Recent Advances in Acute Leukemias and Myelodysplastic Syndromes

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Learning Objectives

- Review new classification systems and recently approved drugs for lower risk myelodysplastic syndromes
- Discuss treatment of NPM1-mutated AML
- Highlight shifting paradigms in the upfront treatment of B-ALL

Myelodysplastic Syndromes

(Myelodysplastic Neoplasms?)

MDS in the WHO5 Classification System

Table 3. Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

Khoury et al, Leukemia 2022

MDS in the ICC Classification System

Table 20. Myelodysplastic syndromes (MDS) and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)

	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics[b]***	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1[c]	≥1	0	<5% BM <2% PB	Any, except isolated del(5q), -7/del(7q), abn3q26.2, or complex	*SF3B1* (≥10% VAF), without multi-hit *TP53*, or *RUNX1*
MDS with del(5q) [MDS-del(5q)]	Typically ≥1[c]	≥1	Thrombocytosis allowed	<5% BM <2% PB[d]	del(5q), with up to 1 additional, except -7/del(7q)	Any, except multi-hit *TP53*
MDS, NOS - without dysplasia	0	≥1	0	<5% BM <2% PB[d]	-7/del(7q) or complex	Any, except multi-hit *TP53* or *SF3B1* (≥10% VAF)
MDS, NOS - with single lineage dysplasia	1	≥1	0	<5% BM <2% PB[d]	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*;not meeting criteria for MDS-*SF3B1*
MDS, NOS - with multilineage dysplasia	≥2	≥1	0	<5% BM <2% PB[d]	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*,; not meeting criteria for MDS-*SF3B1*
MDS with excess blasts (MDS-EB)	Typically ≥1[c]	≥1	0	5-9% BM, 2-9% PB[d]	Any	Any, except multi-hit *TP53*
MDS/AML	Typically ≥1[c]	≥1	0	10-19% BM or PB[e]	Any, except AML-defining[f]	Any, except *NPM1*, bZIP *CEBPA* or *TP53*

[a]Cytoses: Sustained white blood count ≥13 x 10^9/L, monocytosis (≥0.5 x 10^9/L and ≥10% of leukocytes), or platelets ≥450 x 10^9/L; thrombocytosis is allowed in MDS-del(5q) or in any MDS case with inv(3) or t(3;3) cytogenetic abnormality.

[b]*BCR*::*ABL1* rearrangement or any of the rearrangements associated with myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions exclude a diagnosis of MDS, even in the context of cytopenia.

[c]Although dysplasia is typically present in these entities, it is not required.

[d]Although 2% PB blasts mandates classification of an MDS case as MDS-EB, the presence of 1% PB blasts confimed on two separate occasions also qualifies for MDS-EB.

[e]For pediatric patients (<18 years), the blast thresholds for MDS-EB are 5-19% in BM and 2-19% in PB, and the entity MDS/AML does not apply.

[f]AML-defining cytogenetics are listed in the AML section.

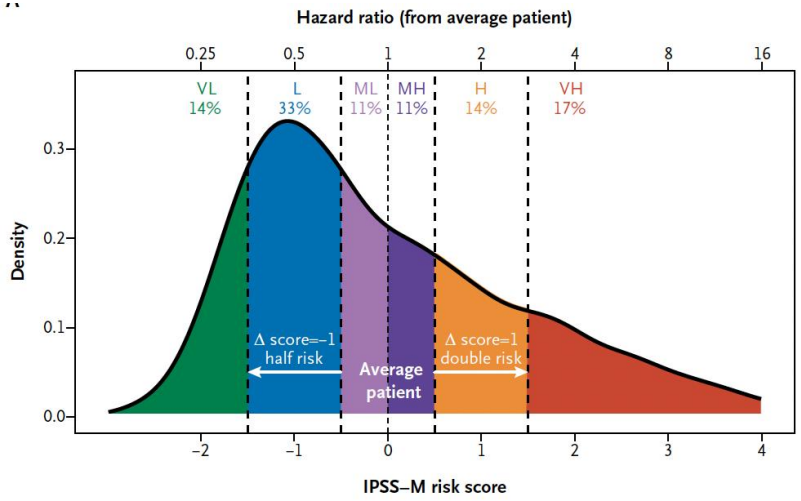
Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation[a], or *TP53* mutation (VAF >10%) and complex karyotype often with loss of 17p[b]
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF >10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF >10%)

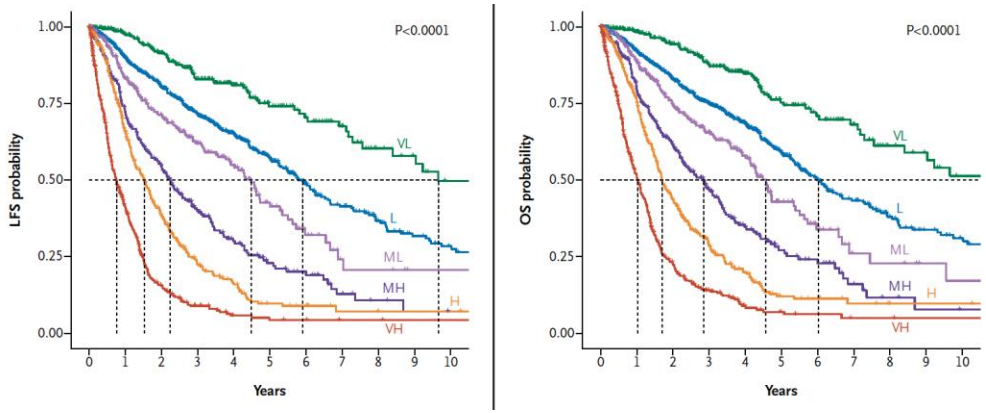
[a]Defined as two distinct *TP53* mutations (each VAF >10%) OR a single *TP53* mutation with either 1) 17p deletion on cytogenetics; 2) VAF of >50%; or 3) Copy-neutral loss of heterozygosity (LOH) at the 17p *TP53* locus.

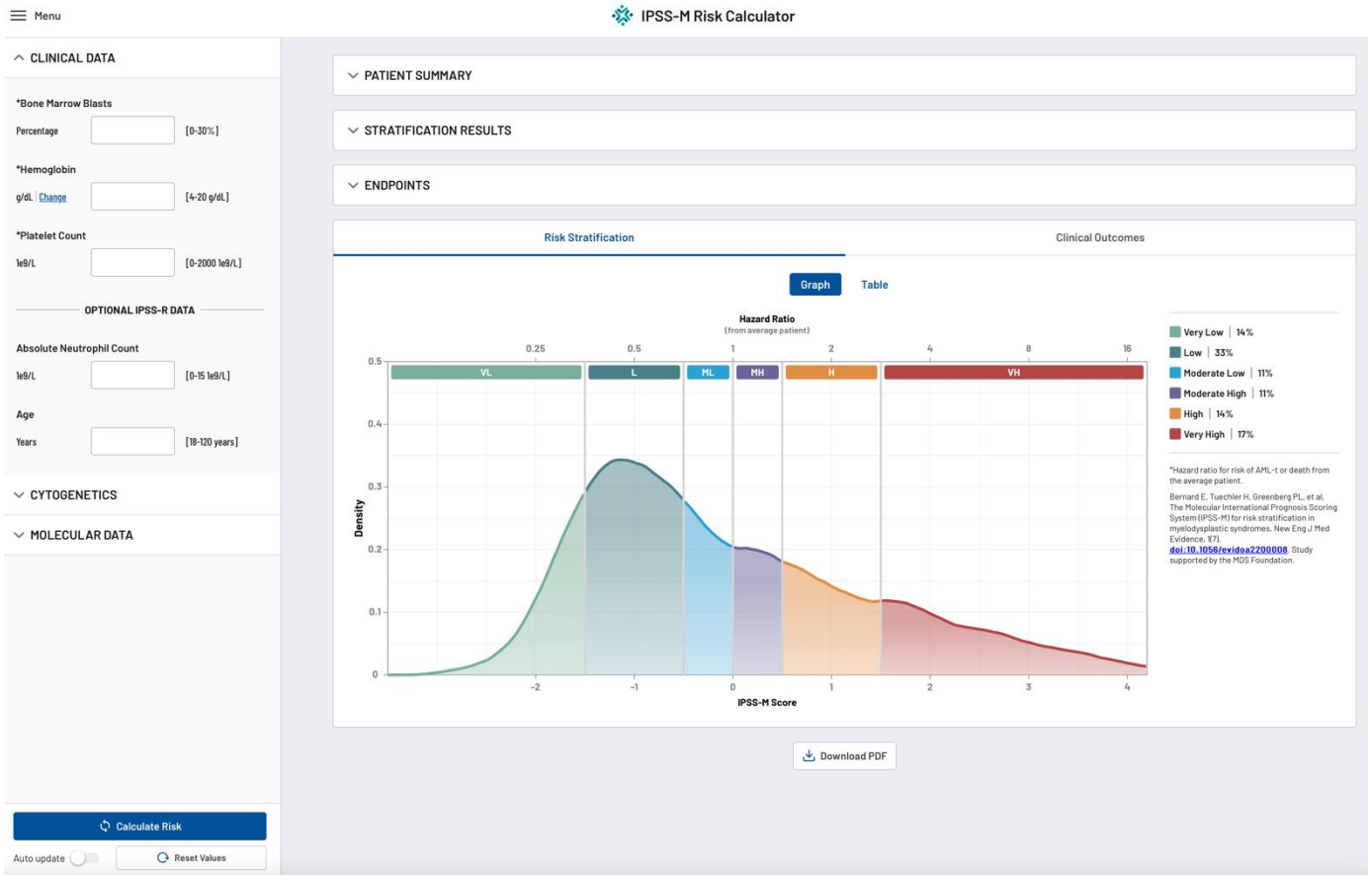
[b]If *TP53* locus LOH information is not available

Arber et al, Blood 2022

IPSS-M





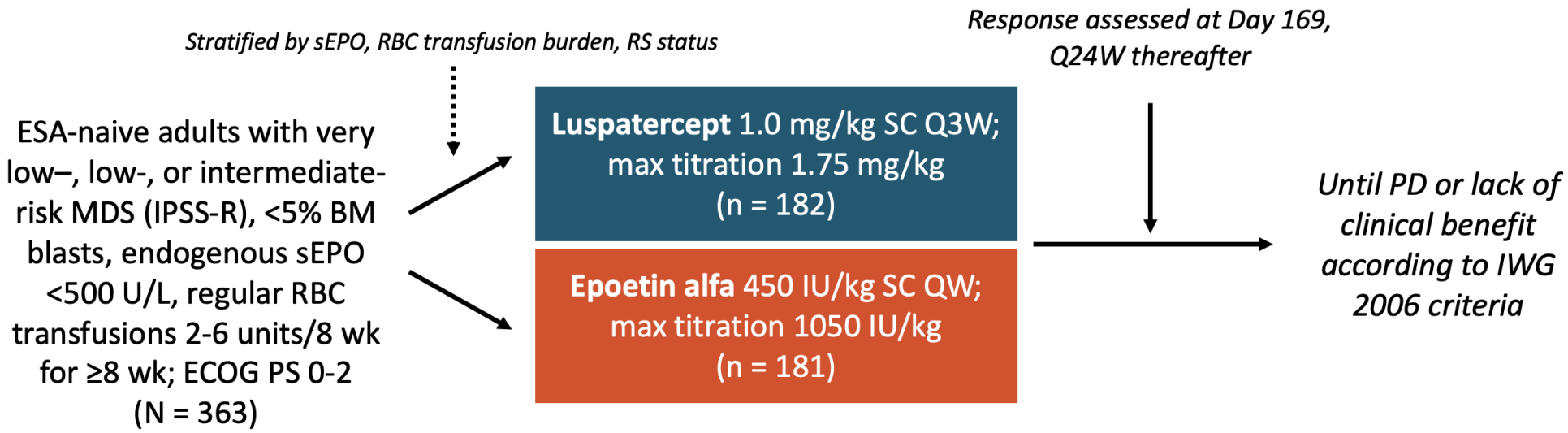


Bernard et al, NEJM Evidence 2022.

COMMANDS: Study Design

Luspatercept is a first-in-class erythroid maturation agent

- Global, open-label, randomized phase III trial; data cutoff March 31, 2023



- **Primary endpoint:** RBC-TI ≥12 wk with concurrent mean Hb increase ≥1.5 g/dL, Wk 1-24
- **Key secondary endpoints:**
  - HI-E ≥8 wk per IWG criteria; RBC-TI ≥12 wk and at 24 wk; RBC-TI ≥24 wk, Wk 1-48 (exploratory); safety

NCT03682536. Garcia-Manero. ASH 2023. Abstr 193.

COMMANDS: Baseline Characteristics

Characteristic	Luspatercept (n = 182)	Epoetin alfa (n = 181)
Median age, yr (range)	74 (46 to 93)	74 (31 to 91)
Female sex, n (%)	73 (40.1)	89 (49.2)
Median time since diagnosis, mo (range)	7.97 (-0.4 to 243.1)	5.13 (-0.3 to 171.6)
ECOG PS, n (%)		
▪ 0	74 (40.7)	69 (38.1)
▪ 1	104 (57.1)	94 (51.9)
▪ 2	4 (2.2)	18 (9.9)
Median RBC TB, U/8 wk (range)	3 (1-10)	3 (0-14)
RBC TB, n (%)		
▪ <4 U/8 wk	118 (64.8)	111 (61.3)
▪ ≥4 U/8 wk	64 (35.2)	70 (38.7)
Median Hb, g/dL (range)	7.8 (4.7 to 9.2)	7.8 (4.5 to 10.2)

Characteristic, n (%)	Luspatercept (n = 182)	Epoetin alfa (n = 181)
sEPO		
▪ ≤200 U/L	145 (79.7)	144 (79.6)
▪ >200 to < 500 U/L	37 (20.3)	37 (20.4)
SF3B1 mutation		
▪ Mutated	114 (62.6)	101 (55.8)
▪ Wild type	65 (35.7)	72 (39.8)
▪ Missing	3 (1.6)	8 (4.4)
RS		
▪ RS+	133 (73.1)	130 (71.8)
▪ RS-	49 (26.9)	50 (27.6)
▪ Missing	0	1 (0.6)

Garcia-Manero. ASH 2023. Abstr 193.

COMMANDS: Efficacy

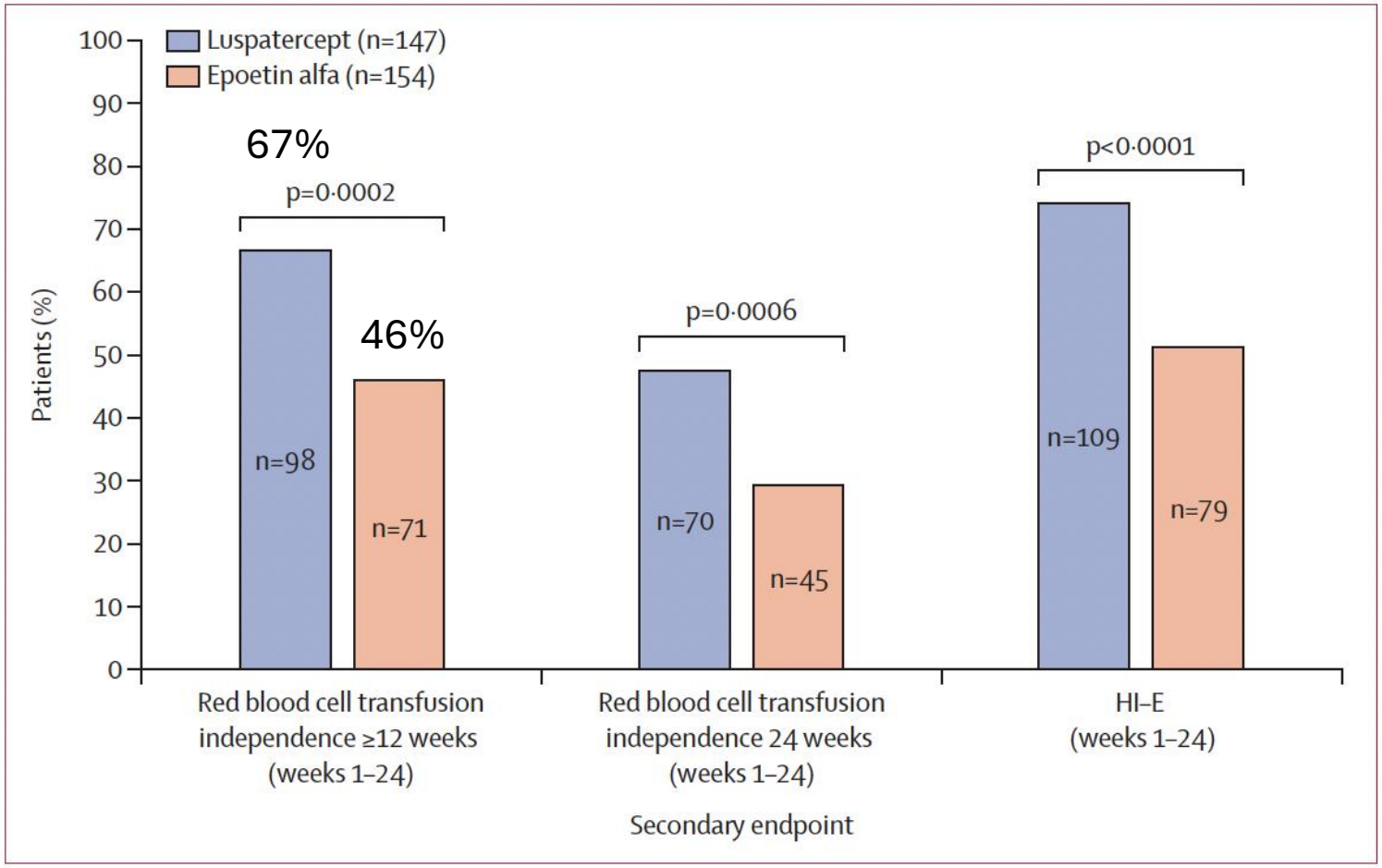


Figure 2: **Red blood cell transfusion independence and HI-E response during weeks 1–24**
Only patients who received their first dose of treatment at least 24 weeks (169 days) before the data cutoff (Aug 31, 2022), including those who discontinued treatment, were included in the analysis. HI-E=haematological improvement-erythroid.

<u>Primary Endpoint:</u>
RBC TI for at least 12 weeks and increase in Hgb at least 1.5g/dL
59% vs 31%, p<0.0001

<u>Among 12-Wk TI responders:</u>
Median DoR 127 wks

Platzbecker et al, Lancet 2023.

COMMANDS: Adverse Events

	Luspatercept (n=178)		Epoetin alfa (n=176)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
General disorder or administration site conditions				
Fatigue	26 (15%)	1 (1%)	12 (7%)	1 (1%)
Peripheral oedema	23 (13%)	0	12 (7%)	0
Asthenia	22 (12%)	0	25 (14%)	1 (1%)
Infections and infestations				
COVID-19	19 (11%)	6 (3%)	17 (10%)	2 (1%)
Gastrointestinal disorders				
Diarrhoea	26 (15%)	2 (1%)	20 (11%)	1 (1%)
Nausea	21 (12%)	0	13 (7%)	0
Respiratory, thoracic, or mediastinal disorders				
Dyspnoea	21 (12%)	7 (4%)	13 (7%)	2 (1%)
Vascular disorders				
Hypertension	23 (13%)	15 (8%)	12 (7%)	8 (5%)
Blood and lymphatic system disorders				
Anaemia	17 (10%)	13 (7%)	17 (10%)	12 (7%)

Data are n (%), where n=number of patients. Events of grade 1–4 severity (Common Terminology Criteria for Adverse Events version 4.03) occurring in at least 10% of patients in either group are shown. System organ classes and preferred terms were coded with the Medical Dictionary for Regulatory Activities (version 25.0). Treatment-emergent adverse events were defined as adverse events that started on or after the first treatment of study medication until 42 days after the last dose of any study drug. A patient was counted only once for the maximum severity for multiple events under the same preferred term within system organ class.

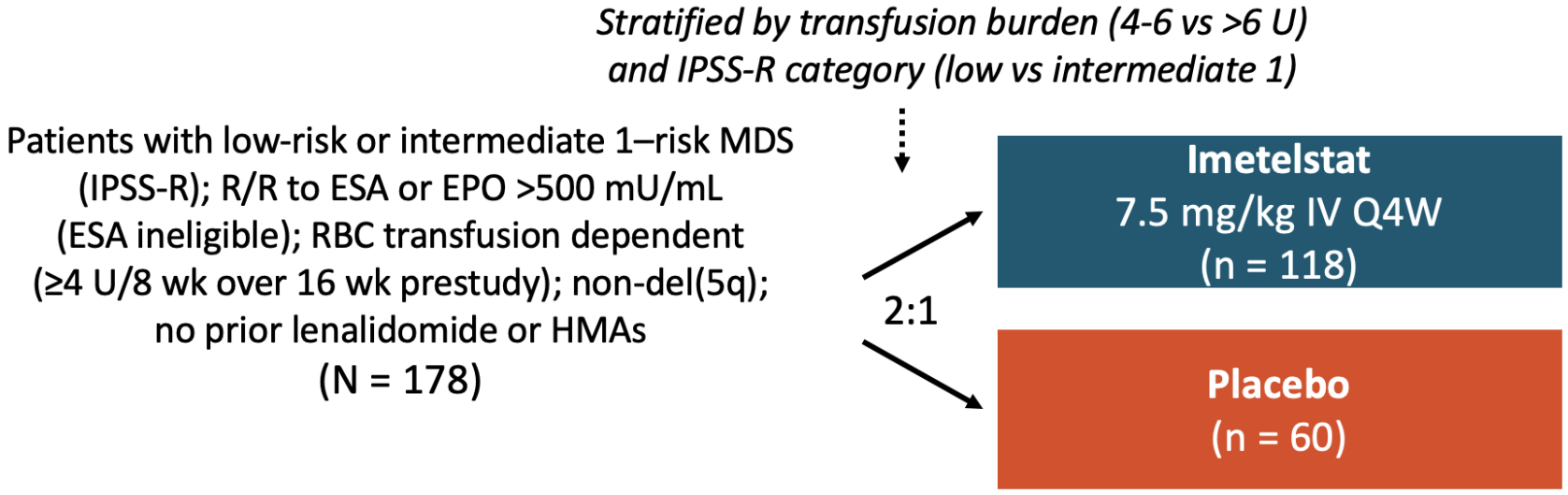
Table 2: **Adverse events of any grade severity occurring in at least 10% of patients (safety population)**

Platzbecker et al, Lancet 2023.

IMerge: Study Design

Imetelstat is a first-in-class competitive telomerase inhibitor

- International, double-blind, randomized phase III trial



- **Primary endpoint:** 8-wk RBC-TI
- **Key secondary endpoints:** 24-wk RBC-TI, TI duration, HI-E, safety
- **Key exploratory endpoints**: changes in VAF, PRO (FACIT-Fatigue)

Zeidan. ASCO 2023. Abstr 7004.

Slide credit: clinicaloptions.com

IMerge: Baseline Characteristics

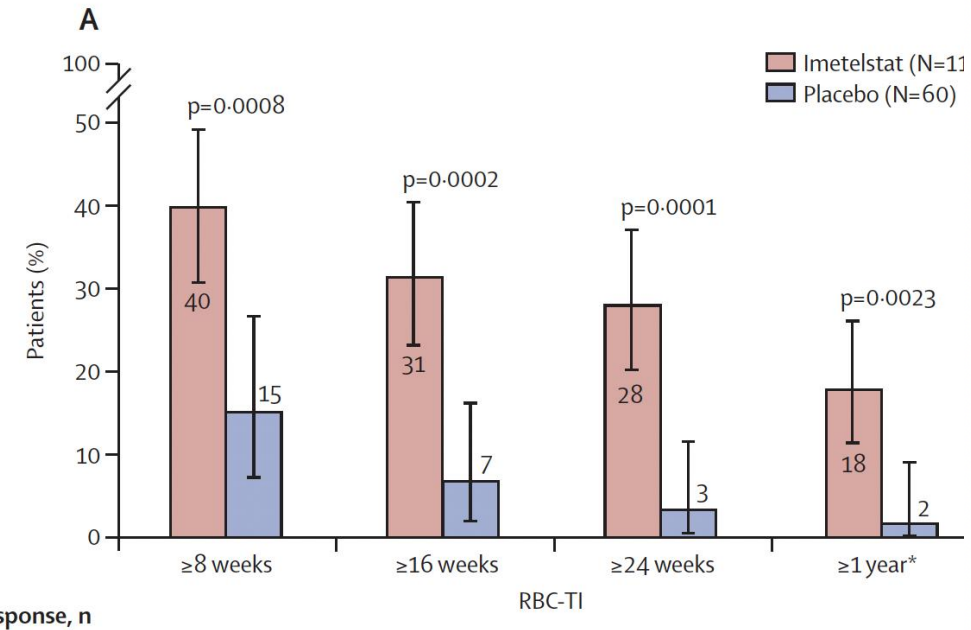
	Imetelstat (n = 118)	Placebo (n = 60)
Median age, yr (range)	72 (44-87)	73 (39-85)
Male, n (%)	71 (60)	40 (67)
Median time since MDS diagnosis, yr (range)	3.5 (0.1-26.7)	2.8 (0.2-25.7)
WHO classification, n (%)		
▪ RS-	44 (37)	23 (38)
▪ RS+	73 (62)	37 (62)
Baseline IPSS-R risk, n (%)		
▪ Low	80 (68)	39 (65)
▪ Intermediate-1	38 (32)	21 (35)

	Imetelstat (n = 118)	Placebo (n = 60)
Median Hb, g/dL (range)	7.9 (5.3-10.1)	7.8 (6.1-9.2)
Median prior RBC transfusion burden, RBC U/8 wk (range)	6 (4-33)	6 (4-13)
Prior RBC transfusion burden, n (%)		
▪ ≥4 to ≤6 U/8 wk	62 (53)	33 (55)
▪ ≥7 U/8 wk	56 (48)	27 (45)
Median sEPO, mU/mL (range)	174.9 (6.0-4460.0)	277.0 (16.9-5514.0)
sEPO level,* n (%)		
▪ ≤500 mU/mL	87 (74)	36 (60)
▪ >501 mU/mL	26 (22)	22 (37)
Prior ESA use, n (%)	108 (92)	52 (87)
Prior luspatercept use, n (%)	7 (6)	4 (7)

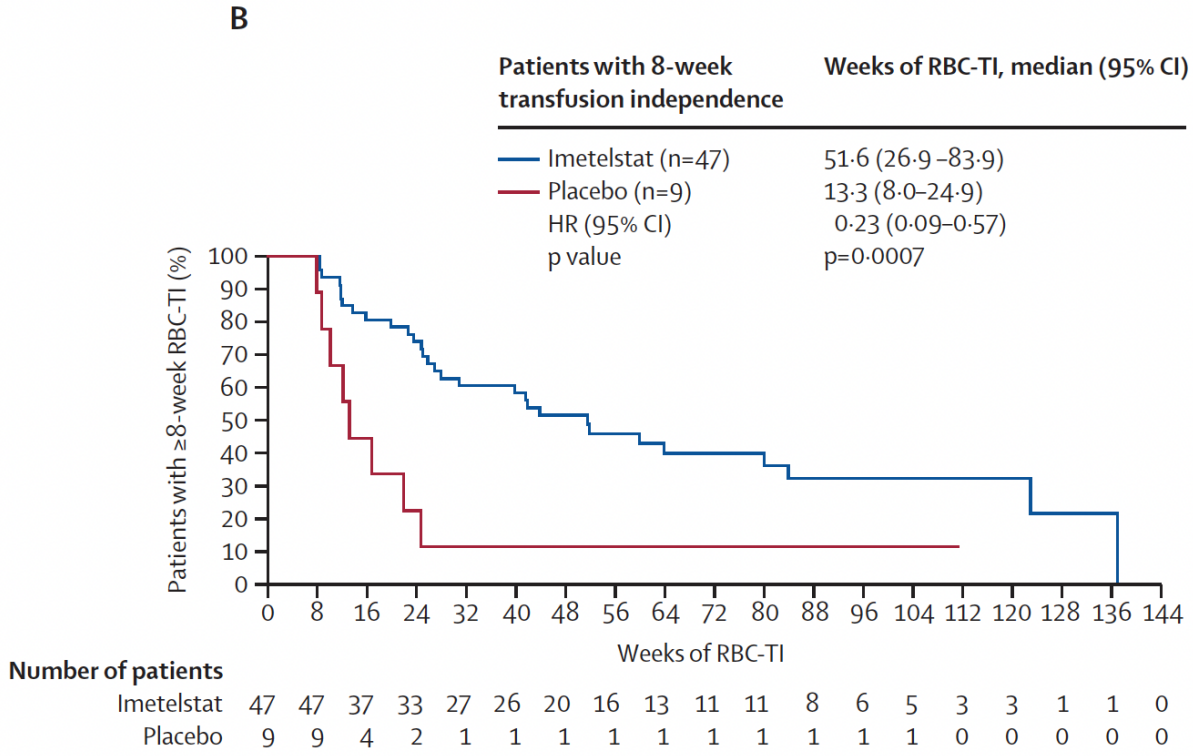
*Data missing for 5 patients in imetelstat group and 2 in placebo group.

Zeidan. ASCO 2023. Abstr 7004.

IMerge: Efficacy and Duration of Response



Patients with response, n (% [95% CI])				
Imetelstat	47 (40% [31–50])	37 (31% [23–41])	33 (28% [20–37])	21 (18% [11–26])
Placebo	9 (15% [7–27])	4 (7% [2–16])	2 (3% [0·4–12])	1 (2% [0·04–9])



Number of patients																			
Imetelstat	47	47	37	33	27	26	20	16	13	11	11	8	6	5	3	3	1	1	0
Placebo	9	9	4	2	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0

<u>Among 8-Wk TI responders:</u>
Hgb rise median 3.6 vs 0.8
Hgb peak median 11.3 vs 8.9

Zeidan et al, ASCO 2023.
Platzbecker et al, Lancet 2024.

IMerge: Adverse Events

	Imetelstat (N=118)		Placebo (N=59)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Haematological				
Thrombocytopenia	89 (75%)	73 (62%)	6 (10%)	5 (8%)
Neutropenia	87 (74%)	80 (68%)	4 (7%)	2 (3%)
Anaemia	24 (20%)	23 (19%)	6 (10%)	4 (7%)
Leukopenia	12 (10%)	9 (8%)	1 (2%)	0
General disorders and administration site conditions				
Asthenia	22 (19%)	0	8 (14%)	0
Oedema peripheral	13 (11%)	0	8 (14%)	0
Pyrexia	9 (8%)	2 (2%)	7 (12%)	0
COVID-19	22 (19%)†	3 (3%)‡	8 (14%)†	3 (5%)‡
Gastrointestinal disorders				
Diarrhoea	14 (12%)	1 (1%)	7 (12%)	1 (2%)
Constipation	9 (8%)	0	7 (12%)	0
Headache	15 (13%)	1 (1%)	3 (5%)	0
Alanine aminotransferase increased	14 (12%)	3 (3%)	4 (7%)	2 (3%)
Hyperbilirubinaemia	11 (9%)	1 (1%)	6 (10%)	1 (2%)

*Includes all patients who received at least one dose of study drug. †Includes COVID-19, asymptomatic COVID-19, and COVID-19 pneumonia. ‡Only COVID-19 pneumonia events were classified as grade 3–4 events for COVID-19.

Table 3*: Number of patients with treatment-emergent adverse events occurring in at least 10% of patients in the safety population

- Median duration of G3/4 thrombocytopenia and neutropenia was <2wks and >80% resolved to G2 or better within 4wks
- Occurred most often during C1-3
- Infection and bleeding similar between arms
- 49% required dose reductions due to AEs and 8% discontinued treatment due to AEs of neutropenia or thrombocytopenia

Platzbecker et al, Lancet 2024.

Recent FDA approvals in MDS:

- ***Luspatercept*** is approved for:
  - Anemia without previous ESA in adults with very low to intermediate risk MDS who may require RBC transfusions
  - Anemia failing an ESA and requiring 2 or more RBC units over 8 weeks in adults with very low to intermediate risk MDS-RS or MDS/MPN-RS-T
- ***Imetelstat*** is approved for treatment of adult patients with low- to intermediate-1 risk MDS with transfusion-dependent anemia requiring 4 or more RBC units over 8 weeks who have not responded to or have lost response to or are ineligible for ESA.

Acute Myeloid Leukemia

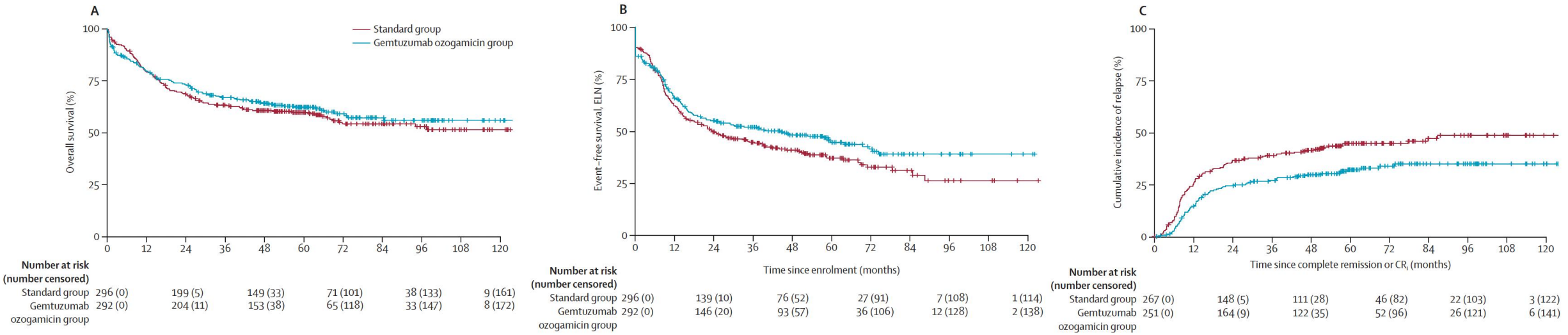
AML with NPM1 Mutation

- WHO5 - Acute myeloid leukemia with *NPM1* mutation
  - Can be diagnosed irrespective of blast count
- ICC 2022 - Acute myeloid leukemia with mutated *NPM1*
  - Can be diagnosed with 10% or more blasts
- Favorable risk by ELN 2022, with caveats
  - Favorable risk in the context of intensively treated patients and in younger patients
  - Adverse risk if it has concurrent adverse risk cytogenetic abnormalities
  - Intermediate risk if is has concurrent FLT3-ITD mutation

Khoury et al, Leukemia 2022
Arber et al, Blood 2022

GO for AML with *NPM1* mutation

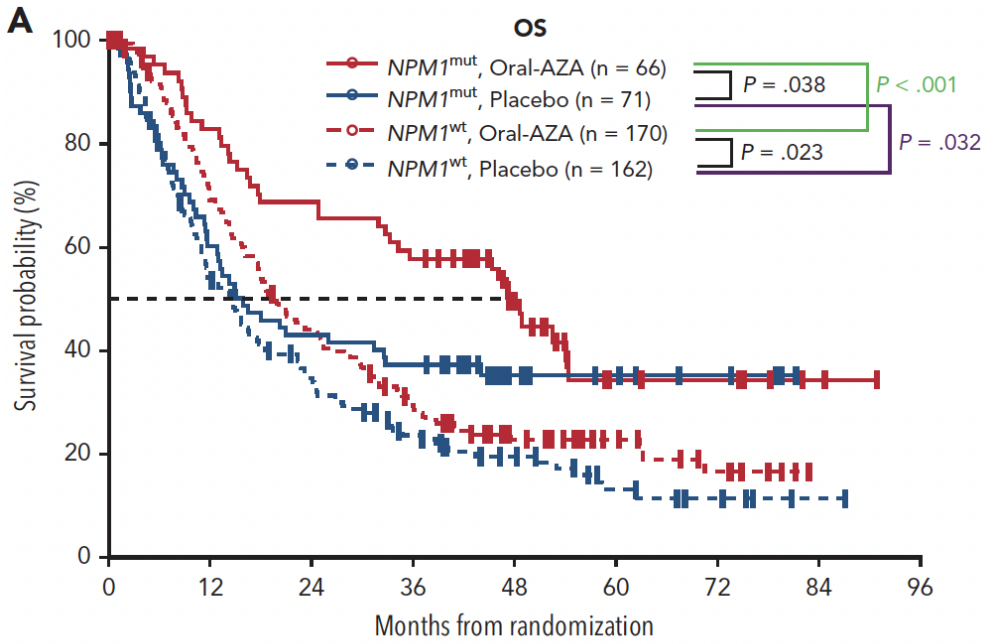
AMLSG 09-09 Study – Added a dose of GO 3mg/m2 to 2 cycles of 7+3 based induction and the first of 3 cycles of HiDAC
No OS or EFS advantage but addition of GO significantly decreased cumulative incidence of relapse



Dohner et al, Lancet Haematology 2023.

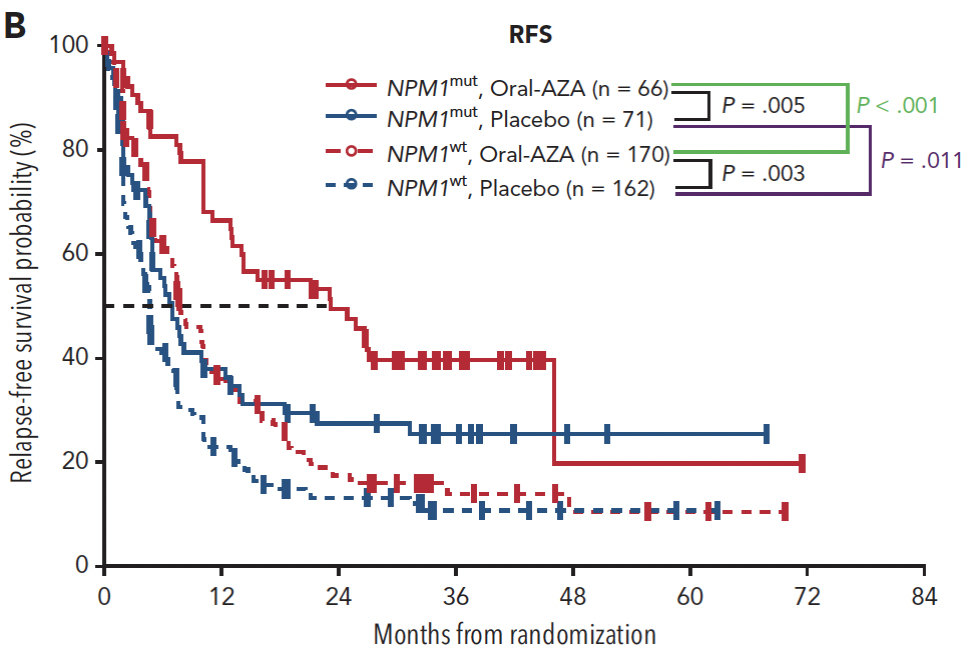
Oral Azacitidine for AML with *NPM1* mutation

- QUAZAR phase 3 trial led to the approval of oral Aza for maintenance for patients with AML in remission
- Post hoc analysis of NPM1-mutated patients on the QUAZAR trial showed significant improvements in OS and RFS vs placebo



Median OS, months

NPM1^{mut}, Oral-AZA	**47.2**	*NPM1*^{wt}, Oral-AZA	**19.6**
NPM1^{mut}, Placebo	**15.9**	*NPM1*^{wt}, Placebo	**14.6**

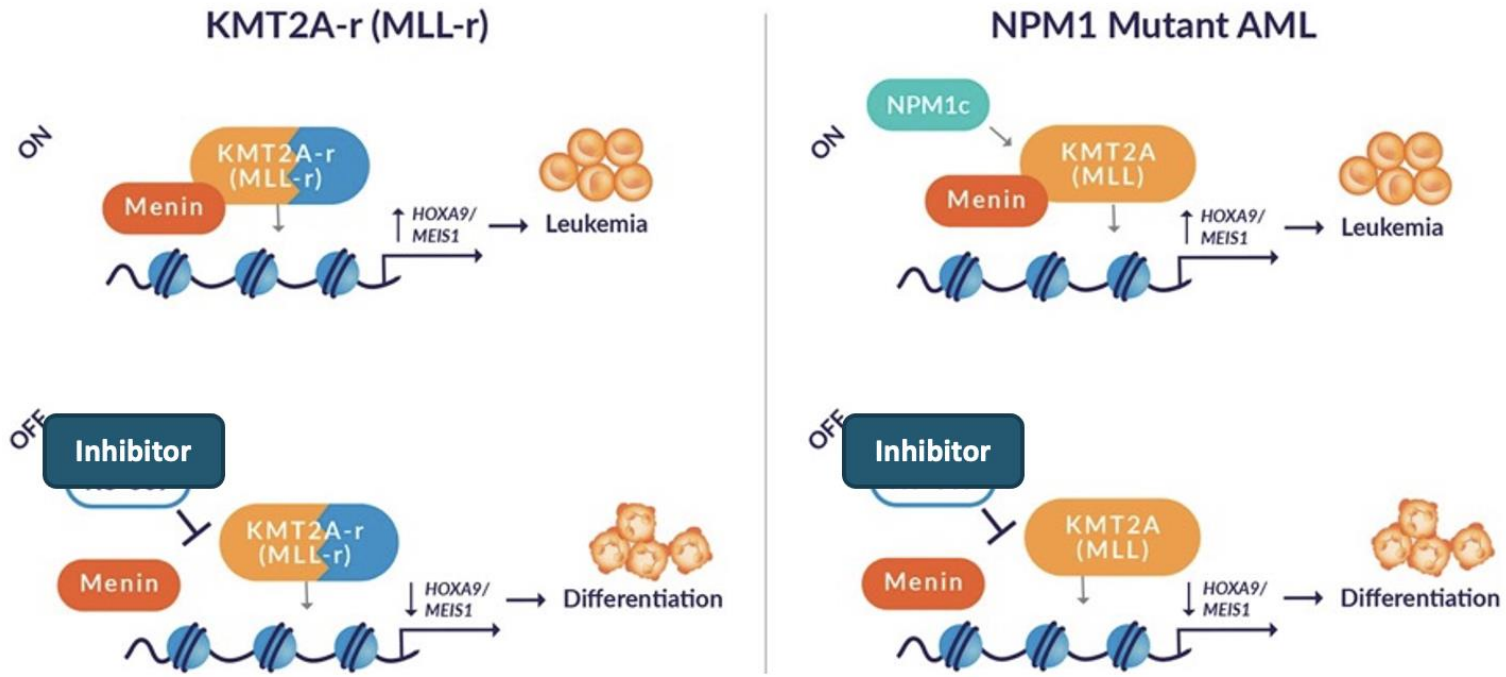


Median RFS, months

NPM1^{mut}, Oral-AZA	**23.2**	*NPM1*^{wt}, Oral-AZA	**7.7**
NPM1^{mut}, Placebo	**6.9**	*NPM1*^{wt}, Placebo	**4.6**

Dohner et al, Blood 2022.

Menin Inh for AML with *NPM1* mutation



Targeting the menin-KMT2A(MLL) interaction to reverse epigenetic dysregulation in MLL-rearranged AML

A central role for menin-KMT2A(MLL) interaction in epigenetic dysregulation in NPM1-mutant AML

Kühn. Cancer Discov. 2016;6:1166. Thorsteinsdottir. Mol Cell Biol. 2001;21:224.
Patel. Curr Hematol Malig Rep. 2020;15:350. Brunetti. Cancer Cell. 2018;34:499.

Slide credit: clinicaloptions.com

Menin Inhibitors in Clinical Development

Trial Name (NCT #)	Agent (Route)	Phase I/II Expansion Cohorts for R/R Disease	Phase/# Patients	Current Trial Status
AUGMENT-101 (NCT04065399)	**Revumenib (SNDX-5613)** PO BID	(a)ALL or MPAL with *KMT2Ar* (b)AML with *KMT2Ar; (c) NPM1*	Phase I/II (n = 413)	In Ph II expansion FDA breakthrough NDA pending
KOMET-001 (NCT04067336)	**Ziftomenib (KO-539)** PO QD	(a)AML with KMT2Ar (b)AML with NPM1c	Phase I/II (n = 199)	In Ph II expansion (52 sites) Actively recruiting
CR108998 (NCT04811560)	**JNJ-75276617** PO QD	(a)AML/ALL with *KMT2Ar* (b)AML with *NPM1c*	Phase I/II (n = 150)	Recruiting (24 sites)
DSP-5336-101 (NCT04988555)	**DSP-5336** PO QD	RR-AML/R/R-ALL Ph II : *NPM1/KMT2Ar*	Phase I/II (n = 70)	Recruiting (11 sites)
COVALENT 101 (NCT05153330)	**BMF-219 PO**	(a) AML/ ALL (KMT2Ar, *NPM1*) (b)DLBCL; (c) MM; (d) CLL/SLL	Phase I (n = 177)	Multiple cohorts Actively enrolling

ClinicalTrials.gov.

<u>Open at UCD:</u>
COVALENT 101
and
CTEP P1 trial of revumenib plus 7+3 for NPM1-mutated AML (OSU: Dr. Alice Mims)

Slide credit: clinicaloptions.com

AUGMENT-101 - Revumenib

Table 2 | Responses to treatment

Response	Efficacy population (*n*=60)	*KMT2A*r (*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)

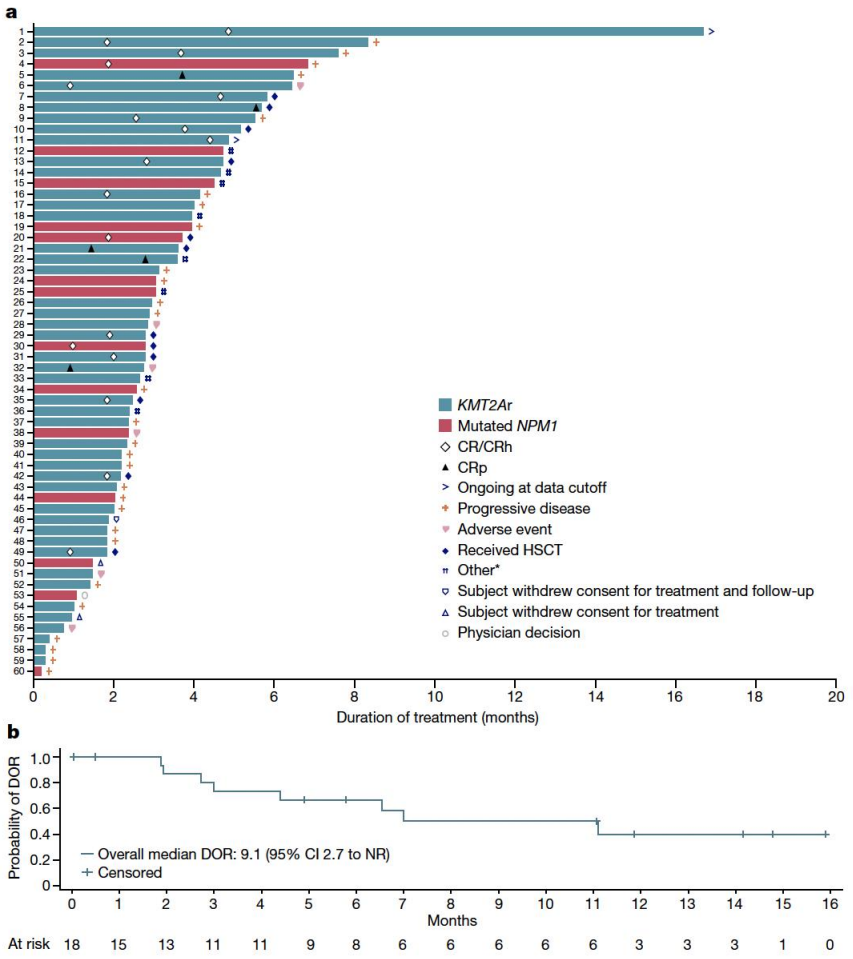


Table 1 | Any-grade treatment-related and TEAEs, regardless of causality

Event	Overall population (*n*=68)
Any-grade TRAE (5% or over)	53 (77.9%)
ECG QT prolonged	36 (52.9%)
Nausea	18 (26.5%)
Differentiation syndrome	11 (16.2%)
Vomiting	11 (16.2%)
Diarrhoea	7 (10.3%)
Decreased appetite	5 (7.4%)
Dysgeusia	5 (7.4%)
Any-grade TEAE (20% or over)	67 (98.5%)
ECG QT prolonged	38 (55.9%)
Nausea	34 (50.0%)
Vomiting	27 (39.7%)
Febrile neutropenia	21 (30.9%)
Diarrhoea	20 (29.4%)
Fatigue	18 (26.5%)
ALT increased	17 (25.0%)
Headache	16 (23.5%)
Hyperphosphataemia	16 (23.5%)
Hypokalaemia	15 (22.1%)
Hyponatraemia	15 (22.1%)
Thrombocytopenia	15 (22.1%)
Epistaxis	14 (20.6%)
Peripheral oedema	14 (20.6%)

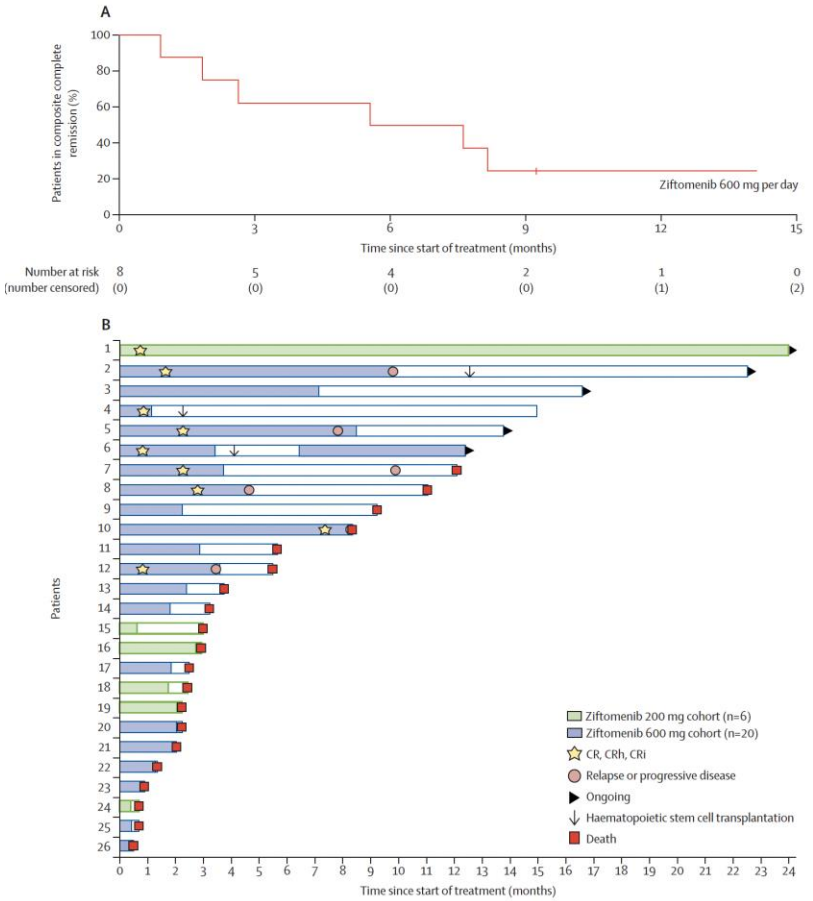
All AEs shown as *n* (%).
ALT, alanine aminotransferase.

Issa et al, Nature 2023.

KOMET-001 - Ziftomenib

	Patients with *NPM1* mutation or *KMT2A* rearrangement with 600 mg ziftomenib (n=38)	Patients with *NPM1* mutation with 200 mg ziftomenib (n=6)	Patients with *NPM1* mutation with 600 mg ziftomenib (n=20)	Patients with *NPM1* mutation with 200 mg or 600 mg ziftomenib (n=26)
CR	7 (18%; 7·7–34·3)	1 (17%; 0·4–64·1)	7 (35%; 15·4–59·2)	8 (31%; 14·3–51·8)
CR/CRh	9 (24%; 11·4–40·2)	1 (17%; 0·4–64·1)	7 (35%; 15·4–59·2)	8 (31%; 14·3–51·8)
CRc*	11 (29%; 15·4–45·9)	1 (17%; 0·4–64·1)	8 (40%; 19·1–63·9)	9 (35%; 17·2–55·7)
Overall response†	12 (32%; 17·5–48·7)	2 (33%; 4·3–77·7)	9 (45%; 23·1–68·5)	11 (42%; 23·4–63·1)
MRD negative CR/CRh‡	6/9 (67%; 29·9–92·5)	1/1 (100%; 2·5–100)	4/7 (57%;§ 18·4–90·1)	5/8 (63%; 24·5–91·5)
CR/CRh in patients with previous venetoclax therapy	4/26 (15%; 4·4–34·9)	..	2/13 (15%; 1·9–45·4)	..
CR/CRh in patients with no previous venetoclax therapy	5/12 (42%; 15·2–72·3)	..	5/7 (71%; 29·0–96·3)	..
Median duration of CRc (95% CI)	5·6 (1·2–8·2)	32·6¶	6·6 (1·0–NE)	7·7 (1·0–NE)
Median duration of CRc censored at HSCT (95% CI)	3·1 (1·2–7·7)	..	5·6 (1·0–NE)	5·6 (1·0–8·2)
Median duration of CR/CRh (95% CI)	3·1 (0·6–8·2)	32·6¶	5·6 (0·6–8·2)	6·6 (0·6–NE)
Median duration of CR/CRh censored at HSCT (95% CI)	3·1 (0·6–7·7)	..	5·6 (0·6–NE)	5·6 (0·6–8·2)
Median overall survival, months (95% CI)	5·7 (3·2–8·4)	2·7 (0·7–NE)	5·6 (2·1–12·1)	3·5 (2·3–9·3)
Transfusion independence rate|| for patients who were independent at baseline				
Platelet	2/8 (25%)	1/3 (33%)	2/6 (33%)	3/9 (33%)
RBC	1/3 (33%)	0/1	1/3 (33%)	1/4 (25%)
Platelet or RBC	1/3 (33%)	0/1	1/3 (33%)	1/4 (25%)
Transfusion independence|| rate for patients who were dependent at baseline				
Platelet	7/30 (23%)	0/3	4/14 (29%)	4/17 (24%)
RBC	10/35 (29%)	1/5 (20%)	6/17 (35%)	7/22 (32%)
Platelet or RBC	7/35 (20%)	1/5 (20%)	5/17 (29%)	6/22 (27%)

Differentiation Syndrome, n/N (%)	Ziftomenib 200 mg (n = 17)	Ziftomenib 600 mg (n = 36)
***NPM1*m**		
▪ All grades	0/4 (0)	4/20 (20.0)
▪ Grade ≥3	0/4 (0)	1/20 (5.0)



Wang et al, Lancet Oncology 2024. Erba et al, ASH 2022.

HIT vs LIT?

High intensity therapy vs low intensity therapy in AML – which is better and which groups?
PARADIGM trial – randomized phase 2 trial comparing Aza-Ven to IC for newly diagnosed fit adults with AML

UCD Retrospective Study

IM Resident: Margaret Krackeler

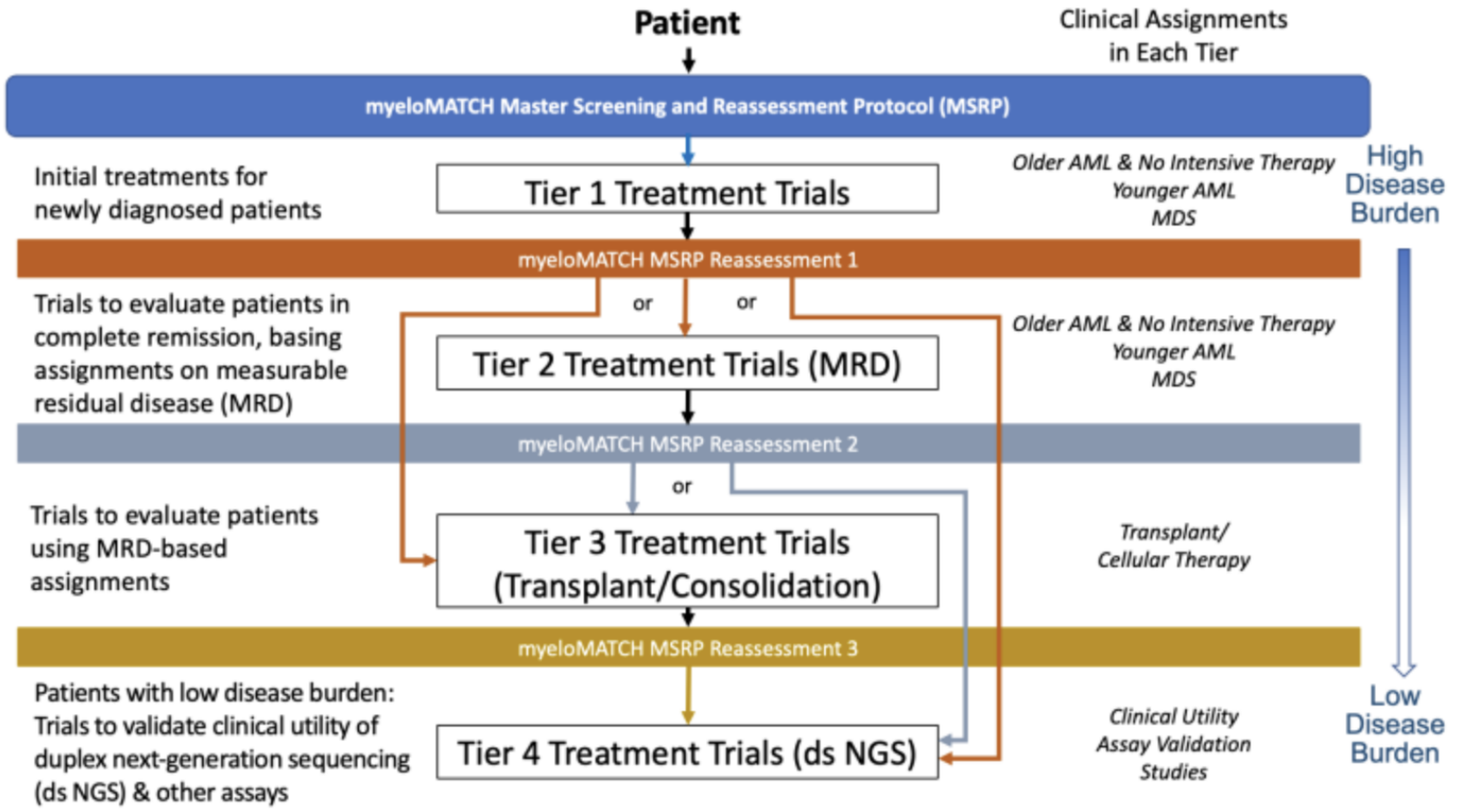
Table 1. Patient demographics	HMA-Ven (n = 49)	7+3 (n = 60)	CPX-351 (n = 7)
Age			
Median (range) – yr	**72** (64-90)	**56** (20-79)	**60** (48-68)
≥75 yr - no. (%)	**16** (33)	**1** (2)	**0** (0)
AML type - no. (%)			
De novo	**37** (76)	**56** (93)	**2** (29)
Secondary	**12** (24)	**4** (7)	**5** (71)
Secondary AML - no./total no. (%)			
Hx of MDS or CMML	**8/12** (67)	**4/4** (100)	**3/5** (60)
Therapy-related AML	**4/12** (33)	**0/4** (0)	**2/5** (40)
ECOG performance-status - no. (%)			
0-1	**42** (86)	**58** (97)	**7** (100)
2-3	**7** (14)	**2** (3)	**0** (0)
Bone marrow blast count - no. (%)			
<30%	**14** (29)	**7** (12)	**2** (29)
≥30-50%	**14** (29)	**14** (29)	**2** (29)
≥50%	**21** (43)	**39** (65)	**3** (43)
Cytogenetic risk category - no. (%)			
Intermediate	**31** (63)	**33** (55)	**3** (43)
Normal karyotype - no.	**30**	**27**	**3**
Trisomy 8; +8 alone - no.	**1**	**6**	**0**
Poor	**10** (20)	**10** (17)	**4** (57)
7 or 7q deletion - no.	**6**	**4**	**1**
5 or 5q deletion - no.	**3**	**0**	**0**
Complex, >3 clonal abnormal - no.	**2**	**6**	**3**
Somatic mutations - no. (%)			
IDH1 or IDH2	**17** (35)	**15** (25)	**1** (14)
FLT3-ITD or TKD	**4** (8)	**19** (32)	**1** (14)
NPM1	**4** (8)	**17** (28)	**2** (29)
TP53	**4** (8)	**1** (2)	**0** (0)
Baseline cytopenia grade ≥ 3			
Anemia - no. (%)	**29** (59)	**24** (40)	**2** (29)
Neutropenia - no. (%)	**32** (65)	**19** (32)	**4** (57)
Thrombocytopenia - no. (%)	**23** (47)	**30** (50)	**3** (43)
Only reached CRi	**13** (27)	**0** (0)	**0** (0)

Table 2. Primary and Secondary HRU Outcomes		HMA-Ven (n = 49)	7+3/CPX-351 (n = 67)	p-value
HRU to CR/CRi median (range)	pRBC units	**4.0** (0-20)	**9.0** (4-24)	<0.001
	Plt units	**2.0** (0-19)	**9.0** (3-30)	<0.001
	Hospital Days	**9.0** (0-45)	**33** (23-57)	<0.001
HRU 60 days post-CR/CRi median (range)	pRBC units	**0.0** (0-8)	**2.0** (0-11)	0.01
	Plt units	**0.0** (0-12)	**2.0** (0-23)	<0.001
	Hospital Days	**0.0** (0-34)	**10** (0-44)	<0.001
HRU 90 days post-CR/CRi median (range)	pRBC units	**0.0** (0-15)	**3.0** (0-17)	<0.001
	Plt units	**0.0** (0-12)	**4.0** (0-44)	<0.001
	Hospital Days	**0.0** (0-41)	**16** (0-64)	<0.001
Time to count recovery days (range)	ANC > 1000	**41** (3-284)	**27** (19-67)	<0.001
	Plt > 50	**24** (1-168)	**23** (17-92)	0.94
Time to CR/CRi days (range)		**31** (21-284)	**34** (23-190)	0.026
Duration of remission months (range)		**11.9** (1.1-47)	**14.6** (1.1-117)	0.46
Non-responders				
HRU 30 days post-tx start median (range)		*n = 19*	*n = 60*	
	pRBC units	**2.0** (0-9)	**9.0** (1-25)	<0.001
	Plt units	**4.0** (0-12)	**11** (0-47)	0.003
	Hospital Days	**9.0** (4-20)	**30** (15-30)	<0.001
HRU 60 days post-tx start median (range)		*n = 11*	*n = 49*	
	pRBC units	**8.0** (0-24)	**12** (6-36)	0.037
	Plt units	**8.0** (0-81)	**17** (0-88)	0.008
	Hospital Days	**14** (4-60)	**49** (24-60)	<0.001

Krackeler et al, ASH 2022.

MyeloMatch

Precision Medicine initiative in AML and MDS from the NCI and NCTN

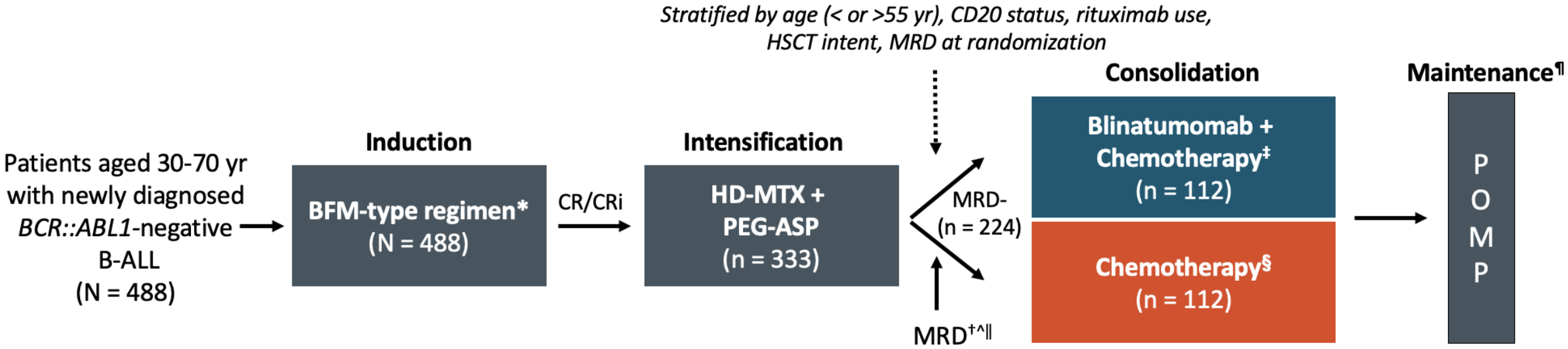


Acute Lymphoblastic Leukemia

ECOG-ACRIN E1910: Study Design

Blinatumomab is a CD3-CD19 BiTE

- Multicenter, randomized, open-label phase III trial



*Regimen adapted from E2993/UKALLXII trial, including extended remission induction, addition of PEG-ASP for patients <55 yr of age, and addition of rituximab for CD20+ disease. †MRD assessed centrally by 6-color flow cytometry, with cutoff of ≤0.01% for MRD negativity. ^286 patients underwent MRD assessment, with 224 being negative and 62 being positive. ‖After blinatumomab regulatory approval in March 2018 for MRD^{pos} *BCR::*$ABL1^{neg}$ B-ALL, MRD^{pos} patients were assigned to blina arm and no longer randomized. ‡Two 28-day cycles of blina → 3 cycles of CT → 1 cycle of blina → 1 cycle of CT → 1 cycle of blina; 72% received 72-hr or 96-hr infusions. §Four cycles of consolidation CT. ¶2.5 yr of maintenance POMP timed from start of intensification. Patients could undergo alloHSCT at discretion of treating physician, ideally after first 2 cycles of blina in experimental arm or at any time following intensification in control arm.

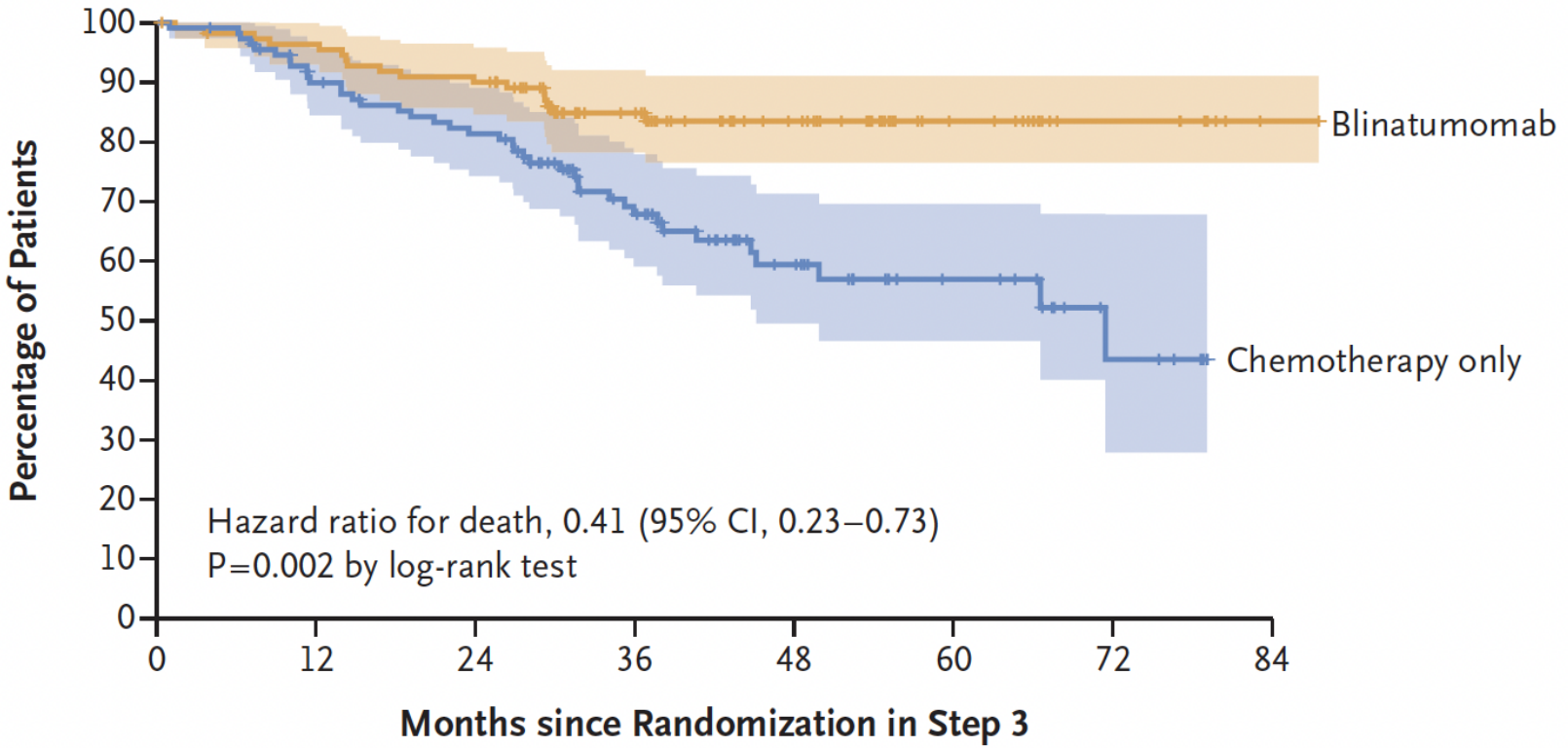
- **Primary endpoint:** OS in MRD^{neg} patients
- **Key secondary endpoints:** MRD status, RFS

Litzow. ASH 2022. Abstr LBA1.

Slide credit: clinicaloptions.com

E1910: Primary Endpoint

A Overall Survival among Patients with MRD-Negative Status



No. at Risk								
Blinatumomab	112	106	99	65	41	19	8	1
Chemotherapy only	112	96	85	53	28	15	5	0

Litzow et al, NEJM 2024

E1910: Adverse Events

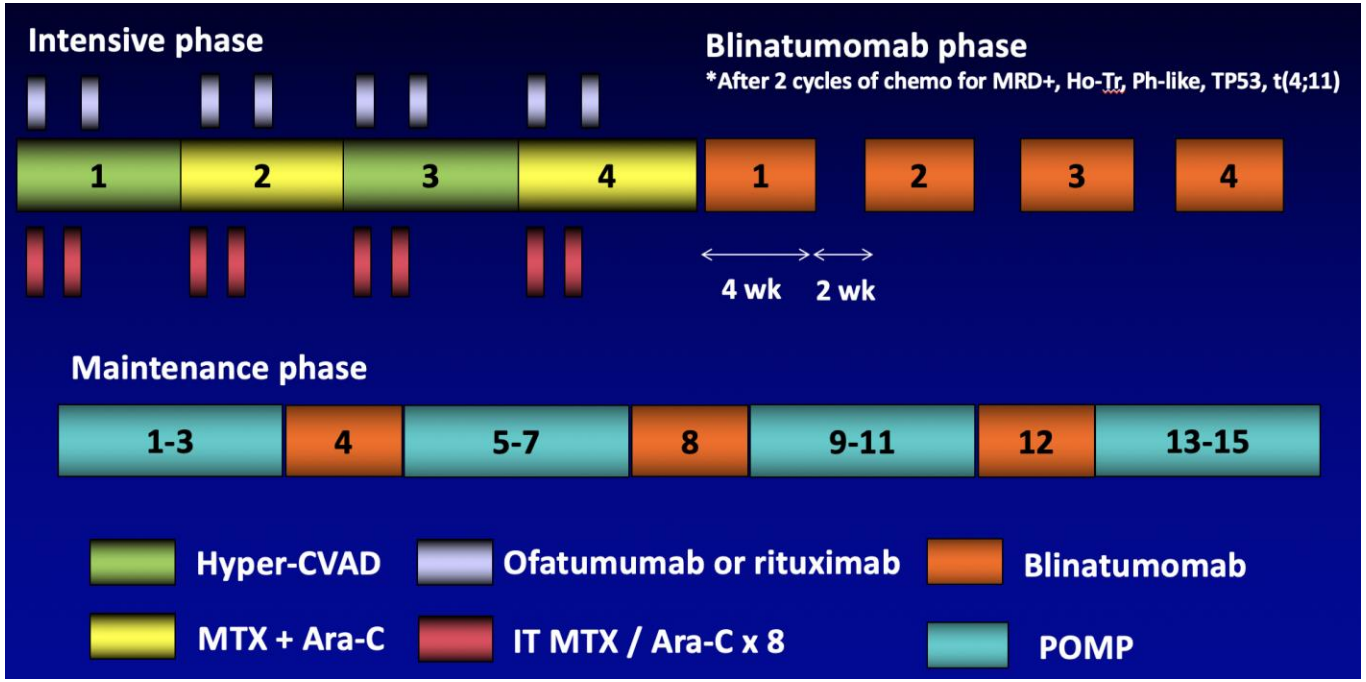
Table 2. Treatment-Related Toxic Effects during Consolidation Therapy in Patients with MRD-Negative Status.*

Event	Blinatumomab + Chemotherapy (N = 112)			Chemotherapy Only (N = 112)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
	percentage of patients					
Anemia	20	1	0	35	2	0
Leukopenia	4	27	0	2	52	0
Neutropenia	3	55	0	1	86	0
Lymphopenia	3	8	0	6	17	0
Thrombocytopenia	9	40	0	10	59	0
Febrile neutropenia	16	1	0	21	2	0
Sepsis	0	4	1	0	6	1
Hyperglycemia	3	1	0	6	2	0
Fatigue	3	0	0	4	0	0
ALT increased	3	0	0	5	1	0
AST increased	1	0	0	1	2	0
Hypertriglyceridemia	0	3	0	1	3	0
Nausea	3	0	0	1	0	0
Vomiting	2	0	0	3	0	0
Headache	3	0	0	5	0	0
Syncope	3	0	0	3	0	0
Other infection	2	1	0	2	1	0
Catheter-related infection	1	0	0	3	1	0
Upper respiratory tract infection	1	0	0	3	0	0

Treatment-related neurologic or psychiatric adverse event of grade 3 or higher in 23% of patients receiving blinatumomab vs 5% in the chemotherapy-only group ($p < 0.001$).

Litzow et al, NEJM 2024

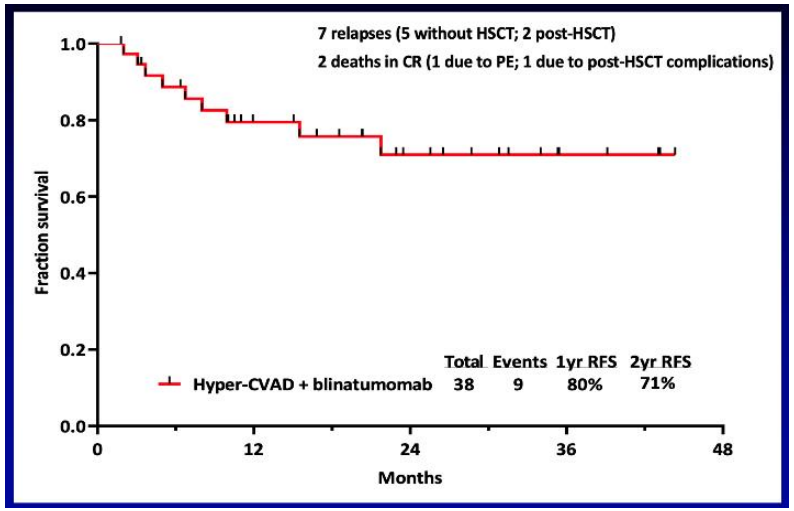
Hyper-CVAD plus Blinatumomab

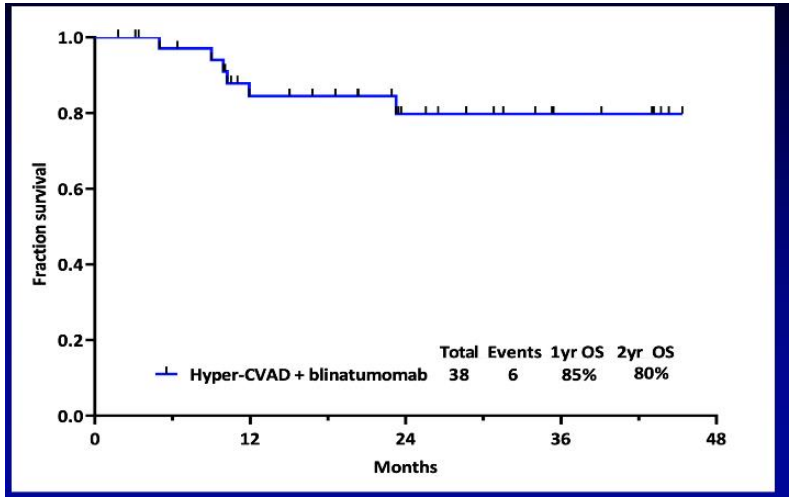


N=38, Median age 37 (17-59)
CRS 13%, 3% G3
Blin-related Neuro events 45%, 13% G3

Response*	n/N (%)
CR after induction	26/32 (81)
CR at any time	32/32 (100)
MRD negativity after induction	24/34 (71)
MRD negativity at anytime	33/34 (97)
30-day mortality	0

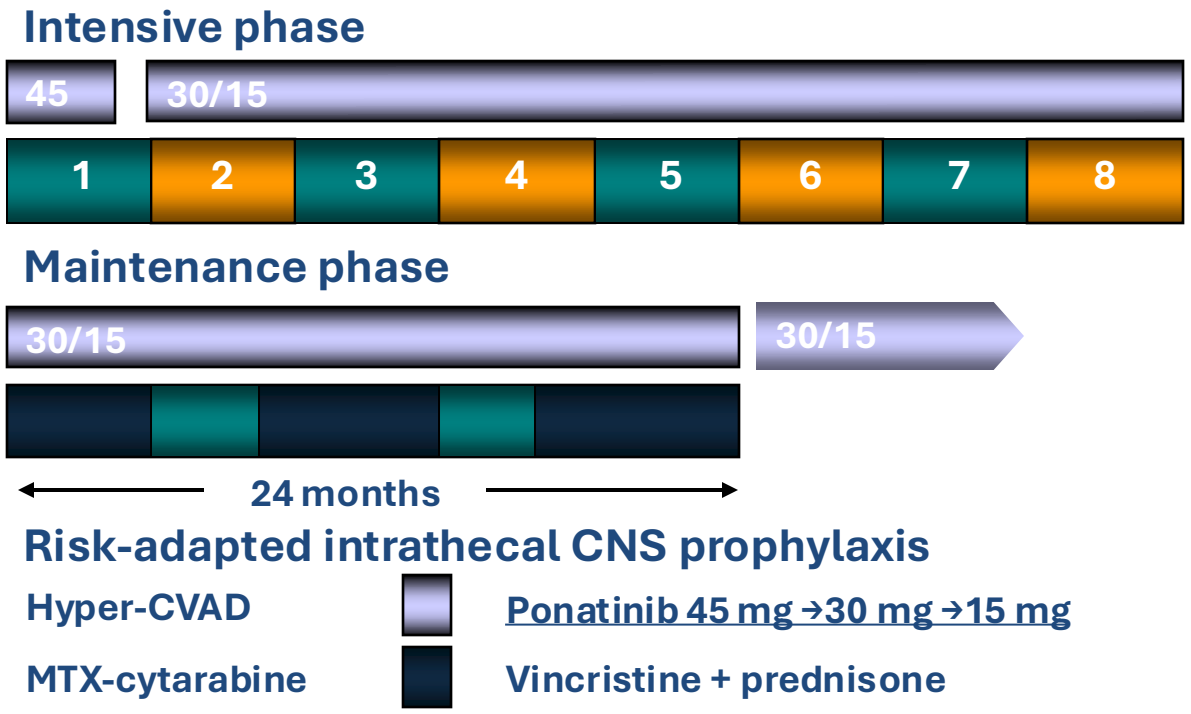
*6 pts in CR at start; 4 pts MRD negative at start





Short et al. ASH 2020 Abstract #464.

Hyper-CVAD plus Ponatinib



Characteristic	Category	N (%) / median [range]
Age (years)		46 (21-80)
	≥60	20 (23)
Performance status	0-1	78 (91)
	2	8 (9)
WBC ($x10^9$/L)		13.6 [0.9-629.4]
CNS involvement		5 (6)
CD20 positivity		30 (35)
BCR-ABL transcript	p190	63 (73)
	p210	21 (24)
	Unknown	2 (2)
Karyotype	Ph+	58 (67)
	Diploid/IM (FISH/PCR+)	28 (33)
CNS disease at diagnosis		6 (7)
≥ 1 baseline CV risk factor		56 (65)

N=86

After the emergence of vascular toxicity, protocol was amended:
Beyond induction, ponatinib 30 mg daily, then 15 mg daily once in CMR

12 doses of IT chemo (d2 and d7 cycles 1-6)
8 doses of R (cycles 1-4) for CD20+

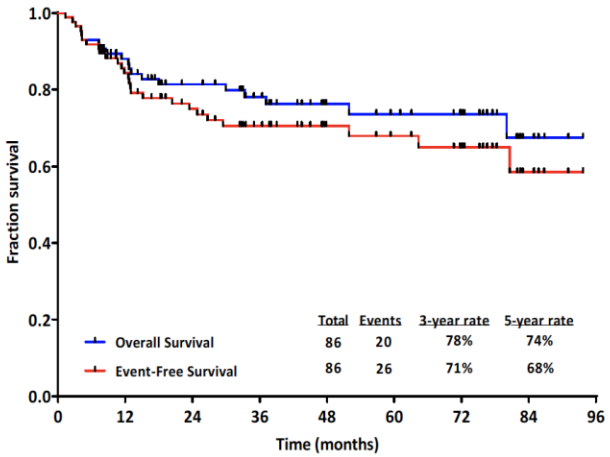
Short et al. ASH 2019 Abstract #283.
Jabbour et al Lancet Oncology 2015.
Rausch et al, Cancer 2020.

Hyper-CVAD plus Ponatinib: Efficacy and Safety

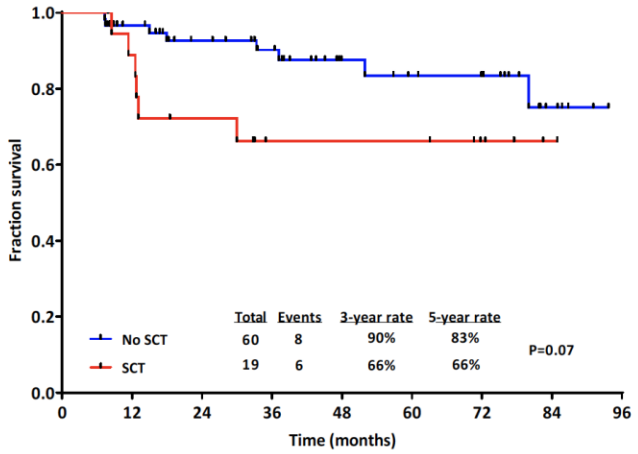
Overall Response	n/N (%)
CR*	68/68 (100)
CCyR^	58/58 (100)
MMR#	80/85 (94)
CMR#	73/85 (86)
Flow negativity#	83/85 (95)
Early death	0

74% CMR at 3 months

EFS and OS



Impact of alloHCT: 6 month landmark



19 (22%) underwent Allo-HCT in CR1

3 relapses on ponatinib and no CNS relapses (12 IT ppx)
Toxicities – VTE (13%), Arterial CV events (7%); Grade 3+ infections (88%), AST/ALT elevation (29%), pancreatitis (15%), hyperbilirubinemia (15%), bleeding (14%), HTN (14%), rash (10%)
73% of VTE events at 45mg Pon; 67% of arterial CV events at 30-45mg Pon
No treatment related deaths after amendment of Pon dosing (2 died from MI prior)

Short et al. ASH 2019 Abstract #283.
Jabbour et al Lancet Oncology 2015.
Rausch et al, Cancer 2020.

Hyper-CVAD plus Ponatinib at UCDCCC

Leukemia Research 119 (2022) 106885

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Clinical experience with frontline Hyper-CVAD-based regimens, including Hyper-CVAD plus ponatinib, in patients with acute lymphoblastic leukemia treated at a comprehensive cancer center

Tamer Othman [a,1], Benjamin N. Moskoff [b,1], Gwendolyn Ho [c], Matthew E. Tenold [a], Tali Azenkot [d], Margaret L. Krackeler [d], Samantha C. Fisch [e], Laura A. Potter [e], Paul R. Kaesberg [b], Jeanna L. Welborn [a], Ted Wun [a], Naseem S. Esteghamat [a], Rasmus T. Hoeg [a], Aaron S. Rosenberg [a], Mehrdad Abedi [a], Joseph M. Tuscano [a], Brian A. Jonas [a,*]

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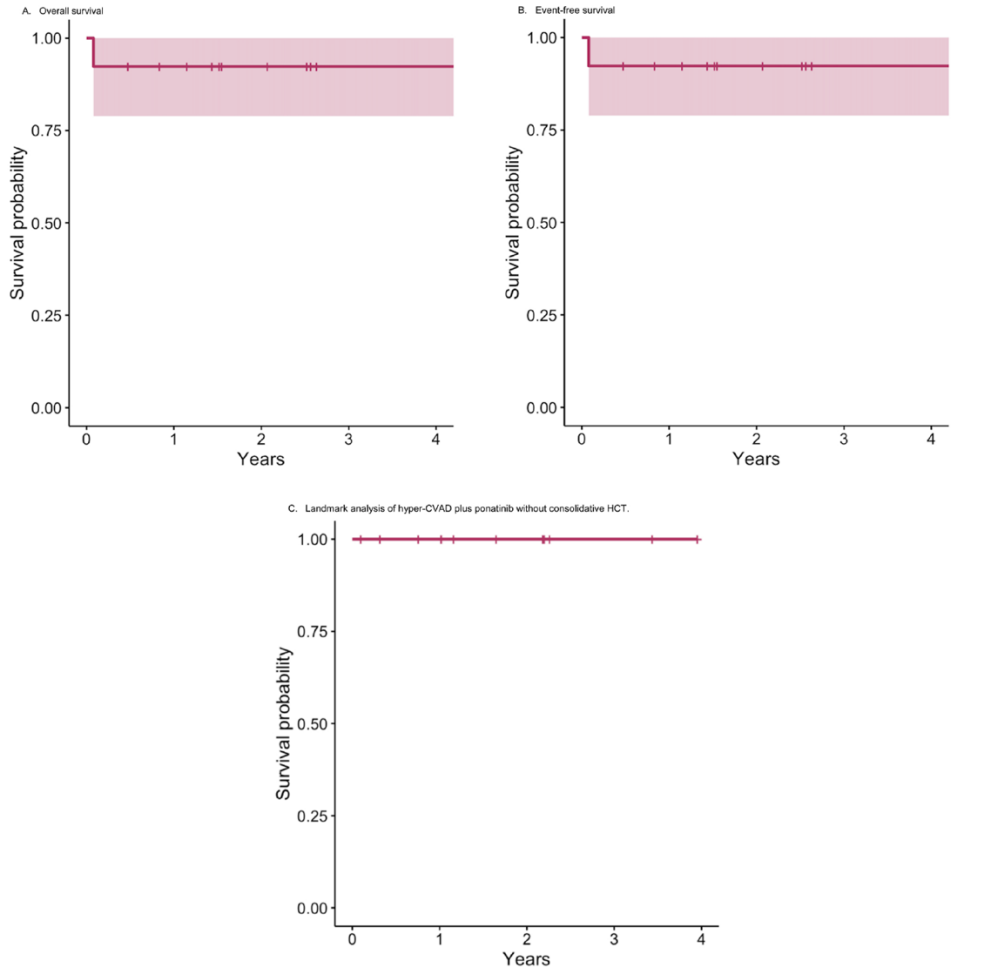
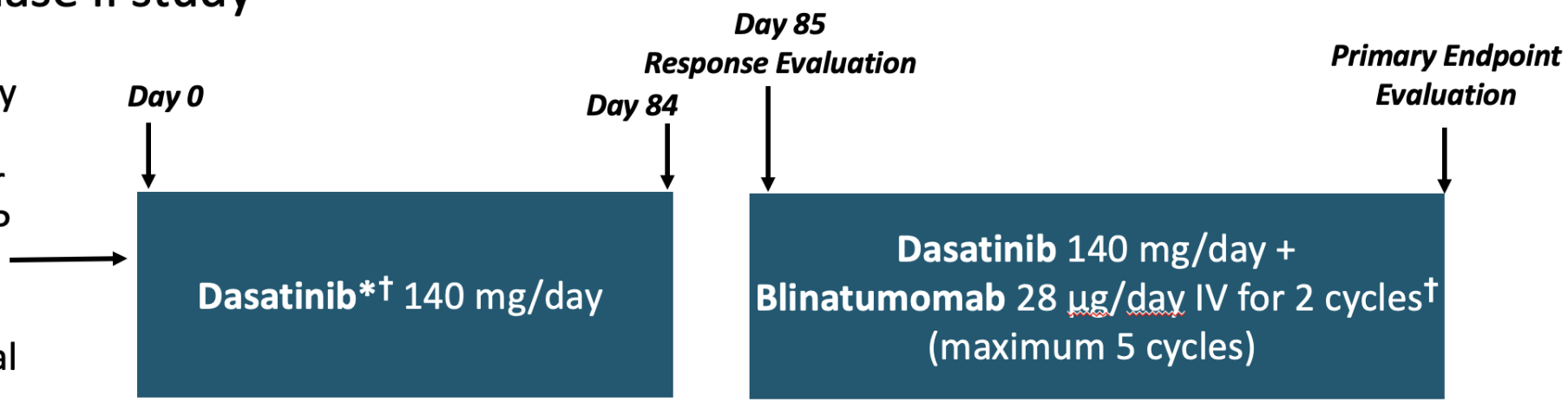


Fig. 2. : Impact of hyper-CVAD plus ponatinib on Ph+ ALL A. Overall survival. B. Event-free survival. C Landmark analysis of hyper-CVAD plus ponatinib without consolidative HCT.

Dasatinib + Blinatumomab for Ph+ ALL: Study Design

- Multicenter, phase II study

Adult patients with newly diagnosed B-precursor Ph+ ALL; ECOG PS 0-1 or WHO PS ≤ 2; AST, ALT, AP all < 2 x ULN; total bilirubin < 1.5 x ULN; CrCl ≥ 50 mL/min; normal cardiac function; HIV-1 RNA, HBV DNA, and HCV RNA negative
(N = 63)



*Prednisone administered from Day -6 to Day 0 at escalating doses up to 60 mg/m^2; continued up to Day 24 and tapered to Day 31.
†CNS prophylaxis throughout treatment.

- Primary endpoint: CMR and MRD negativity after 2 cycles
- Secondary endpoints: CMR after dasatinib induction, CMR duration, OS, DFS, CIR, safety, MRD change after blinatumomab

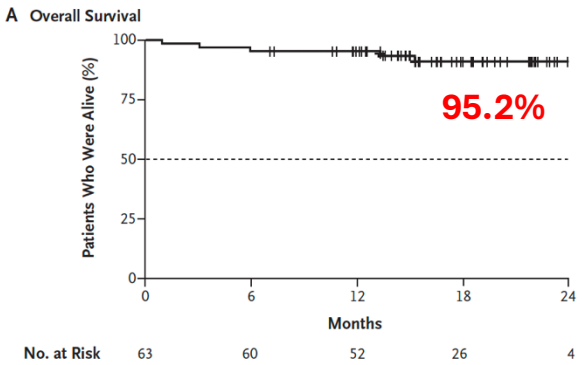
Chiaretti. ASH 2019. Abstr 740.

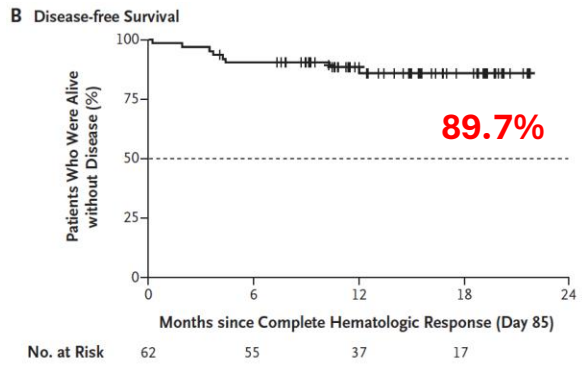
Slide credit: clinicaloptions.com

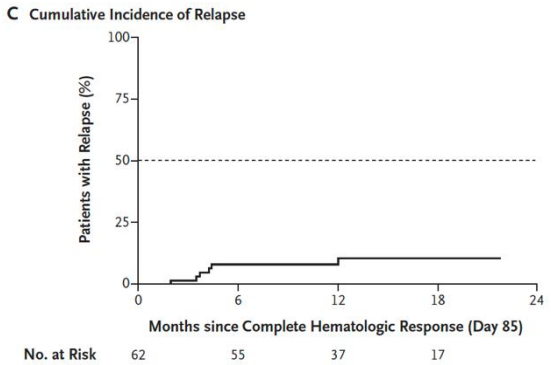
D-ALBA – Dasatinib plus Blinatumomab

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.

Characteristic	Enrolled Patients (N = 63)
Age — yr	
Median	54
Range	24–82
Sex — no. (%)	
Male	29 (46)
Female	34 (54)
White-cell count — per mm^3	
Median	13,000
Range	600–88,000
Fusion protein — no. (%)	
p190	41 (65)
p210	17 (27)
p190 and p210	5 (8)



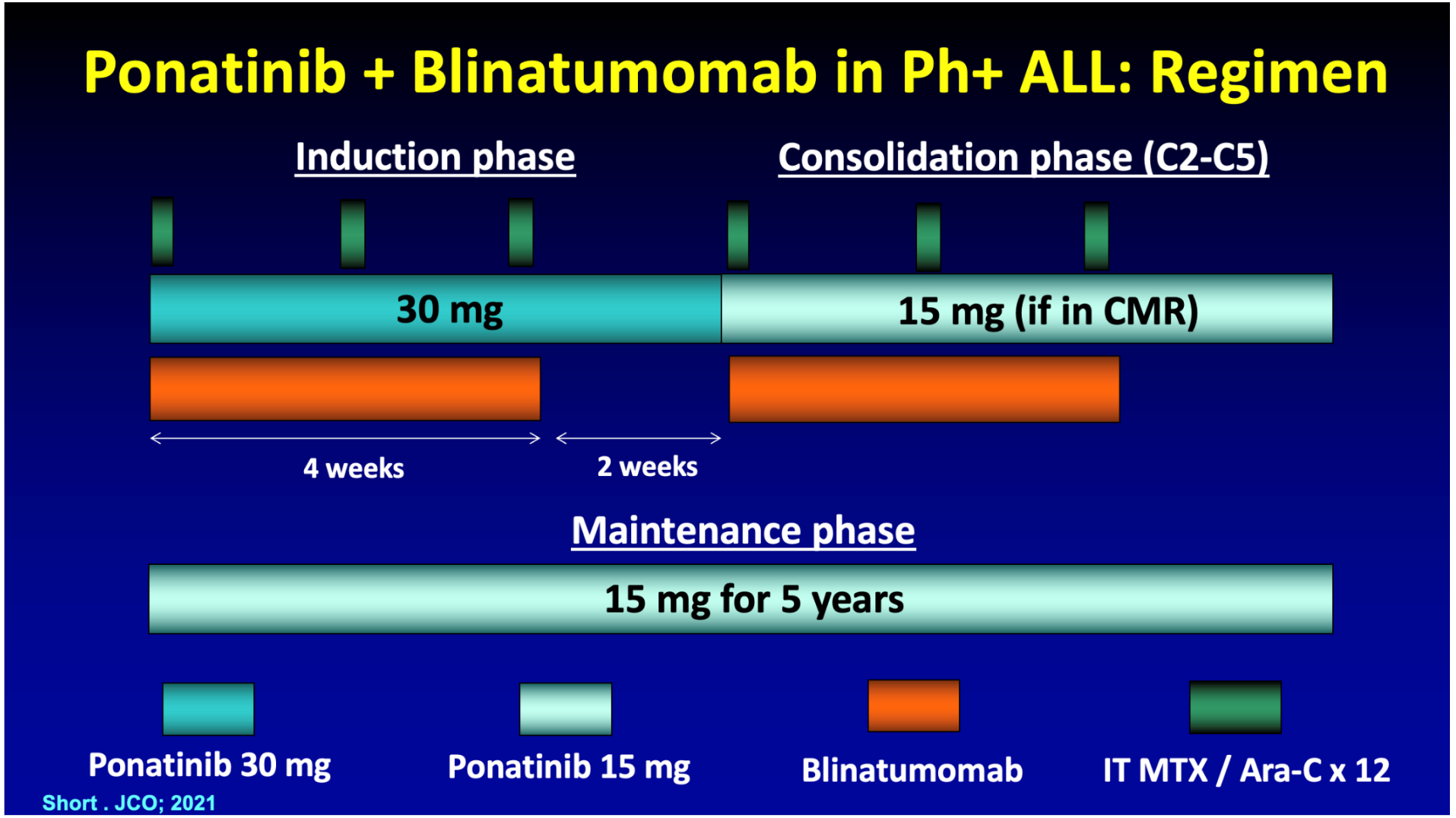




Induction: 98% CHR, 29% molecular response
60.4% with CMR or non-quantifiable level after Cycle 2
Overall: 52% with molecular response
Median follow-up 14.3mo
Allo-HCT in 24pts

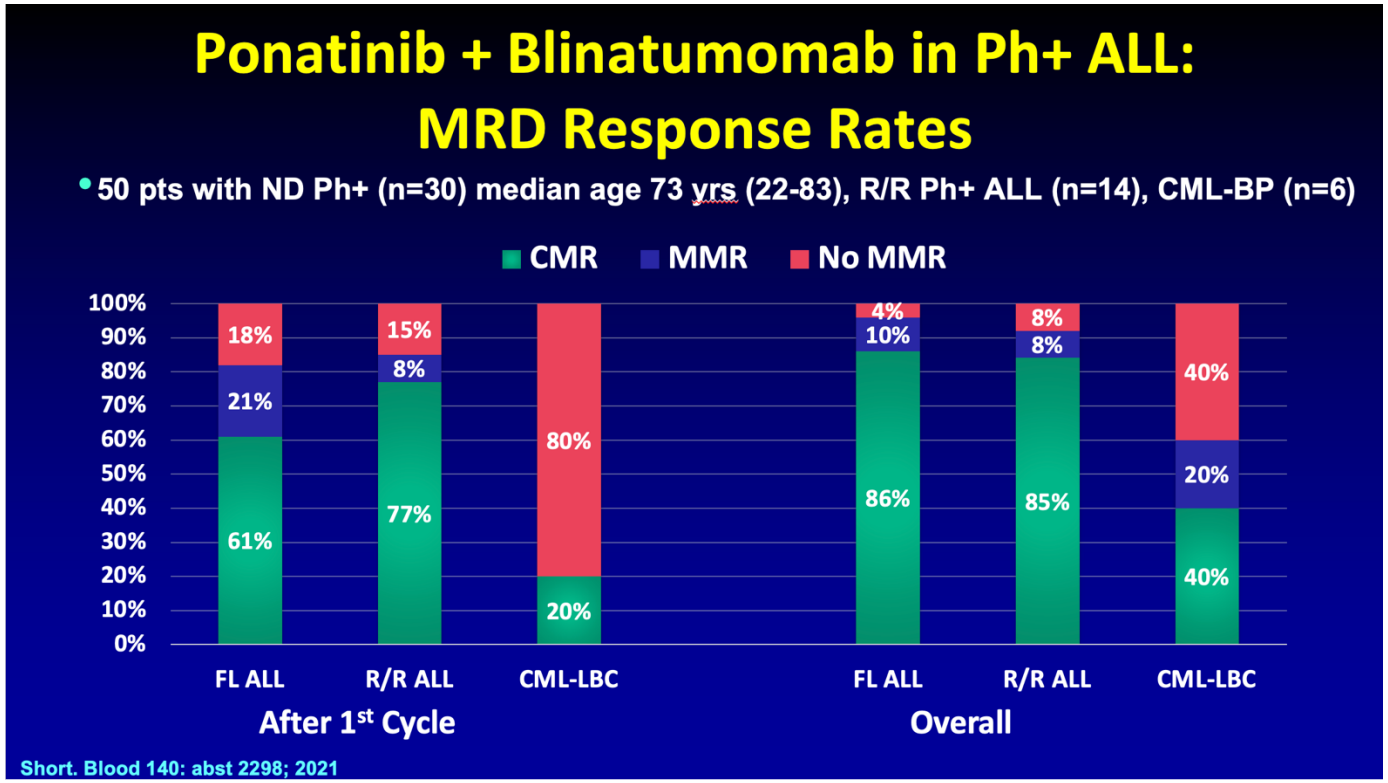
Foa et al. NEJM 2020.

Patients aged ≥18 yr with newly diagnosed Ph+ ALL, R/R Ph+ ALL, or lymphoid AP/BP CML; ECOG PS 0-2 (N = 55)



Primary outcome measures: CMR rate (newly diagnosed Ph+ and/or *BCR-ABL*+ ALL), ORR (R/R ALL), relapse-free survival, EFS, and OS

Short et al, ASCO 2022.
Jabbour et al, Lancet Haem 2023.
Kantarjian et al, JCO 2024.



N=60 FL Ph+ B-ALL pts
39 untreated
21 in CR after 1-2 course of chemotherapy within a median 49d and a median duration of prior TKI therapy 49d

TABLE 2. Hematologic and Molecular Responses

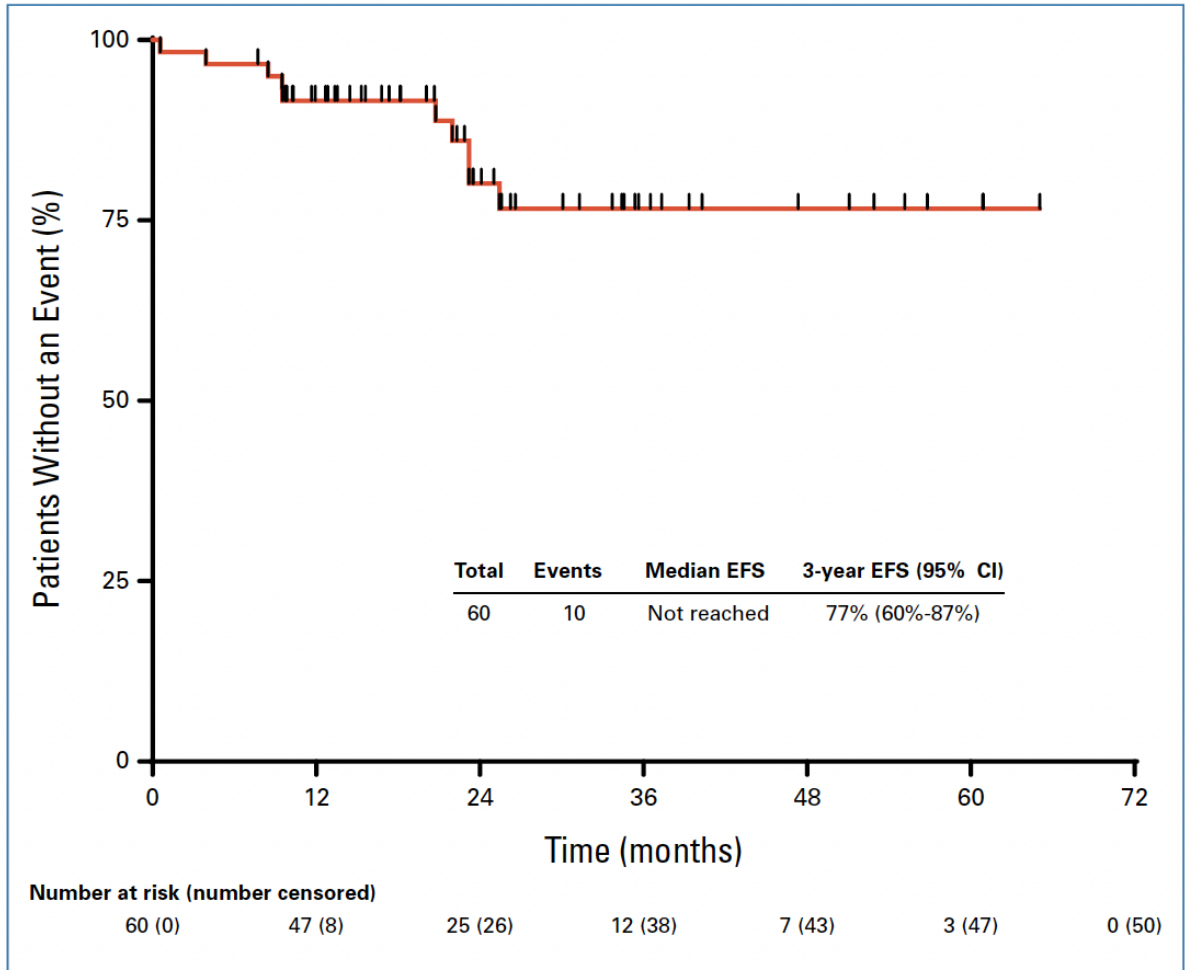
Parameter	n/N (%)
Overall response rate[a]	
CR	37/39 (95)
CRi	1/39 (2)
Early death	1/39 (3)
CMR[b]	
After cycle 1	36/54 (67)
Overall	45/54 (83)
MRD negativity by NGS/ClonoSEQ	
After cycle 1	10/22 (45)
Overall	44/45 (98)
EFS	
3-year rate, % (95% CI)	77 (60 to 87)
No. of events	10 (17)
OS	
3-year rate, % (95% CI)	91 (76 to 97)
No. of events	4 (7)

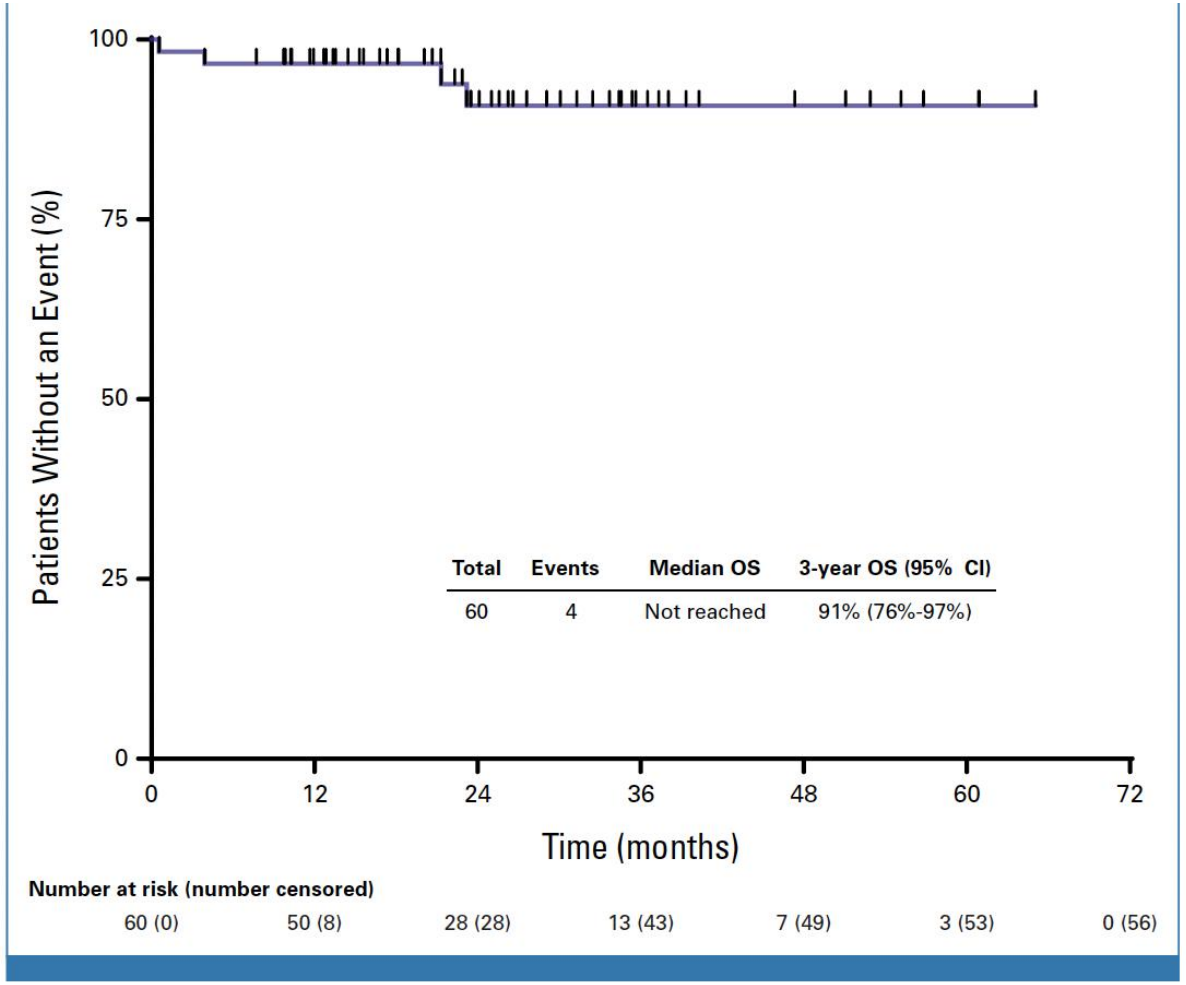
Abbreviations: CMR, complete molecular response; CR, complete remission; CRi, CR with incomplete hematologic recovery; EFS, event-free survival; MRD, measurable residual disease; NGS, next-generation sequencing; OS, overall survival.
[a]Twenty-one patients in CR at the start of therapy.
[b]Six patients in CMR at the start of therapy.

Short et al, ASCO 2022.
Jabbour et al, Lancet Haem 2023.
Kantarjian et al, JCO 2024.

Blinatumomab plus Ponatinib - Outcomes

Median follow-up 24 months





Kantarjian et al, JCO 2024.

Recent FDA approvals in ALL and Ongoing Questions

- ***Blinatumomab*** is approved for CD19+ Ph- B-ALL in the consolidation phase of multiagent chemotherapy
  - Question – how to give the Blina?
    - With E1910
    - With Hyper-CVAD
    - With other regimens, such as CALGB10403?
- ***Ponatinib*** is approved for newly diagnosed Ph+ ALL, in combination with chemotherapy
  - Question – how to give the ponatinib?
    - With Hyper-CVAD or a Hyper-CVAD-like regimen
    - With Blinatumomab
    - Randomized EA9181 trial comparing TKI+Chemo vs TKI+Blina
    - How many IT chemo treatments?

Questions?

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