pulsant A, et al. *Cancer Cell*. 2014;25(2):226-242.

Presented at the ASH 63rd Annual Meeting and Exposition, December 11-14, 2021, Atlanta, GA

Matrix Combination Assays

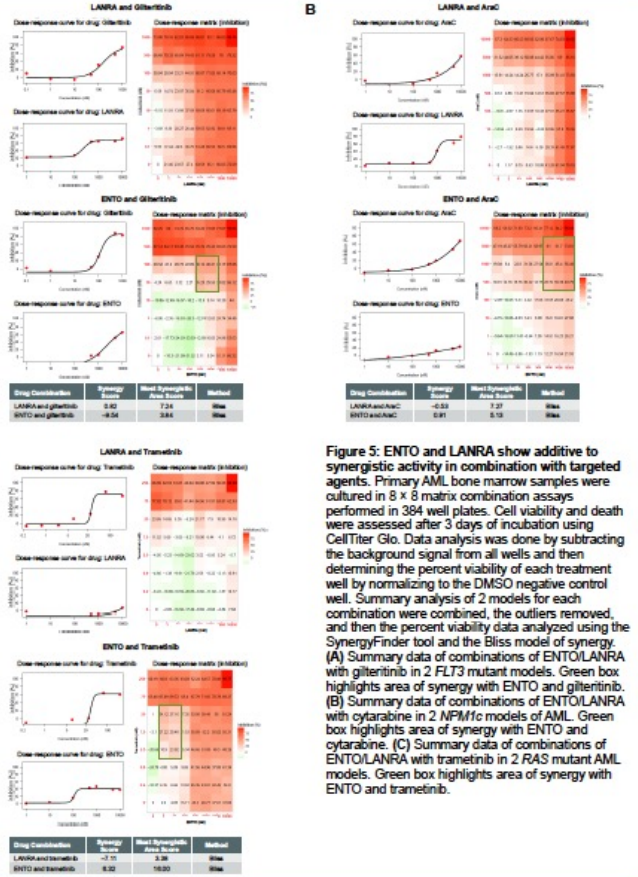


Figure 5: ENTO and LANRA show additive to synergistic activity in combination with targeted agents. Primary AML bone marrow samples were cultured in 8 x 8 matrix combination assays performed in 384 well plates. Cell viability and death were assessed after 3 days of incubation using CellTiter Glo. Data analysis was done by subtracting the background signal from all wells and then determining the percent viability of each treatment well by normalizing to the DMSO negative control well. Summary analysis of 2 models for each combination were combined, the outliers removed, and then the percent viability data analyzed using the SynergyFinder tool and the Bliss model of synergy. **(A)** Summary data of combinations of ENTO/LANRA with gilteritinib in 2 *FLT3* mutant models. Green box highlights area of synergy with ENTO and gilteritinib. **(B)** Summary data of combinations of ENTO/LANRA with cytarabine in 2 *NPM1c* models of AML. Green box highlights area of synergy with ENTO and cytarabine. **(C)** Summary data of combinations of ENTO/LANRA with trametinib in 2 *RAS* mutant AML models. Green box highlights area of synergy with ENTO and trametinib.

Conclusions

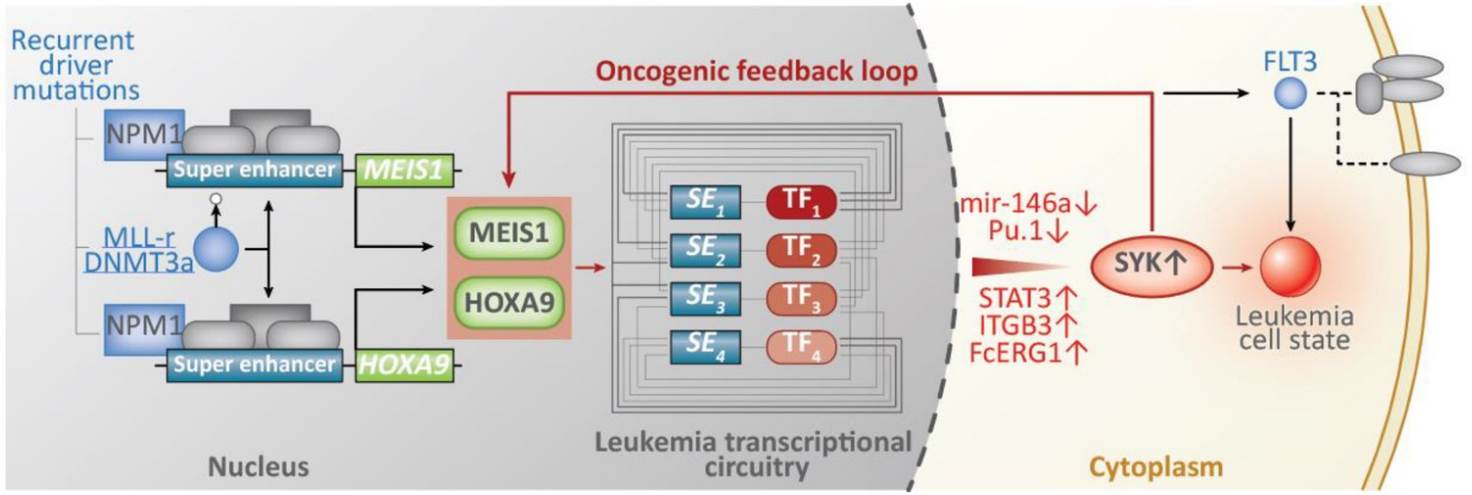
- LANRA and ENTO display comparable effects on viability among 44 AML patient-derived leukemic isolates.
- Only the *FLT3* mutational background showed differences between ENTO and LANRA, with slightly lower IC_{50} values in the presence of ENTO, most likely due to the inhibitory activity of ENTO against *FLT3*;[3] this is consistent with the hypothesis that SYK inhibition drives the majority of the activity.
- The results for LANRA and ENTO in the various combinations were similar, indicating the utility of both compounds in combinatorial treatment paradigms.

A phase 3 clinical trial, NCT05020665, with ENTO in combination with the 7 + 3 regimen in *NPM1*-mutated AML patients is currently enrolling.

A phase 1/2 clinical trial, NCT05028751, with LANRA in combination with gilteritinib in *FLT3*-mutated AML patients is currently enrolling.

Spleen Tyrosine Kinase as an Oncogenic Driver in Acute Myeloid Leukemia[1,2]

A



Adapted from Mohr S, et al. *Cancer Cell*. 2017;31(4):549-562.e11.

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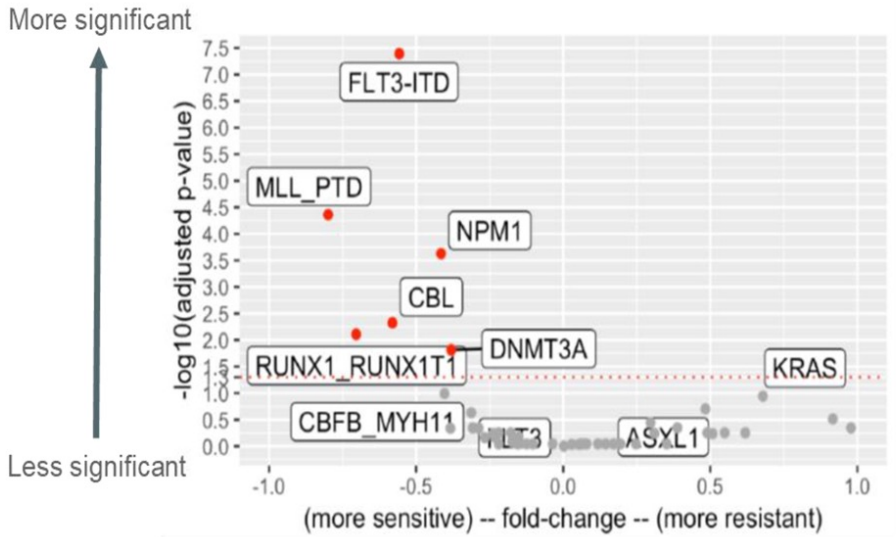


ENTO Ex Vivo Sensitivity

Day MAL et al. ASH 2021;Abstract 3356.

2564

CDK9 Inhibition via KB-0742 Is a Potential Strategy to Treat Transcriptionally Addicted Cancers

Melinda A. L. Day[1], Douglas C. Saffran[1], Tressa Hood[1], Nikolaus Obholzer[1], Akanksha Pandey[1], Akul Singhania[1], Charles Y. Lin[1], Pavan Kumar[1], Daniel M. Freed[2], Jorge DiMartino[1]

[1]Kronos Bio, Inc., San Mateo, CA; [2]Chordoma Foundation, Durham, NC

Abstract

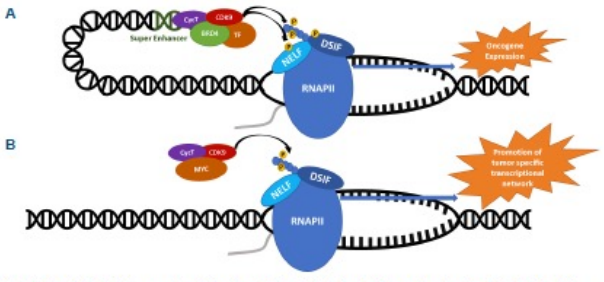
- Transcriptional addiction is defined as a state in which a tumor cell is critically dependent (more than normal cells) on highly efficient functioning of the transcriptional machinery for its growth and survival. This can be due to requirements for high rates of transcription of a critical oncogene such as *MYC*. Alternatively, certain tumors rely on dysregulated activity of a particular transcription factor to drive their malignant phenotype. These include the fusion gene *EWS-FLI1* in Ewing sarcoma, *PAX3/7-FOXO1* fusions in rhabdomyosarcoma, and *brachyury (T)* in chordoma. Cyclin-dependent kinase 9 (CDK9) controls progression through the elongation phase of the transcription cycle and represents a promising target in transcriptionally addicted tumors. We have developed a potent, selective, and orally bioavailable CDK9 inhibitor, KB-0742, which is currently in the dose-escalation stage of a phase 1/2 study (NCT04718675).
- Using the BROAD PRISM screen, we observed a trend in Ewing sarcoma cell lines, with lower half maximal inhibitory concentrations (IC_{50}s) in higher expressing *MYC* cell lines. We pulled out three cell lines and grew individually to assess sensitivity to KB-0742. All 3 Ewing sarcoma cell lines tested were sensitive to KB-0742, showing maximum inhibition rates of over 100%. We then evaluated the activity of KB-0742 in 5 patient-derived cell line (PDC) models, with all 5 showing a cytotoxic response to treatment as measured by negative growth rate (GR) efficacy (GR_{max}) values. KB-0742 was also found to be active in a single patient-derived organoid (PDO) model of adult rhabdomyosarcoma.
- The activity of KB-0742 was assessed in vivo using 2 patient-derived xenograft (PDX) models of chordoma. In model CF466, a dose-dependent response was observed as evidenced by increased tumor growth inhibition (TGI) activity and target engagement. We then evaluated KB-0742 as a single agent and in combination with afatinib (an EGFR inhibitor and preclinical gold standard compound for chordoma) in the CF539 model. KB-0742 as a single agent showed similar TGI activity as afatinib, whereas the combination showed an increased response.

CDK9 Is a Key Dependency in Tumor Transcriptional Reprogramming

As a transcriptional regulator, CDK9 is a key dependency in transcriptionally addicted tumors. CDK9 helps promote the tumor-associated transcriptional landscape through 2 mechanisms:

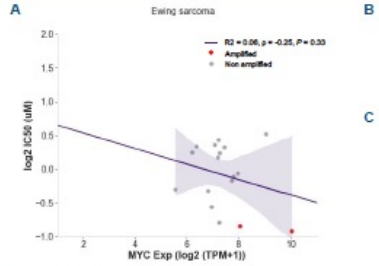
(A) Supporting expression of key oncogenes, and

(B) Working as a cofactor to oncogenic transcription factors such as MYC to promote high rates of transcription

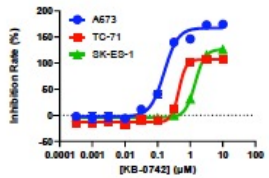


BRD4 = bromodomain protein 4; CycT = cyclin T; DSIF = 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole sensitivity-inducing factor; NELF = negative elongation factor; P = phosphate; RNAPII = RNA polymerase II; TF = transcription factor.

Sarcoma Cell Lines Are Sensitive to KB-0742



Cell Line	IC_{50} (μM)	Maximum % Inhibition
A673	0.11	174.4
TC-71	0.46	107.1
SK-ES-1	1.25	125.8



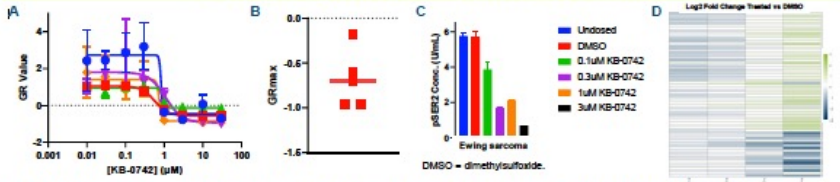
TPM = transcripts per kilobase million.

Immortalized cell lines were screened for sensitivity to KB-0742. All the cell lines were treated with a range of concentrations of KB-0742, and the IC_{50} was calculated. **(A)** In the Broad PRISM screen, a trend was observed in Ewing sarcoma with cells expressing higher levels of the oncogenic transcription factor *MYC*, having lower IC_{50}s to treatment with KB-0742. Additionally, the 2 *MYC*-amplified cell lines had the lowest IC_{50}s of the Ewing sarcoma lines tested. **(B)** Three Ewing Sarcoma cell lines were tested individually for response to KB-0742. All 3 cell lines showed maximum inhibition rates of over 100% and 2 of the 3 cell lines had IC_{50}s below 500 nM. **(C)** Dose-response curves of the 3 Ewing sarcoma cell lines.

Acknowledgements: The authors would like to thank K2 Oncology (Beijing, China) for patient-derived organoid cultures; Imagen Therapeutics (Manchester, UK) for patient-derived cell line studies; Broad Institute of MIT and Harvard (Cambridge, MA) for immortalized cell line studies; WuXi AppTec (Shanghai, China) for immortalized cell line studies; Qiagen (Germantown, MD) for sequencing services.

Presented at the American Association for Cancer Research Annual Meeting; April 8-13, 2022; New Orleans, LA.

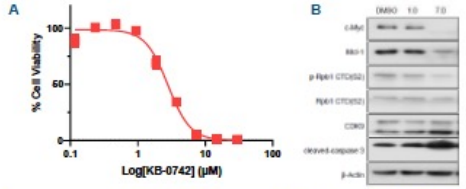
KB-0742 Is Cytotoxic in PDC Models of Sarcoma



DMSO = dimethylsulfoxide.

Five models of sarcoma, including 3 Ewing sarcoma models, were treated with concentrations of KB-0742 ranging from 30 μM down to 10 nM and were incubated for 72 hours. **(A)** GR values were calculated for each concentration of KB-0742 by comparing to a time 0 cell count number and graphed as a dose-response curve. **(B)** KB-0742 was cytotoxic in all 5 models as determined by negative values for GR_{max}. **(C)** Target engagement was assessed in 1 model of Ewing sarcoma. Cells were treated with the noted concentrations of KB-0742 for 6 hours before being collected and lysed for protein analysis. RNAPII pSER2 levels were measured using a Meso Scale Discovery assay. KB-0742 treatment reduces pSER2 protein in a dose-dependent manner. **(D)** RNA-sequencing analysis of the same model as (C) showed reduction of gene expression with KB-0742 treatment, indicating transcriptional repression.

KB-0742 Is Active in a PDO Model of Adult Rhabdomyosarcoma

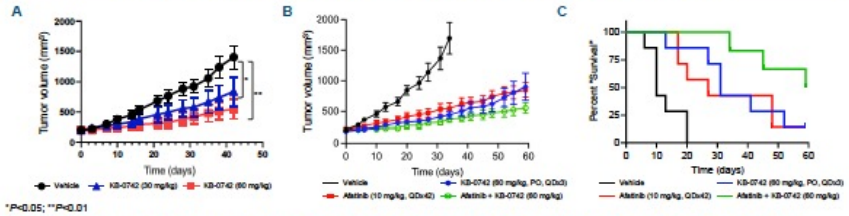


(A) A PDO model of treatment-naive adult rhabdomyosarcoma was treated with a titration curve of KB-0742. Treatment with KB-0742 resulted in an IC_{50} of 2.75 μM and a max inhibition rate of 98.61%.

(B) The same model was treated with DMSO and KB-0742 at 1 μM and 7 μM concentrations for 4 hours. Protein lysates were analyzed by western blot. KB-0742 treatment resulted in reductions in MYC, MCL-1, and pSER2 protein levels and an increase in cleaved-caspase 3 in a dose-dependent manner.

CTD = C-terminal domain; p-Rpb1 = Phospho-RNAPII subunit B1.

KB-0742 Shows Antitumor Activity in PDX Models of Chordoma



*P<0.05; **P<0.01

PDX models of chordoma were tested for sensitivity to KB-0742. **(A)** Model CF466 was treated with vehicle or KB-0742 at 30 mg/kg or 60 mg/kg (oral administration [PO], 3 days on/4 days off), and tumor volume was followed for 42 days. KB-0742 showed significant TGI activity in a dose-dependent manner (48% and 55%, respectively). Of the 7 mice treated in the KB-0742 60 mg/kg group, 2 had complete responses and were considered tumor-free survivors. **(B)** Model CF539 was treated with vehicle, KB-0742 (60 mg/kg, PO, 3 days on/4 days off), afatinib (10 mg/kg, PO, once daily [QD]), or the combination of KB-0742 plus afatinib for up to 60 days. Tumor volume GR curves were plotted over time, showing antitumor activity in all 3 treatment arms with the combination having the greatest reduction in growth. %TGI for each treatment arm was 74% ($P<0.0001$ vs control) for 60 mg/kg KB-0742, 77% ($P<0.0001$ vs control) for afatinib, and 88% ($P<0.0001$ vs control, $P=0.0951$ vs afatinib) for the combination. **(C)** Time to the tumors reaching 500 mm^3 was plotted using a Kaplan–Meier survival curve. The median time to 500 mm^3 was 10 days (vehicle), 27 days (afatinib), 31 days (KB-0742), and 59 days (KB-0742 with afatinib).

Conclusions

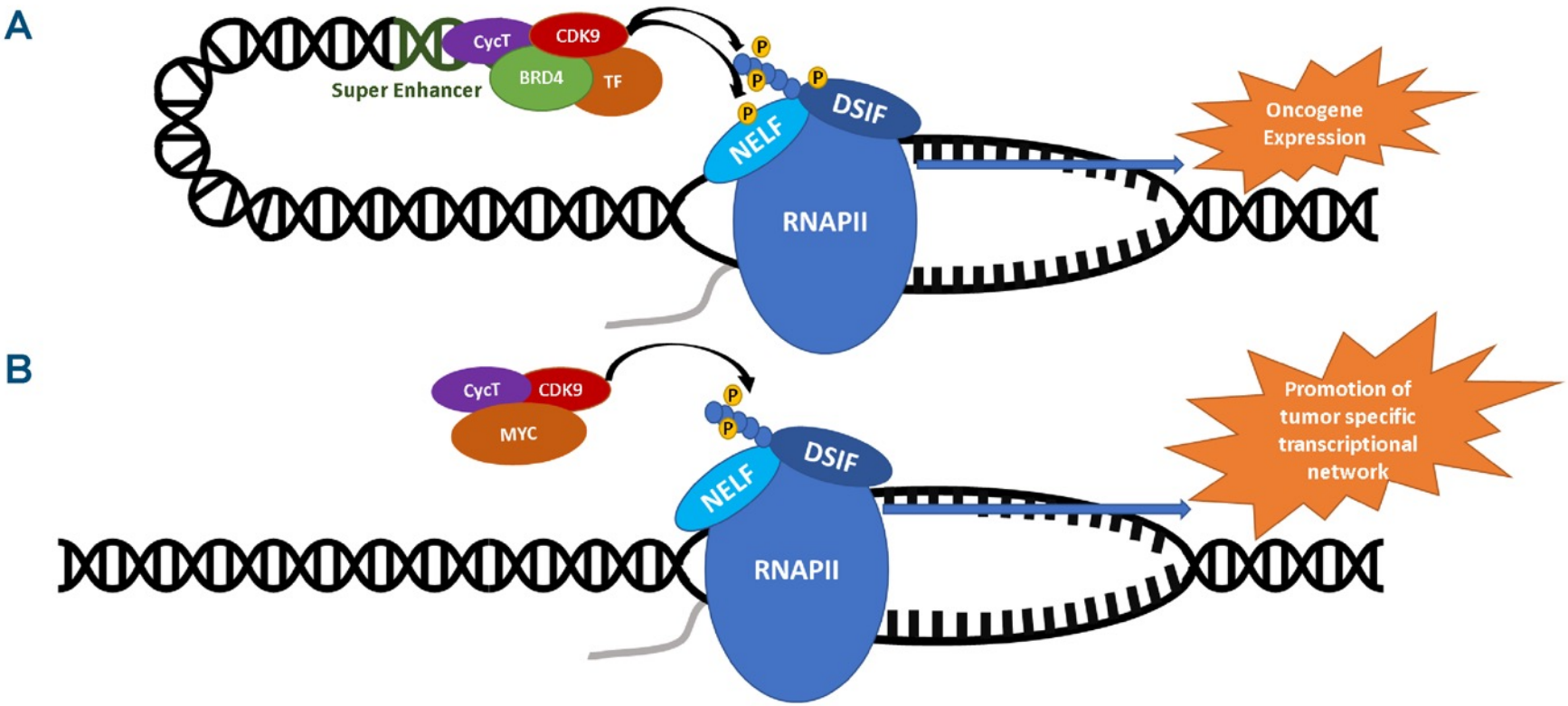
- Immortalized cell lines of sarcoma were sensitive to KB-0742.
- Cytotoxic responses to KB-0742 were observed in PDC models of sarcoma and were associated with a dose-dependent reduction in pSER2 protein levels.
- KB-0742 was shown to reduce c-MYC, MCL-1, and pSER2 protein levels in a PDO model of rhabdomyosarcoma that was associated with an increase in the cell-death marker cleaved-caspase 3.
- In models of chordoma, KB-0742 had antitumor activity that was dose dependent and showed combinatorial activity with the preclinical gold standard compound, afatinib.

Based on these data across multiple translation platforms, an expansion cohort in the ongoing phase 1/2 clinical trial of KB-0742 (NCT04718675) will evaluate the antitumor activity of KB-0742 at the recommended phase 2 dose in patients with relapsed or refractory sarcoma, chordoma, and other transcriptionally addicted solid tumors.

CDK9 Is a Key Dependency in Tumor Transcriptional Reprogramming

As a transcriptional regulator, CDK9 is a key dependency in transcriptionally addicted tumors. CDK9 helps promote the tumor-associated transcriptional landscape through 2 mechanisms:

- **(A)** Supporting expression of key oncogenes, and
- **(B)** Working as a cofactor to oncogenic transcription factors such as MYC to promote high rates of transcription



BRD4 = bromodomain protein 4; CycT = cyclin T; DSIF = 5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole sensitivity-inducing factor; NELF = negative elongation factor; P = phosphate; RNAPII = RNA polymerase II; TF = transcription factor.

Day MA et al. AACR 2022;Abstract 2564.

Abstract 208
PB088

Regulation of oncogenic transcription and tumor growth in pediatric cancers by the CDK9 inhibitor KB-0742

Douglas C. Saffran[1], Evon Poon[2], Glorymar Ibanez[3], Jonathan Nakashima[4], Suha Naffar-Abu Amara[1], Christina Noe[1], Tressa R. Hood[1], Stephanie LaHaye[5], Ming-Ju Tsai[1], Sara Heuss[2]
Jonathan Ball[5], Nikolaus D. Obholzer[1], Pavan Kumar[1], Jorge F. DiMartino[1], Filemon Dela Cruz[3], Louis Chesler[2], Charles Y. Lin[1]

[1]Kronos Bio, Inc., San Mateo, CA, USA; [2]Division of Clinical Studies, The Institute of Cancer Research, London, UK; [3]Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Certis Oncology Solutions, San Diego, CA, USA, [5]Tempus Labs, Chicago, IL, USA

Background

Disruption of transcriptional regulatory networks that drive normal cellular differentiation and development can result in oncogenic transformation and transcriptional addiction. Many pediatric sarcomas are defined by/harbor oncogenic fusion proteins, resulting from chromosomal translocations such as the *EWSR1* gene fused to an ETS family transcription factor (TF) gene (*FLI1* or *ERG*) in Ewing sarcoma, or *PAX3/PAX7* and *FOXO1* translocations in alveolar rhabdomyosarcoma. In neuroblastoma, MYCN, a member of the MYC family of TFs, is often amplified and localizes to super enhancer regions, where it rewires lineage-specific transcriptional programs driving oncogenesis.

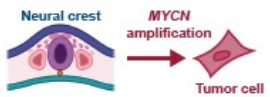
Oncogenic TFs have proven difficult to target directly; we and others have proposed targeting associated transcriptional co-regulators to inhibit their activity. CDK9 interacts with many oncogenic TFs and is essential for TF-mediated transcription elongation through phosphorylation of the C-terminal domain of RNA pol II. KB-0742 is a potent, selective, and orally bioavailable inhibitor of CDK9 currently in clinical development that shows antitumor activity in preclinical models of sarcoma and neuroblastoma.

Materials and methods

Cell lines and low-passage patient-derived cells (PDCs) were tested for antiproliferative effects of KB-0742, using either Cell Titer Glo (Promega) or Alamar Blue cell viability reagent (Bio-Rad). Pharmacodynamic (PD) markers of KB-0742 treatment, including phospho-SER2 (pSER2) on RNA pol II, MYCN, MYC, and cleaved poly ADP ribose polymerase (PARP), were measured by Western blot. The antitumor activity of KB-0742 was evaluated using patient-derived xenograft (PDX) models of Ewing sarcoma and alveolar rhabdomyosarcoma *in vivo*. Tumor samples and plasma were collected to determine PD effects and drug concentrations, respectively. The transgenic TH-MYCN model of neuroblastoma was used to study antitumor effects of KB-0742. All *in vivo* models were performed according to IACUC guidelines.

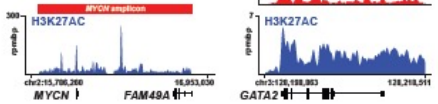
Disrupted transcription regulatory networks in pediatric cancers

Neuroblastoma

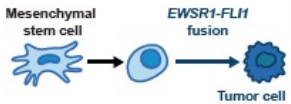


Genetic deregulation of a TF → Rewiring of developmental gene expression programs

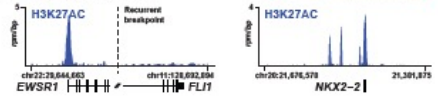
ChIP-seq in Kelly neuroblastoma cells from Poon et al., *JCI 2020*. **Below:** H3K27AC at the *MYCN* amplicon. **Right:** MYCN binding to the *GATA2* TF locus.



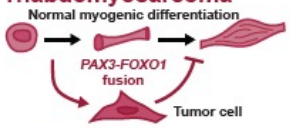
Ewing sarcoma



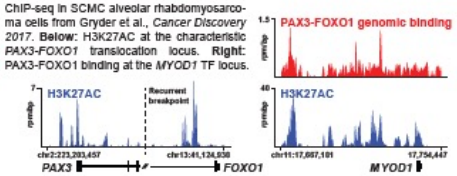
ChIP-seq in SKMNC Ewing sarcoma cells from Riggi et al., *Cancer Cell 2014*. **Below:** H3K27AC at the characteristic *EWSR1-FLI1* translocation locus. **Right:** EWSR1-FLI1 binding at the *NKX2-2* TF locus.



Alveolar rhabdomyosarcoma



ChIP-seq in SCMC alveolar rhabdomyosarcoma cells from Gryder et al., *Cancer Discovery 2017*. **Below:** H3K27AC at the characteristic *PAX3-FOXO1* translocation locus. **Right:** PAX3-FOXO1 binding at the *MYOD1* TF locus.



Overall results

KB-0742 decreased the viability of immortalized and low passage PDCs from Ewing sarcoma, alveolar rhabdomyosarcoma, and neuroblastoma. In neuroblastoma, cell lines with *MYCN* amplification were more sensitive to KB-0742 treatment. KB-0742–treated neuroblastoma cells had decreased pSER2, loss of expression of MYCN and MYC, and an induction of cleaved PARP. KB-0742 treatment of a TH-MYCN transgenic mouse model resulted in regression of established tumors. In PDX models of Ewing sarcoma and alveolar rhabdomyosarcoma, KB-0742 treatment inhibited tumor growth. Analysis of tumor samples revealed decreases in pSER2 and the expression of oncogenic fusion TFs. KB-0742 is being evaluated in a phase I dose-escalation trial in patients with relapsed or refractory solid tumors or Non-Hodgkin's lymphoma (NCT04718675).

KB-0742 inhibits growth of *MYCN*-amplified neuroblastoma

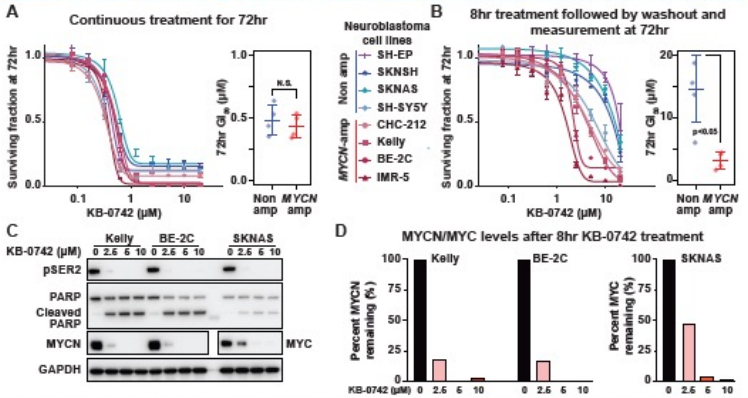


Figure legend: A,B) KB-0742 effects on cell viability across *MYCN*-amplified or non amplified neuroblastoma cell lines (n=4 each) plated for 24hrs and then treated with KB-0742. **A)** Continuous treatment. **B)** 8hr treatment followed by washout. Cell viability measured as surviving fraction of cells 72hrs post treatment. GI_{50} concentrations shown as dot plots next to each graph. Differences between groups assessed by a two-tailed *t*-test. Blue: non amplified lines. Red: *MYCN*-amplified lines. **C)** Western blots were performed on *MYCN*-amplified (Kelly and BE-2C) and non amplified (SKNAS) neuroblastoma cells at 8hr post treatment with measurement of protein levels for biomarkers of CDK9 inhibition (pSER2), induction of apoptosis (full length and cleaved PARP) and MYCN or MYC. GAPDH is provided as a negative control. **D)** Densitometry of MYCN or MYC protein levels from **figure C)** normalized to GAPDH with untreated (0μM) levels set to 100%.

KB-0742 causes tumor regression in MYCN-driven neuroblastoma genetically engineered mouse model

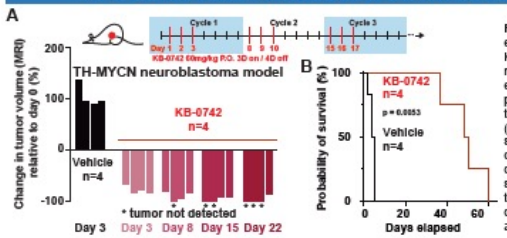


Figure legend: **A)** The TH-MYCN genetically engineered mouse model was used to assess KB-0742 efficacy in a MYCN-driven model of neuroblastoma. In this model, MYCN is expressed from the tyrosine hydroxylase promoter. Mice which developed evident tumors were either treated with vehicle (saline, n=3) or 60mg/kg KB-0742 (n=4) on a schedule of 3-days on/4-days off per weekly cycle. Tumor volume was assessed by MRI at days 3, 8, 15 and 22. **B)** Kaplan-Meier plot showing overall survival of vehicle or KB-0742 treated cohorts. Statistical significance of the difference between cohorts is assessed using a log-rank Mantel-Cox test.

KB-0742 broadly inhibits growth of pediatric sarcoma cell lines

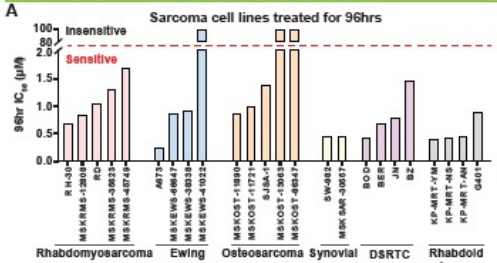


Figure legend: **A)** KB-0742, was screened against 24 cell lines across several pediatric sarcomas. Dose response assessments were performed by integrating 3 serial dose responses with peak values of 100μM, 10μM and 1μM in triplicate. The high controls (HC) contained 1% DMSO (v/v), the low controls (LC) 1μM 'killer mix' in 1% DMSO (v/v) that consists of a proprietary mixture of 6 cytotoxic compounds. The compounds were tested at 1% DMSO (v/v) for 96h. Dose–response curves were fitted using a logistic 4-parameter equation in GraphPad Prism 7 and IC_{50} values were determined.

KB-0742 inhibits growth of TF fusion positive sarcomas *in vivo*

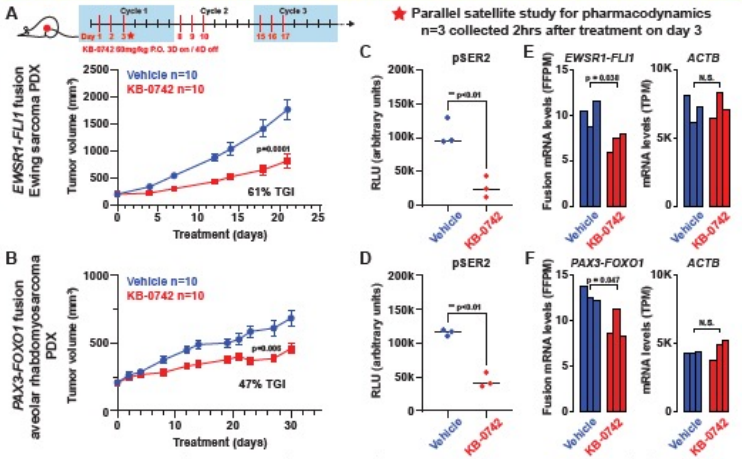


Figure legend: A,B) For PDXs, tumors were subcutaneously engrafted and mice were randomized (n=10 per cohort) at >150mm³ tumor volume. PDX models were treated with vehicle (saline) or 60mg/kg KB-0742 on a 3-days on/4-days off weekly cycle. Tumor volumes and body weights were recorded twice weekly. The statistical difference of growth inhibition between cohorts was denoted and assessed using an unpaired *t*-test with Welch's correction. C-F) A satellite study was conducted in parallel with tumors (n=3) collected 2hrs post treatment on day 3 in which plasma KB-0742 concentrations of 4μM and 2.5μM were measured in the Ewing sarcoma and aveolar rhabdomyosacroma PDXs respectively. C,D) Tumor lysates were prepared and RNA pol II pSER2 was measured using a Meso Scale Discovery (MSD) assay. Differences in pSER2 levels assessed using two-tailed *t*-test. E,F) Whole-transcriptome profiling using the Tempus xT assay. **Left)** RNA fusions detected using STAR-Fusion and Mojo and fusion TF mRNA levels are shown as fusion fragments per million reads (FFPM). **Right)** An unaffected control mRNA *ACTB* is shown in units of transcripts per million (TPM). Differences in mRNA levels assessed using two-tailed *t*-test.

Acknowledgments

The authors would like to thank Giovanni Rivera, Bianca Carapia, Deborah Yan, Javier Rodriguez, Rowan Prendergast, and Jantzen Sperry from Certis Oncology for their contributions

Management of Acute Myeloid Leukemia

Introduction

- AML 2014 to 2022
- Defining AML versus MDS

Case 1: 82-year-old man presenting with cytopenias and AML

- Oral decitabine/cedazuridine
- Management of cytopenias with HMA/venetoclax: Drug-drug interactions
- HMA/venetoclax for younger patients
- Translational biology of AML: New agents and treatment strategies

Case 2: 75-year-old man with p53-mutated AML and complex karyotype

- Anti-CD47 antibody magrolimab

Case 3: 61-year-old woman with MLL-rearranged AML; s/p 7 + 3, FLAG-IDA and aza/ven

- Clinical implications of NPM1 mutation in AML

ASH 2022; other key papers

ELN Risk Stratification Is Not Predictive of Outcomes for Treatment-Naïve Patients with Acute Myeloid Leukemia Treated with Venetoclax and Azacitidine

Döhner H et al.

ASH 2022;Abstract 602 (Oral).

Sunday, December 11, 2022

4:45 PM EST

ASTX727-03: Phase 1 Study Evaluating Oral Decitabine/Cedazuridine (ASTX727) Low-Dose (LD) in Lower-Risk Myelodysplastic Syndromes (LR-MDS) Patients

Garcia-Manero G et al.

ASH 2022;Abstract 461 (Oral).

Sunday, December 11, 2022

5:30 PM EST

Higher-Dose Venetoclax with Measurable Residual Disease-Guided Azacitidine Discontinuation in Newly Diagnosed Patients with Acute Myeloid Leukemia: Phase 2 Hiddav Study

Gutman JA et al.
ASH 2022;Abstract 1421 (Poster).

Molecular MRD By Digital PCR Is Prognostic of Outcomes in AML Patients on Intensive and Non-Intensive Treatment Regimens

Minhujuddin M et al.
ASH 2022;Abstract 2791 (Poster).

Clinical and Molecular Features of Highly Durable Response to Azacitidine + Venetoclax in Acute Myeloid Leukemia

Hayden A et al.
ASH 2022;Abstract 4129 (Poster).

Overall Survival and Its Interplay with Allogeneic Stem Cell Transplant and Age in Newly Diagnosed AML Patients Treated with Ven/Aza

Abbott D et al.

ASH 2022;Abstract 2751 (Poster).

Outcomes with Molecularly Targeted Agents as Salvage Therapy Following Frontline HMA/Venetoclax in Adults with Acute Myeloid Leukemia: A Multi-Center Retrospective Analysis

Khanna V et al.

ASH 2022;Abstract 1429 (Poster).

Response to Intensive Induction Chemotherapy After Failure of Frontline Azacitidine + Venetoclax in Acute Myeloid Leukemia

McMahon CM et al.

ASH 2022;Abstract 2753 (Poster).

Comparison of Patients with Newly Diagnosed (ND) Acute Myeloid Leukemia (AML) Treated with Venetoclax and Hypomethylating Agents vs Other Therapies By TP53 and IDH1/2 Mutation: Results from the AML Real World Evidence (ARC) Initiative

Wolach O et al.
ASH 2022;Abstract 4954 (Poster).

Initial Results from SELECT-AML-1, a Phase 2 Study of Tamibarotene in Combination with Venetoclax and Azacitidine in RARA-Positive Newly Diagnosed AML Patients Ineligible for Standard Induction Chemotherapy

Kambhampati S et al.
ASH 2022;Abstract 1444 (Poster).

Toxicity and Outcomes in Octo- and Nonagenarians with AML Treated with Venetoclax and Hypomethylating Agent Therapy

Madarang E et al.
ASH 2022;Abstract 1434 (Poster).

Treatment Patterns and Outcomes of Patients with Primary or Secondary Acute Myeloid Leukemia By Type of Site (Academic or Community/Government): A CONNECT® Myeloid Registry Study

Scott BL et al.

ASH 2022;Abstract 4023 (Poster).

blood advances

Venetoclax and azacitidine compared with induction chemotherapy for newly diagnosed patients with acute myeloid leukemia

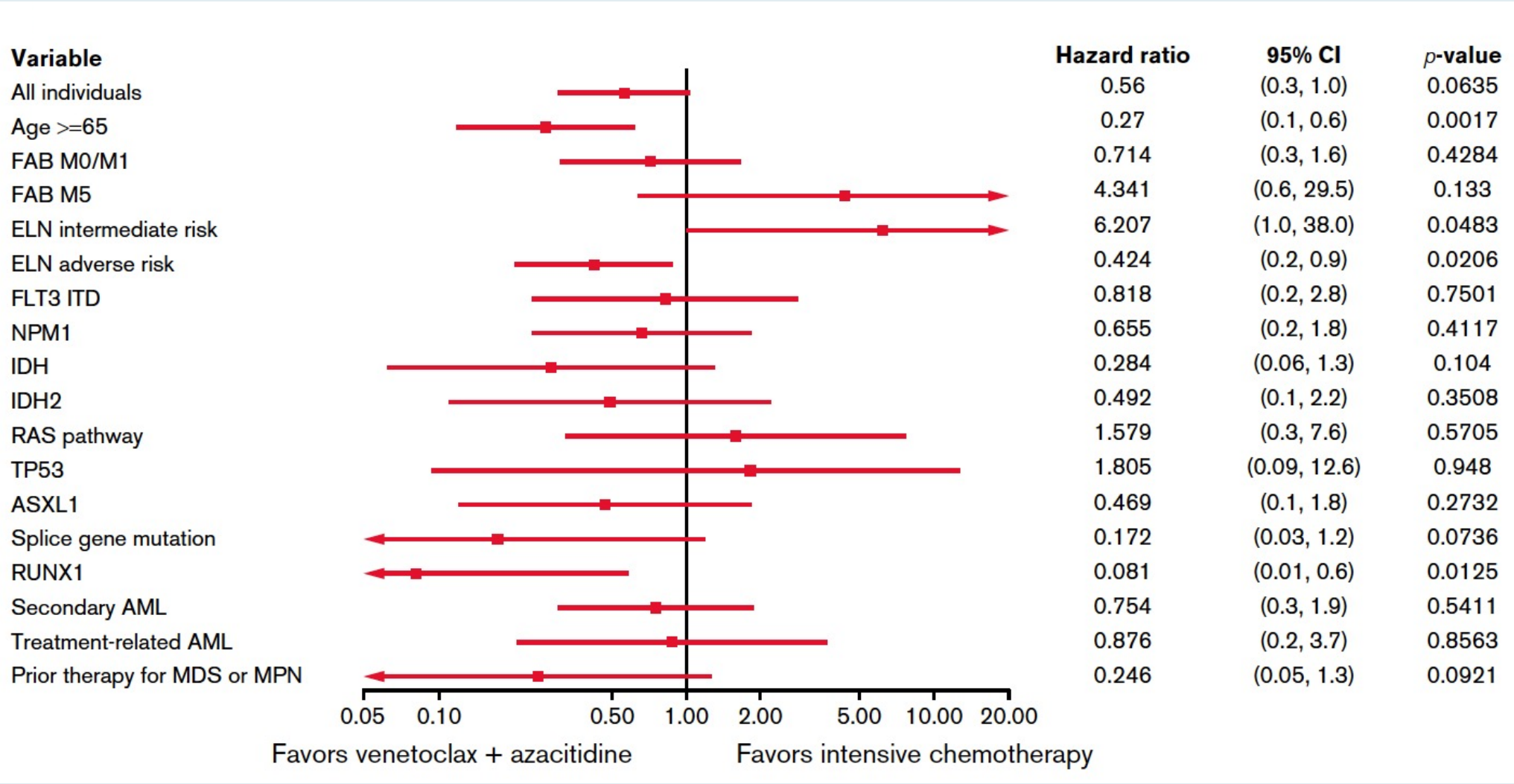
Evan M. Cherry,[1,*] Diana Abbott,[2,*] Maria Amaya,[1] Christine McMahon,[1] Marc Schwartz,[1] Julie Rosser,[3] Audrey Sato,[3] Jeffrey Schowinsky,[3] Anagha Inguva,[1] Mohd Minhajuddin,[1] Shanshan Pei,[1] Brett Stevens,[1] Amanda Winters,[1] Craig T. Jordan,[1] Clayton Smith,[1] Jonathan A. Gutman,[1] and Daniel A. Pollyea[1]

[1]Division of Hematology, Department of Medicine; [2]Center for Innovative Design and Analysis, Department of Biostatistics and Informatics; and [3]Department of Pathology, University of Colorado, Aurora, CO

Blood Adv **2021 December 28;5(24):5565-73.**

Venetoclax/Azacitidine Compared to Induction Chemotherapy for Patients with Newly Diagnosed AML

Factors That Favored Either Regimen for Overall 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 EM et al. *Blood Adv* 2021 December 28;5(24):5565-73.

blood advances

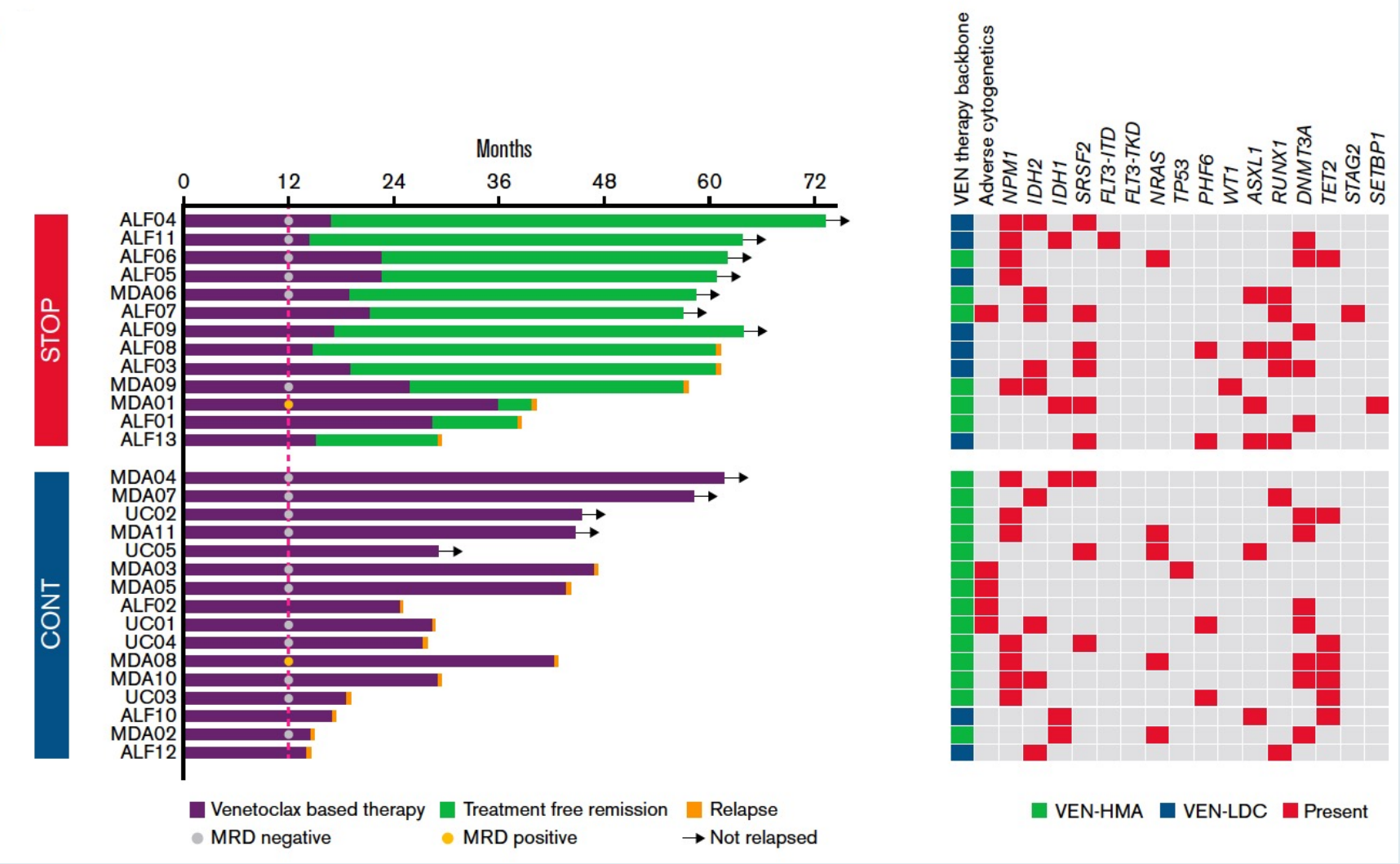
Treatment-free remission after ceasing venetoclax-based therapy in patients with acute myeloid leukemia

Chong Chyn Chua,[1-3] Danielle Hammond,[4] Andrew Kent,[5] Ing Soo Tiong,[1,6] Marina Y. Konopleva,[4] Daniel A. Pollyea,[5] Courtney D. DiNardo,[4] and Andrew H. Wei[1,2,7]

[1]The Alfred Hospital and Monash University, Melbourne, Australia; [2]The Walter and Eliza Hall Institute of Medical Research, Parkville, Melbourne, Australia; [3]Department of Clinical Haematology, Northern Hospital, Melbourne, Australia; [4]University of Texas MD Anderson Cancer Center, Houston, TX; [5]Division of Hematology, University of Colorado School of Medicine, Aurora, CO; [6]Department of Pathology, Peter MacCallum Cancer Centre, Melbourne, Australia; and [7]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and University of Melbourne, Melbourne, Australia

***Blood Adv* 2022 July 12;6(13):3879-83.**

Treatment-Free Remission After Ceasing Venetoclax-Based Therapy for AML



Chua CC et al. *Blood Adv* 2022 Jul 12;6(13):3879-83.

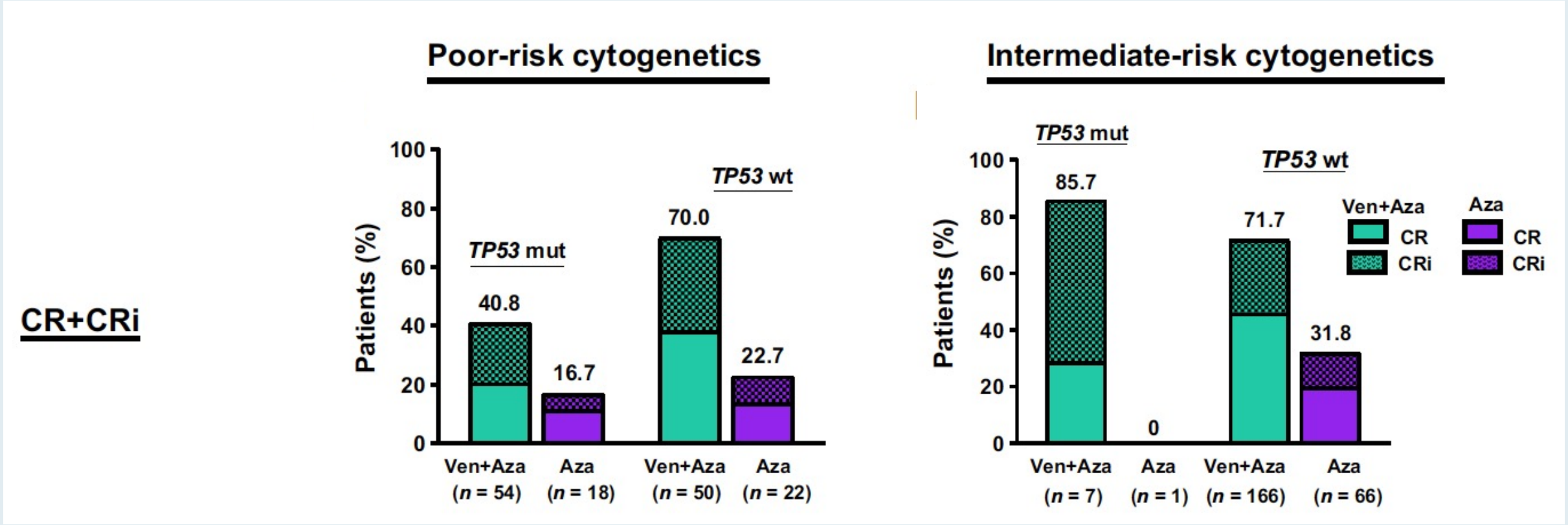
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Outcomes in Patients with Poor-Risk Cytogenetics with or without *TP53* Mutations Treated with Venetoclax and Azacitidine

Daniel A. Pollyea[1], Keith W. Pratz[2], Andrew H. Wei[3], Vinod Pullarkat[4], Brian A. Jonas[5], Christian Recher[6], Sunil Babu[7], Andre C. Schuh[8], Monique Dail[9], Yan Sun[10], Jalaja Potluri[10], Brenda Chyla[10], and Courtney D. DiNardo[11]

***Clin Cancer Res* 2022 August 25;[Online ahead of print].**

Outcomes with Venetoclax and Azacitidine for Patients with Poor-Risk Cytogenetics with or without TP53 Mutations



CR = complete remission; CRi = CR with incomplete hematologic recovery

Pollyea DA et al. *Clin Cancer Res* 2022 August 25;[Online ahead of print].

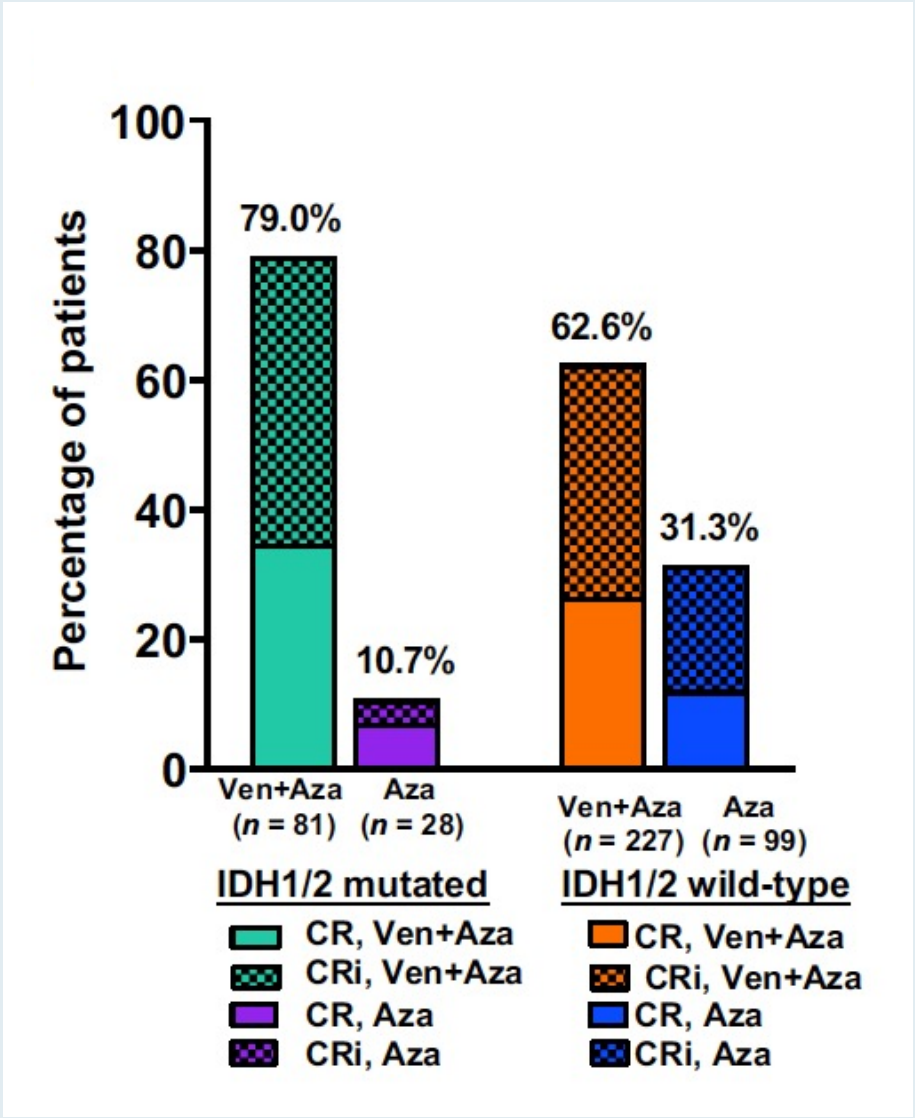
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Impact of Venetoclax and Azacitidine in Treatment-Naïve Patients with Acute Myeloid Leukemia and *IDH1/2* Mutations

Daniel A. Pollyea[1], Courtney D. DiNardo[2], Martha L. Arellano[3], Arnaud Pigneux[4], Walter Fiedler[5], Marina Konopleva[2], David A. Rizzieri[6], B. Douglas Smith[7], Atsushi Shinagawa[8], Roberto M. Lemoli[9,10], Monique Dail[11], Yinghui Duan[12], Brenda Chyla[12], Jalaja Potluri[12], Catherine L. Miller[12], and Hagop M. Kantarjian[2]

Clin Cancer Res **2022 July 1;28(13):2753-61.**

Remission Rates with Venetoclax and Azacitidine for Patients with Treatment-Naïve AML and IDH1/2 Mutations



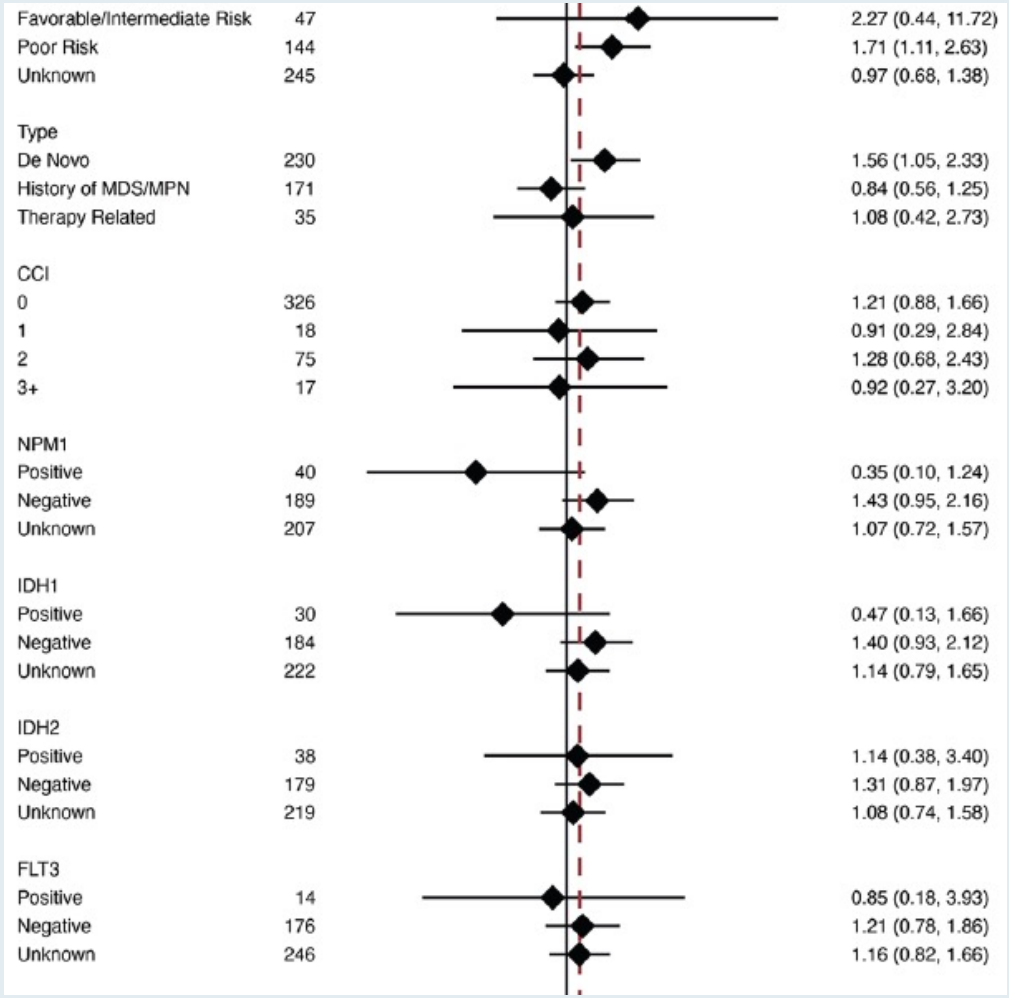
Pollyea DA et al. *Clin Cancer Res* 2022 July 1;28(13):2753-61.

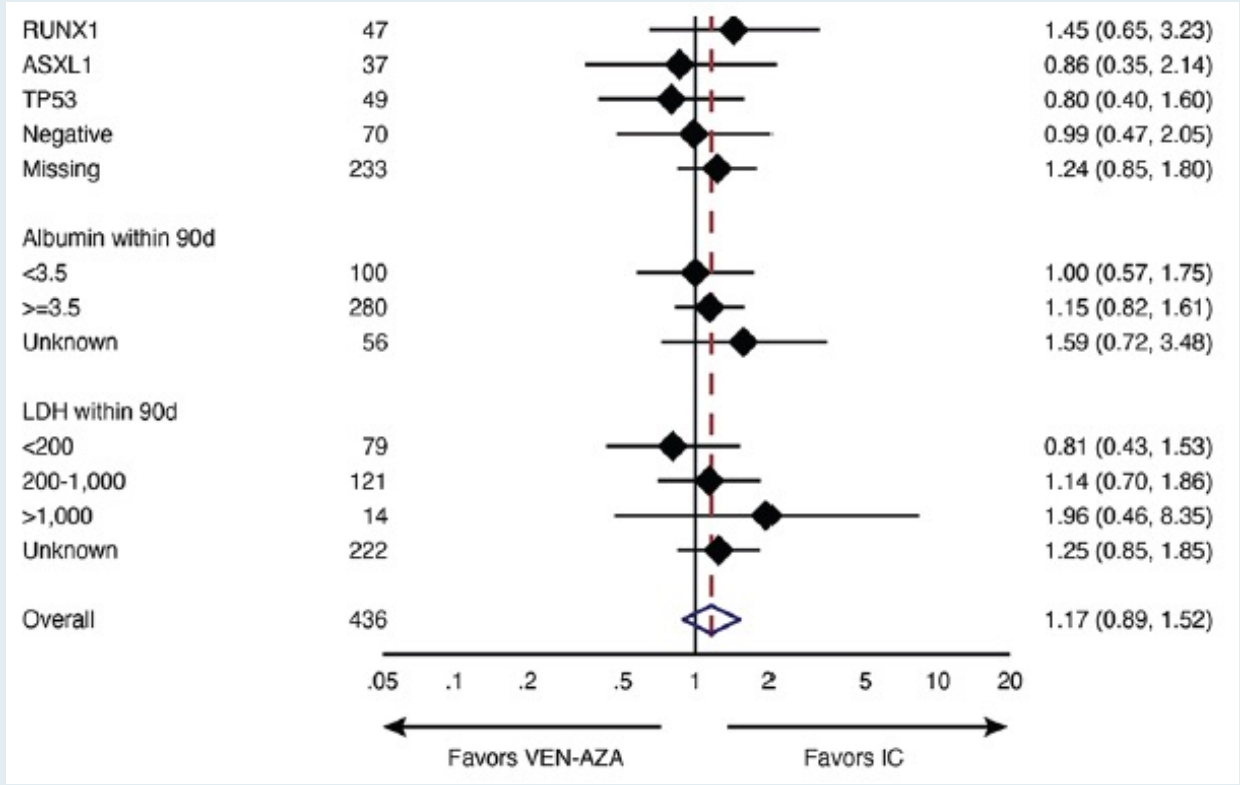
Real-World Efficacy Outcomes of Venetoclax plus Azacitidine vs Intensive Chemotherapy for Induction Therapy in Adult Patients with Acute Myeloid Leukemia

Zeidan AM et al.

EHA 2022;Abstract P570.

Real-World Efficacy Outcomes with Venetoclax and Azacitidine versus Intensive Chemotherapy as Induction Therapy: Subgroup Analysis for Factors in Overall Survival





Zeidan AM et al. EHA 2022;Abstract P570.

BCMA-Directed Therapy in Multiple Myeloma — Expert Opinions and Patient Perspectives

Part 2 of a 2-Part CME/MOC-Accredited Virtual Series

Wednesday, November 30, 2022
5:00 PM – 6:00 PM ET

Faculty

S Vincent Rajkumar, MD

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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