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Southeastern Multidisciplinary Approaches to Cancer Symposium

Novel Therapies in Acute Leukemia

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Disclosures

- Consultant for Novartis, Jazz, Sanofi, Abbvie & Cogent

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

AML Induction

- 7 + 3 has been the intensive chemotherapy regimen of choice for decades for ‘fit’ patients
- 7+ 3 has high regimen related toxicity besides cytopenias leading to mucositis, malnutrition, typhlitis, cardiac dysfunction and decline in performance status
- CR rates poor for adverse risk AML
- High healthcare costs and resource utilization

Azacitidine and Venetoclax

- For the IC-ineligible, VIALE-A established the superiority of azacitidine and venetoclax (Aza-Ven) to azacitidine.
- Aza-Ven was well-tolerated, with low early mortality, and could be administered and managed in clinic.
- Retrospective studies reveal improved outcomes with HMA-Ven vs IC, but no prospective studies have demonstrated an advantage.

The NEW ENGLAND JOURNAL of MEDICINE

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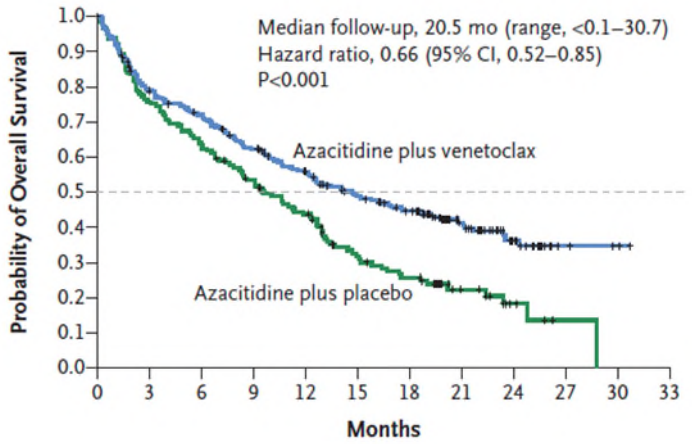
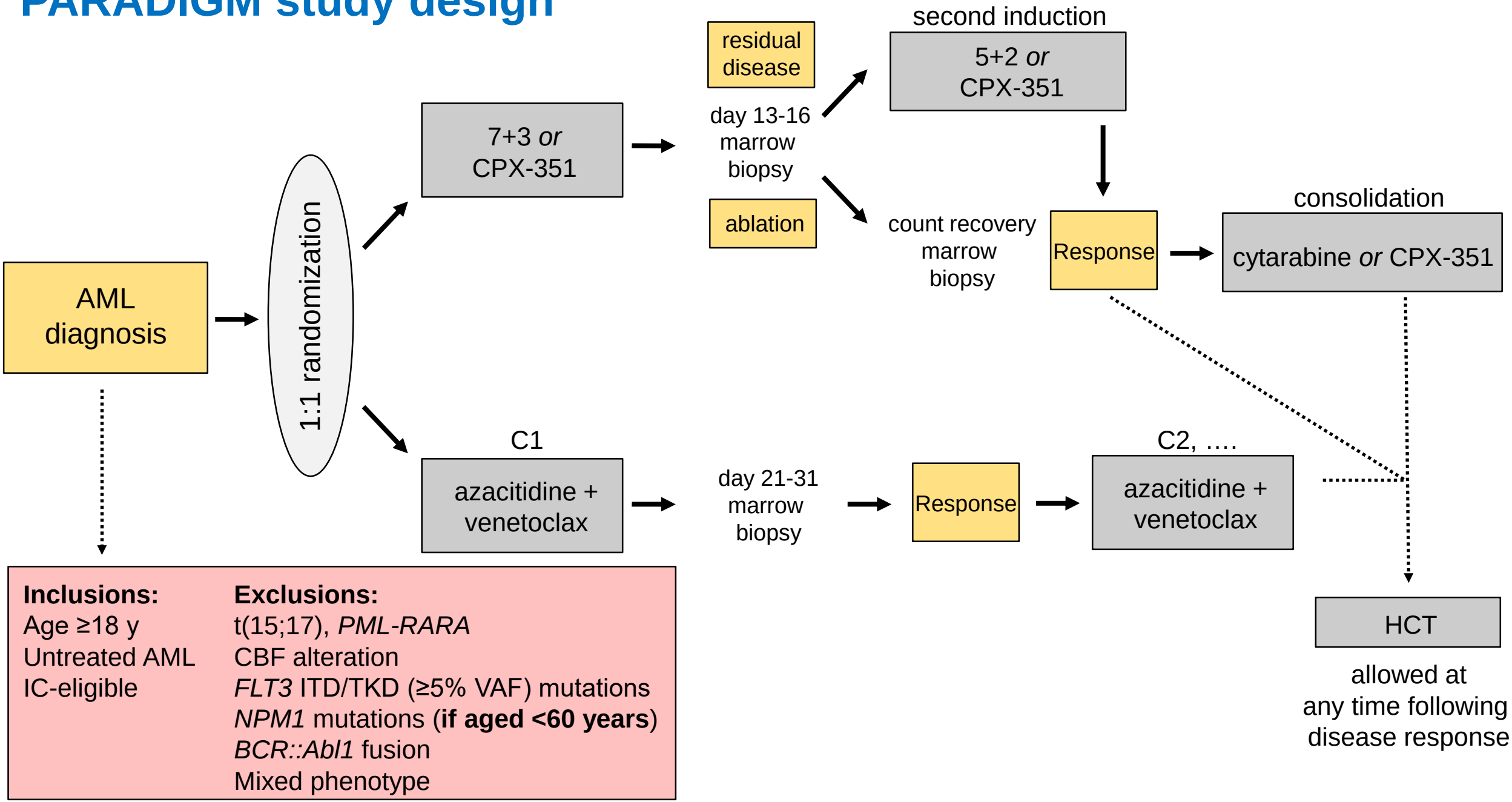
Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

C.D. DiNardo, B.A. Jonas, V. Pullarkat, M.J. Thirman, J.S. Garcia, A.H. Wei, M. Konopleva, H. Döhner, A. Letai, P. Fenaux, E. Koller, V. Havelange, B. Leber, J. Esteve, J. Wang, V. Pejsa, R. Hájek, K. Porkka, A. Illés, D. Lavie, R.M. Lemoli, K. Yamamoto, S.-S. Yoon, J.-H. Jang, S.-P. Yeh, M. Turgut, W.-J. Hong, Y. Zhou, J. Potluri, and K.W. Pratz



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

PARADIGM study design



Baseline Characteristics:

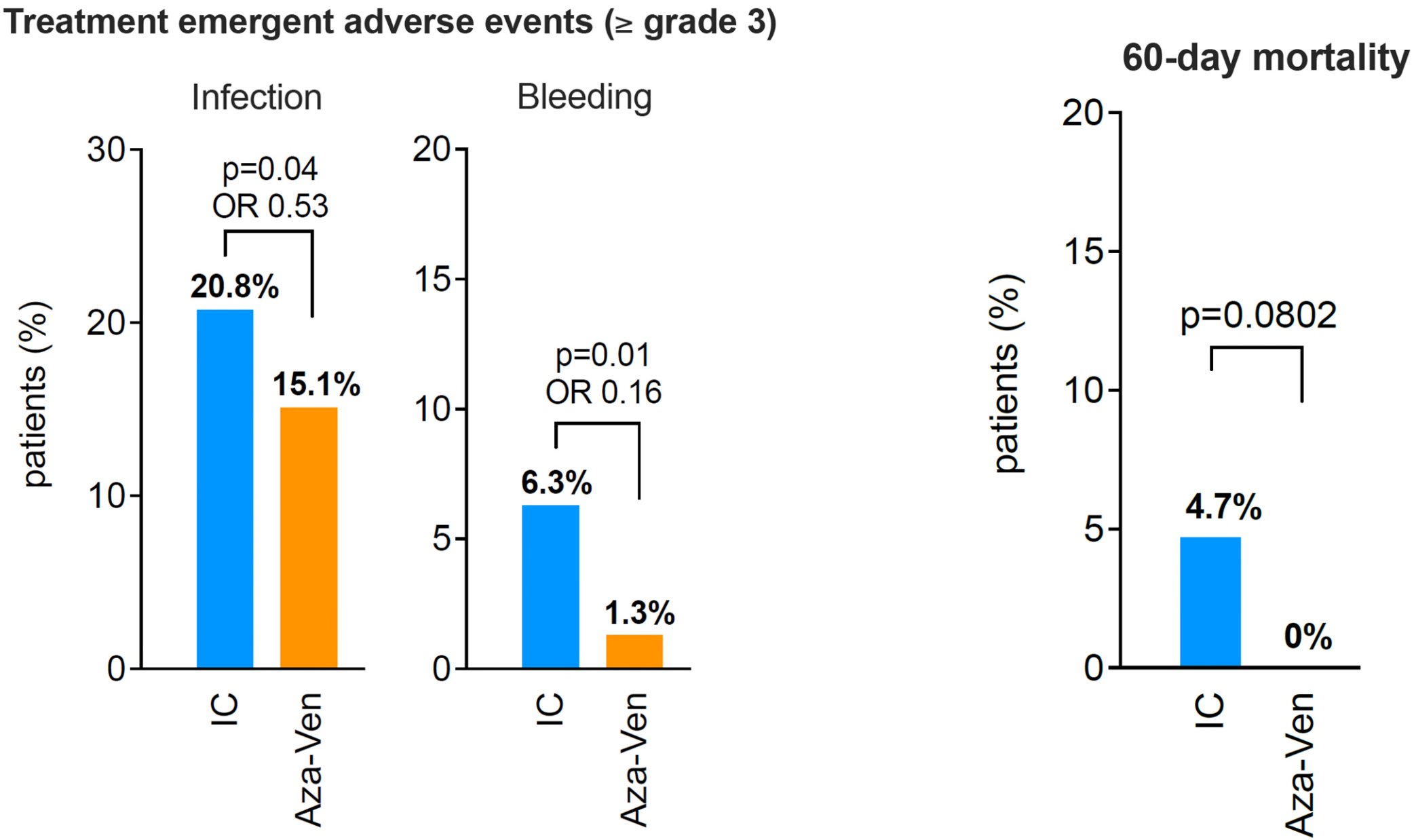
		Total	Aza-Ven	IC
		(N = 172)	(N = 86)	(N = 86)
Age (years)	Median, range	64 (23 - 79)	65 (23 - 79)	64 (28 - 79)
	Less than 65	87 (50.6)	43 (50.0)	44 (51.2)
Sex, n (%)	Male	115 (66.9)	55 (64.0)	60 (69.8)
Race, n (%)	Caucasian	134 (77.9)	65 (75.6)	69 (80.2)
	African American	10 (5.8)	5 (5.8)	5 (5.8)
	Hispanic	13 (7.6)	6 (7.0)	7 (8.1)
	Asian	15 (8.7)	10 (11.6)	5 (5.8)
ECOG, n (%)	0/1	161 (93.6)	79 (91.9)	82 (95.4)
	2	10 (5.8)	7 (8.1)	3 (3.5)
ELN 2022 risk, n (%)	Favorable	22 (12.8)	13 (15.1)	9 (10.5)
	Intermediate	26 (15.1)	15 (17.4)	11 (12.8)
	Adverse	124 (72.1)	58 (67.4)	66 (76.7)
Mutations, n (%)	*NPM1*	16 (9.3)	11 (12.8)	5 (5.8)
	IDH1	15 (8.7)	8 (9.3)	7 (8.1)
	IDH2	28 (16.3)	19 (22.1)	9 (10.5)
	TP53	25 (14.5)	9 (10.5)	16 (18.6)
	RUNX1	32 (18.6)	14 (16.3)	18 (20.9)
	KRAS/NRAS	32 (18.6)	17 (19.8)	15 (17.5)

Safety and Tolerability:

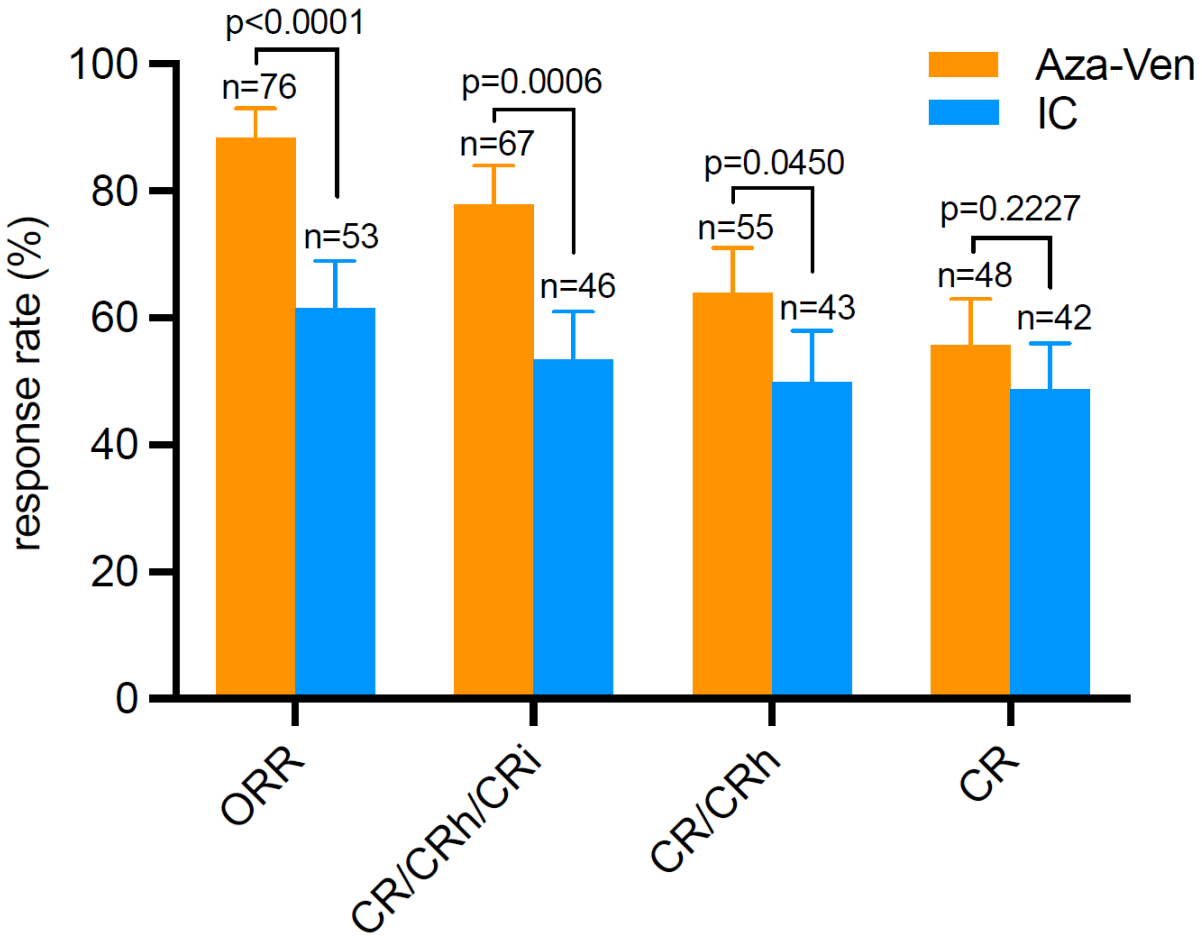
Grade ≥3 TEAEs in ≥10% of Patients

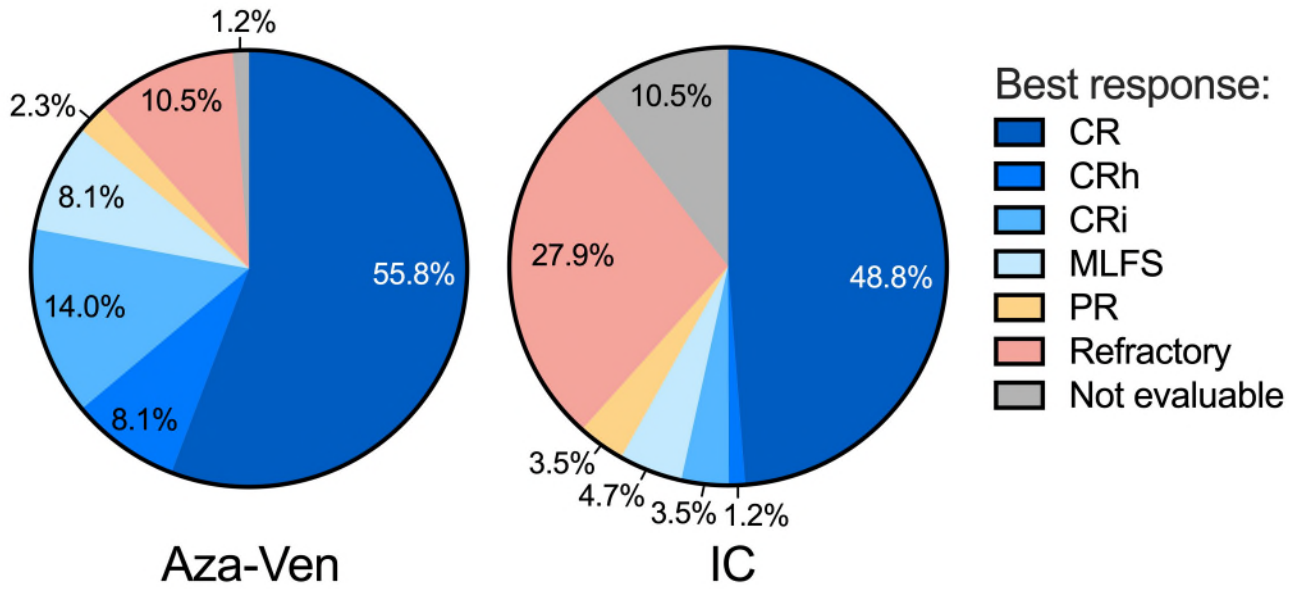
Toxicities (n (%))	IC				Aza-Ven			
	Grade 3	Grade 4	Grade 5	≥ Grade 3	Grade 3	Grade 4	Grade 5	≥ Grade 3
Febrile neutropenia	51 (62.2)	1 (1.2)	0 (0.0)	52 (63.4)	46 (53.5)	3 (3.5)	0 (0.0)	49 (57.0)
Platelet count decreased	3 (3.7)	47 (57.3)	0 (0.0)	50 (58.1)	8 (9.3)	38 (44.2)	0 (0.0)	46 (53.5)
Anemia	35 (40.7)	3 (3.5)	0 (0.0)	38 (46.3)	34 (39.5)	1 (1.2)	0 (0.0)	35 (40.7)
Neutrophil count decreased	1 (1.2)	39 (47.6)	0 (0.0)	40 (48.8)	1 (1.2)	48 (55.8)	0 (0.0)	49 (57.0)
White blood cell decreased	0 (0.0)	20 (24.4)	0 (0.0)	20 (24.4)	2 (2.3)	24 (27.9)	0 (0.0)	26 (30.2)
Lymphocyte count decreased	9 (11.0)	8 (9.8)	0 (0.0)	17 (20.7)	11 (12.8)	6 (7.0)	0 (0.0)	17 (19.8)
Lung infection	11 (15.6)	2 (2.4)	2 (2.4)	15 (18.3)	12 (14.0)	0 (0.0)	0 (0.0)	12 (14.0)
Sepsis	10 (12.2)	2 (2.4)	0 (0.0)	12 (14.6)	5 (5.8)	1 (1.2)	0 (0.0)	6 (7.0)
Anorexia	12 (14.6)	0 (0.0)	0 (0.0)	12 (14.6)	4 (4.7)	0 (0.0)	0 (0.0)	4 (4.7)
Hypoxia	7 (8.5)	2 (2.4)	0 (0.0)	9 (11.0)	4 (4.7)	0 (0.0)	0 (0.0)	4 (4.7)

Safety and Tolerability, Continued.

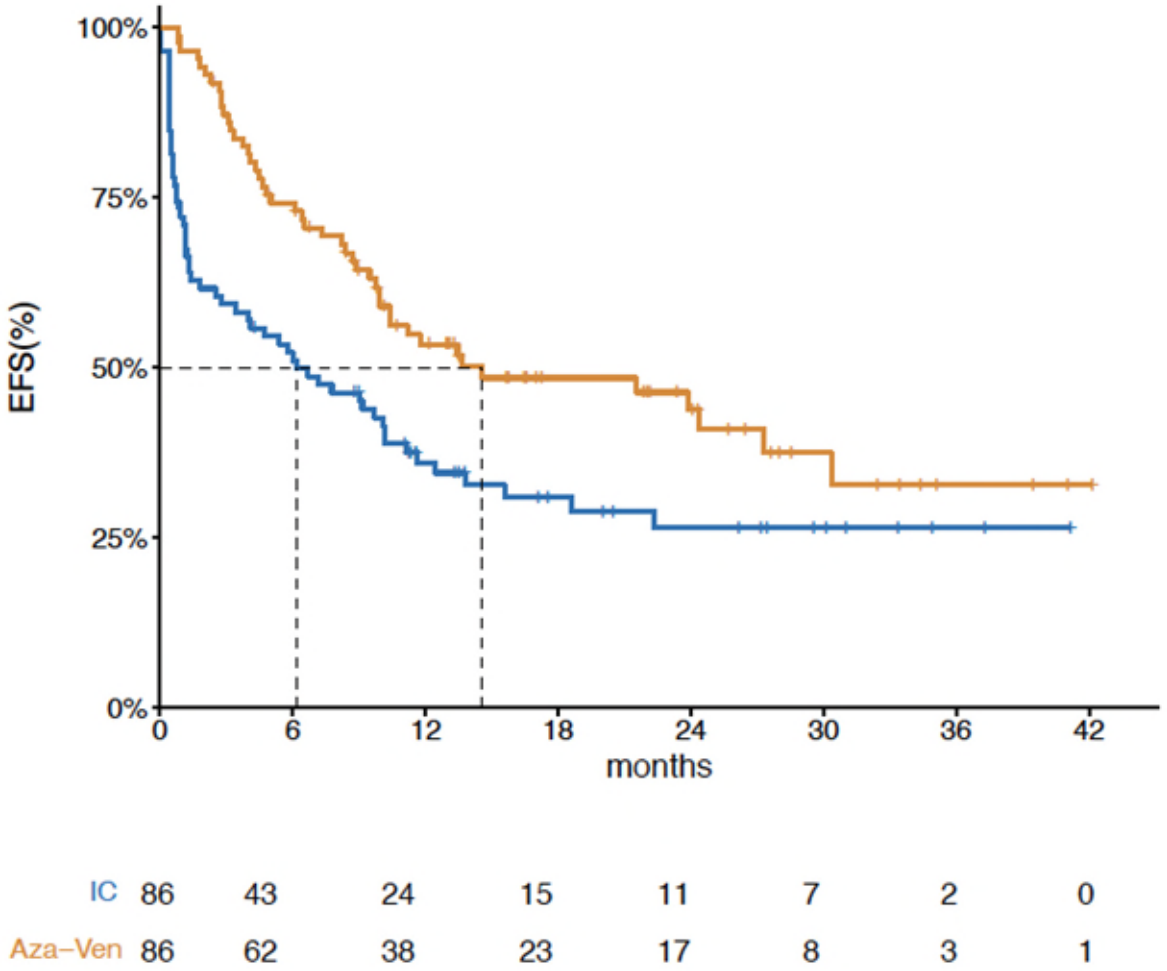


Clinical Activity



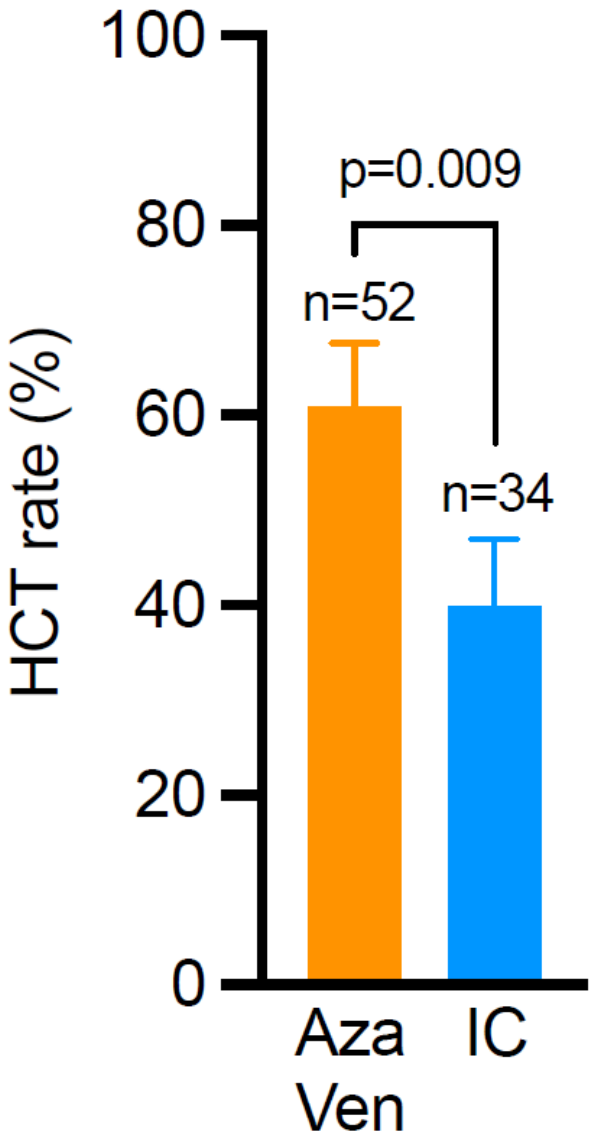


Event-Free Survival



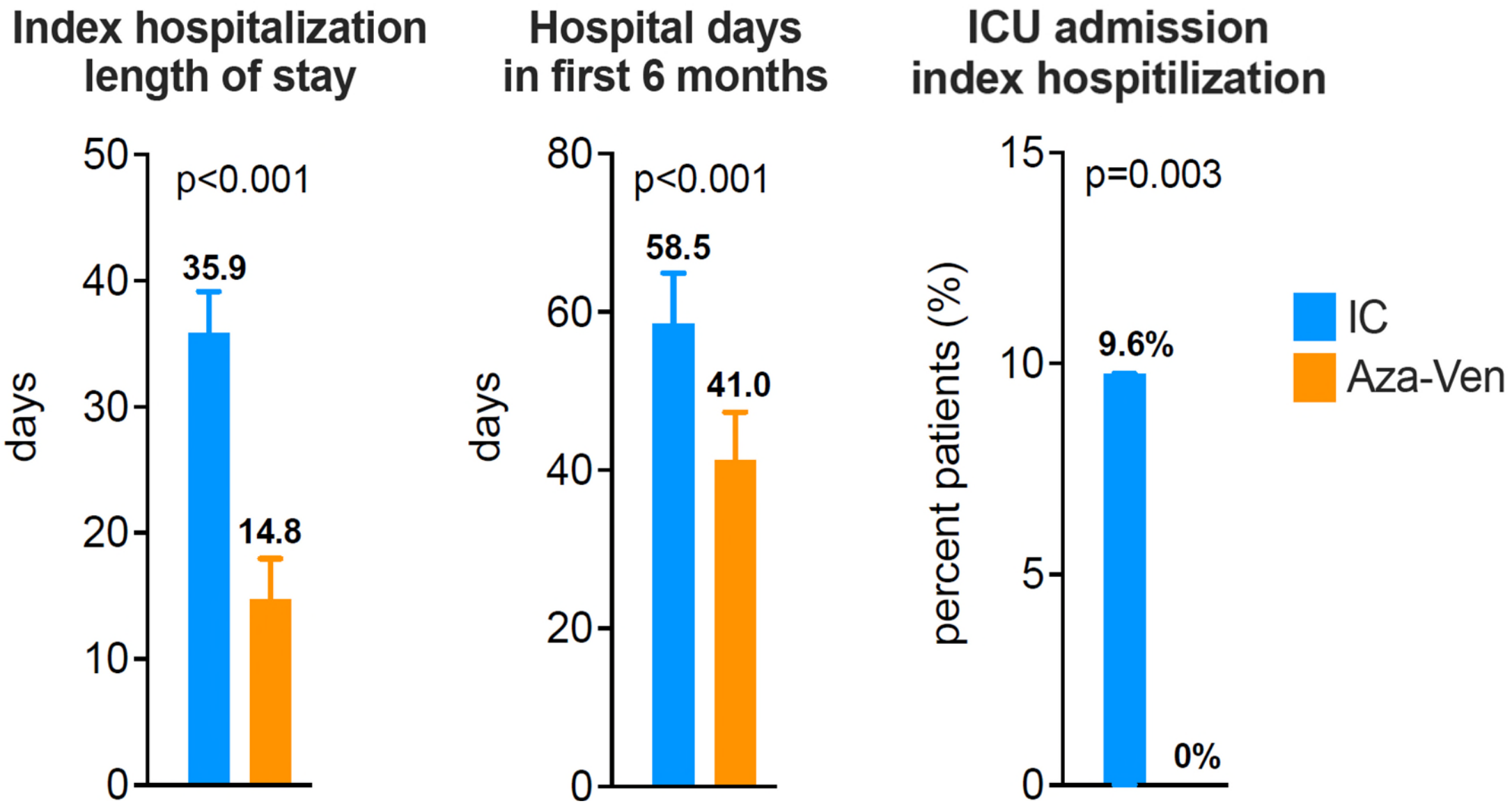
- Median EFS of 14.6 for Aza-Ven vs 6.15 months for IC (P=0.0021).
- One-year EFS was 53.4% for Aza-Ven vs 36.0% for IC.
- The HR for a univariate Cox model was 0.57 (P=0.0022).
- After adjustment for variables in a multivariable model, the effect of Aza-Ven remained protective for EFS (HR:0.66; P=0.0231).

Transplant



- Transplant had a significant protective effect for EFS.
- After adjustment for HCT in univariable and multivariable models for EFS, effect of Aza-Ven remained protective (HR:0.67; P=0.0302).

Healthcare Utilization



Conclusions

- Aza-Ven improves EFS versus conventional IC.
- Aza-Ven leads to higher rates of OR and CCR, when compared to IC.
- A greater proportion of Aza-Ven patients successfully proceeded to HCT following response on trial.
- Aza-Ven was associated with with less early mortality, improved QOL and symptom burden during initial therapy, and less time in the hospital and ICU.
- These data support the use of Aza-Ven in functionally fit patients with intermediate or adverse-risk, *FLT3*-wildtype AML.

All oral regimen decitabine-cedazuridine+ venetoclax

ORIGINAL ARTICLE

All-Oral Treatment of Newly Diagnosed Acute Myeloid Leukemia

Gail J. Roboz, M.D.,[1] Amer M. Zeidan, M.B., B.S., M.H.S.,[2] Gabriel N. Mannis, M.D.,[3] Pau Montesinos, M.D., Ph.D.,[4] Montserrat Arnan, M.D., Ph.D.,[5] Michael R. Savona, M.D.,[6] Olatoyosi Odenike, M.D.,[7] James K. McCloskey, M.D.,[8] Harshad V. Amin, M.D.,[9] Amir T. Fathi, M.D.,[10] Teresa Bernal del Castillo, M.D., Ph.D.,[11] Gabriela Rodríguez-Macías, M.D., Ph.D.,[12] Jane L. Liesveld, M.D.,[13] Annie P. Im, M.D.,[14] Jan Cerny, M.D., Ph.D.,[15] Teresa C. Gentile, M.D., Ph.D.,[16] Aram Oganesian, Ph.D.,[17] Danna Chan, Pharm.D.,[17] Yubing Wan, Ph.D.,[17] Margit Dijkstra, M.D.,[17] Harold N. Keer, M.D., Ph.D.,[17] Elizabeth A. Griffiths, M.D.,[18] and Courtney D. DiNardo, M.D.[19]

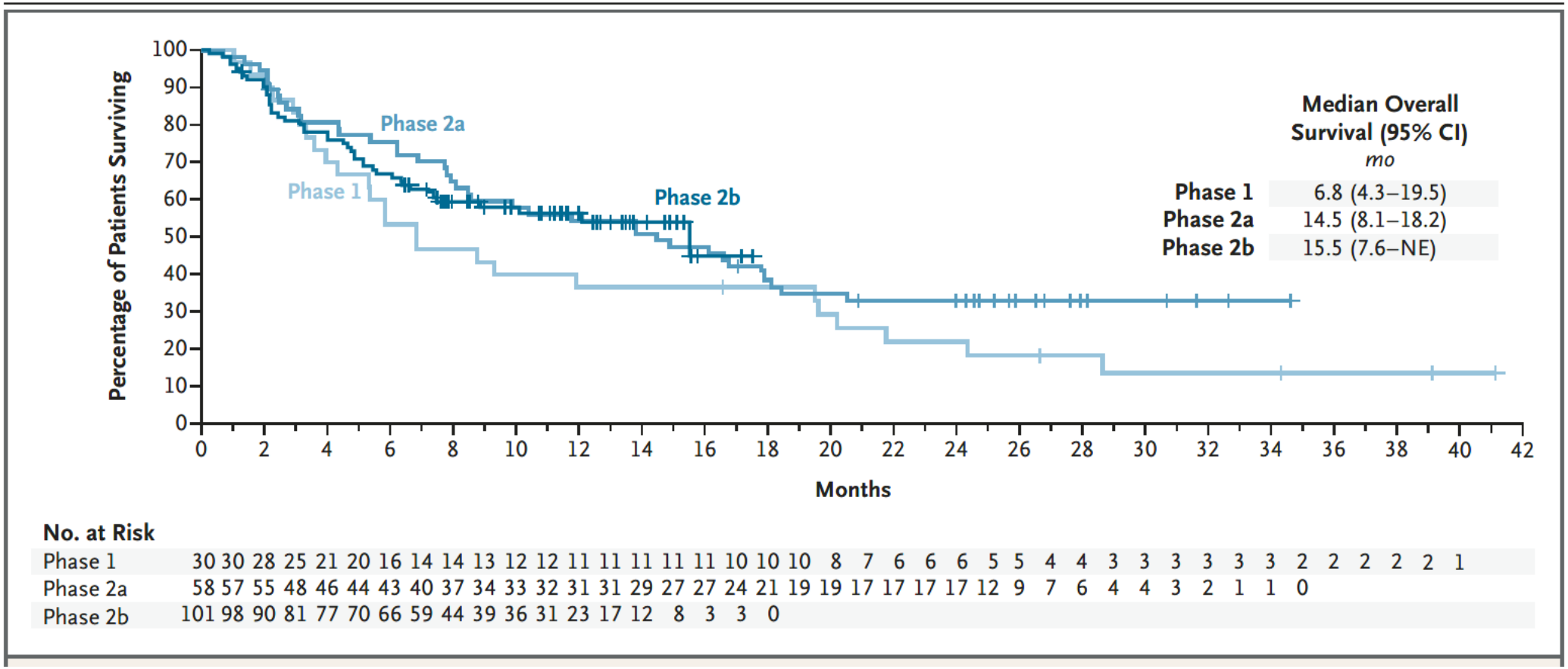
Table 2. Summary of Responses (All-Treated Population).*

Variable	Phase 1 (N=30)	Phase 2a (N=58)	Phase 2b (N=101)
Complete response — % (95% CI)	40 (23–59)	38 (26–52)	47 (36–57)
Complete response with incomplete hematologic recovery — % (95% CI)	23 (10–42)	28 (17–41)	17 (10–26)
Complete response with partial hematologic recovery — % (95% CI)	17 (6–35)	21 (11–33)	5 (2–11)
Complete response or complete response with incomplete hematologic recovery — % (95% CI)	63 (44–80)	66 (52–78)	63 (53–73)
Complete response or complete response with partial hematologic recovery — % (95% CI)	57 (37–74)	59 (45–71)	51 (41–62)
Complete response, complete response with incomplete hematologic recovery, or complete response with partial hematologic recovery — % (95% CI)	63 (44–80)	66 (52–78)	63 (53–73)
Complete response that was sustained at 12 mo — % (95% CI)	75 (41–91)	71 (47–86)	75 (57–87)
Median time to complete response (range) — mo	1.9 (0.9–9.6)	2.4 (0.8–12.2)	2.4 (0.7–15.3)

FDA approved May 2026

Roboz GJ et al N Engl J med 2026; 394: 2107-16

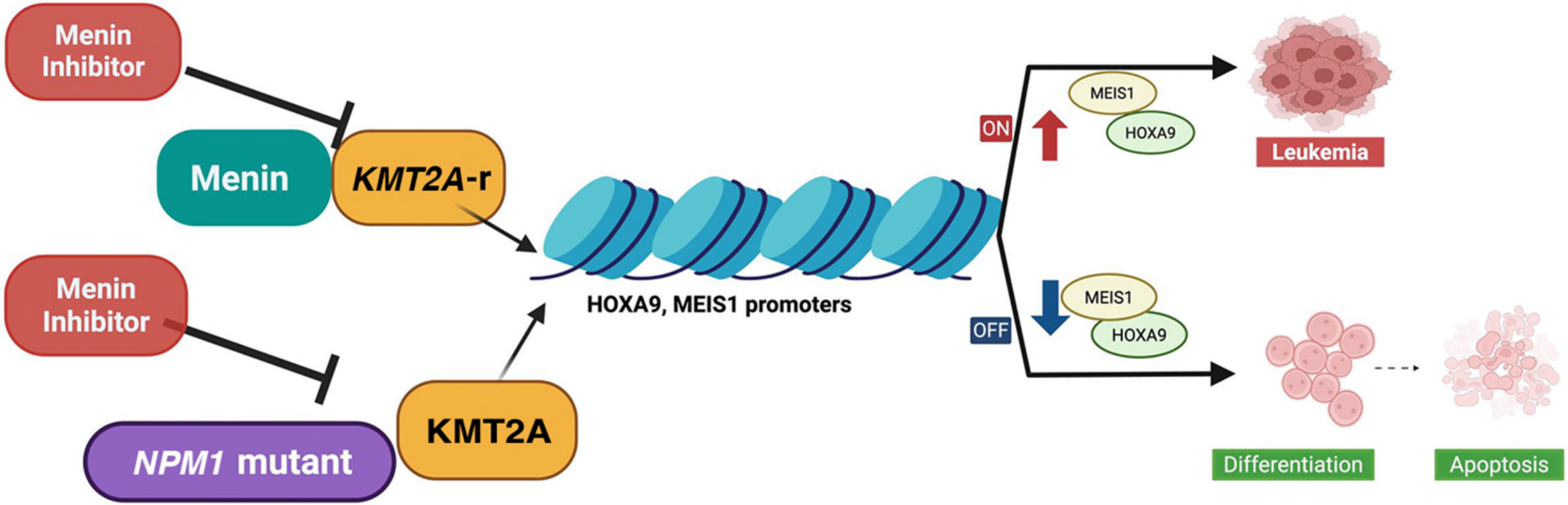
All oral regimen decitabine-cedazuridine+ venetoclax



Roboz GJ et al N Engl J med 2026; 394: 2107-16

Menin inhibitors: background

- KMT2A rearrangements detected in around 5% de novo AML (higher in childhood and infant AML and therapy related) All need HSCT in CR1
- Can have ALL or MPAL phenotype
- Ruveminib approved for R/R KMT2Ar or NPM1m AML, Ziftomenib approved for R/R NPM1m AML
- Many other agents in development and have moved to trials in front line setting in combination with 7+3 or HMA-VEN
- Menin inhibitors also active in NPM1mut AML
- Always test for KMT2Ar by FISH (cannot be detected by NGS)



Rahul K. Thakur,Eunice S. Wang, The promise of menin inhibitors: from approval to triplet regimens, Hematology Am Soc Hematol Educ Program, 2025, Figure 1.

AUGMENT-101 phase 2 study design (NCT04065399)

Phase 1: Dose escalation

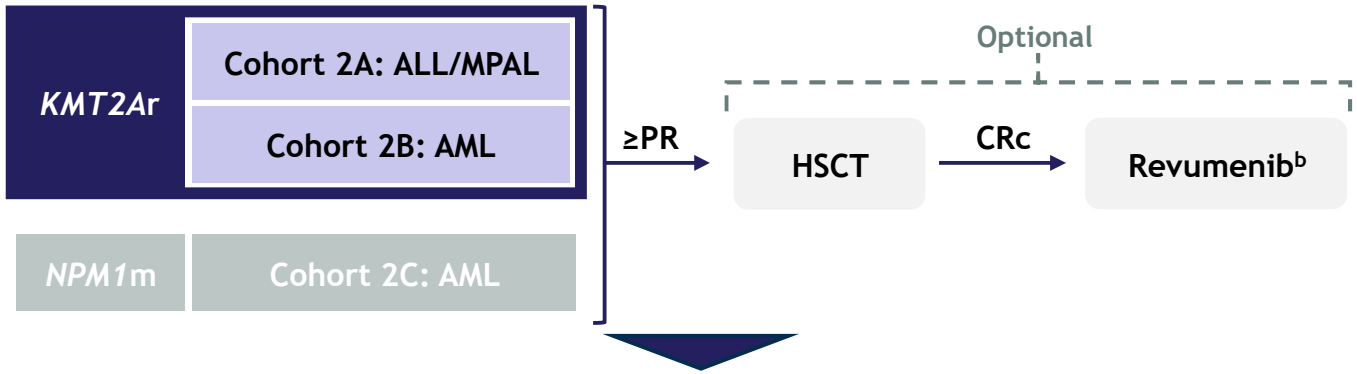
Revumenib RP2D

160 mg q12h orally (95 mg/m^2 if <40 kg) WITH strong CYP3A4i in 28-day cycles[a]

Patient population

Adult and pediatric patients with R/R AL with *KMT2A*r or *NPM1*m

Phase 2: Pivotal trial



FDA-approved dosage

160 mg q12h orally (95 mg/m^2 if <40 kg) WITH strong CYP3A4i in 28-day cycles[a]

or

270 mg q12h orally (160 mg/m^2 if <40 kg) WITHOUT strong CYP3A4i in 28-day cycles[a]

Phase 2 endpoints (DCO: Feb 29, 2024)

Primary
- CR + CRh rate
- Safety and tolerability

Key secondary
- CRc rate[c]
- ORR
- Duration of response
- Time to response
- OS

[a]Revumenib administered until unacceptable toxicity, end of Cycle 4 if no response, or PD without clinical benefit as defined by the investigator. [b]Maintenance therapy with revumenib after HSCT was allowed per protocol amendment for eligible patients, with maintenance treatment continued until disease progression or unacceptable toxicity. [c]CR + CRh + CRp + CRi. CR, complete remission; CRc, composite CR; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; HSCT, hematopoietic stem cell transplant; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial remission.

Demographic and baseline disease characteristics

Characteristic	Efficacy population[a] (N = 97)			Safety population[b] (N = 116)		
	AML (n = 78)	ALL (n = 13)	MPAL (n = 6)	AML (n = 95)	ALL (n = 15)	MPAL (n = 6)
Age, median (range), y	37.5 (1.3–75.0)	37.0 (0.6–73.0)	16.0 (1.0–53.0)	37.0 (1.3–75.0)	31.0 (0.6–73.0)	16.0 (1.0–53.0)
Age group, n (%)						
<18 y	14 (17.9)	3 (23.1)	3 (50.0)	20 (21.1)	5 (33.3)	3 (50.0)
18 to <65 y	55 (70.5)	7 (53.8)	3 (50.0)	64 (67.4)	7 (46.7)	3 (50.0)
≥65 y	9 (11.5)	3 (23.1)	0	11 (11.6)	3 (20.0)	0
Female, n (%)	45 (57.7)	8 (61.5)	2 (33.3)	56 (58.9)	9 (60.0)	2 (33.3)
Race, n (%)						
White	56 (71.8)	9 (69.2)	4 (66.7)	66 (69.5)	10 (66.7)	4 (66.7)
Non-White	12 (15.4)	2 (15.4)	0	12 (12.6)	2 (13.3)	0
Other[c]	10 (12.8)	2 (15.4)	2 (33.3)	17 (17.9)	3 (20.0)	2 (33.3)
Prior lines of therapy, median (range)	2 (1–11)	3 (1–8)	2 (1–4)	2 (1–11)	3 (1–8)	2 (1–4)
≥3, n (%)	30 (38.5)	9 (69.2)	2 (33.3)	38 (40.0)	11 (73.3)	2 (33.3)
≥4, n (%)	15 (19.2)	5 (38.5)	2 (33.3)	19 (20.0)	6 (40.0)	2 (33.3)
Prior therapy, n (%)						
Venetoclax	57 (73.1)	3 (23.1)	2 (33.3)	67 (70.5)	4 (26.7)	2 (33.3)
HSCT	39 (50.0)	4 (30.8)	3 (50.0)	52 (54.7)	4 (26.7)	3 (50.0)

- Median (range) duration of follow-up[d] was 5.9 (0.3–25.7) months for AML, 3.9 (0.3–22.3) for ALL, and 5.4 (0.9–7.4) for MPAL

Data cutoff: February 29, 2024. [a]Efficacy population: patients with centrally confirmed *KMT2Ar* AL who had ≥5% baseline bone marrow blasts within 28 days prior to start of study treatment. [b]Safety population: all enrolled patients who received ≥1 dose of revumenib during the study. [c]Includes "other," "multiple," and "unknown." [d]In the safety population.

Efficacy: Response

Parameter	Efficacy population (N = 97)		
	AML (n = 78)	ALL (n = 13)	MPAL (n = 6)
ORR,[a] n (%)	52 (66.7)	6 (46.2)	4 (66.7)
95% CI[b]	55.1–76.9	19.2–74.9	22.3–95.7
Best overall response, n (%)			
CR	11 (14.1)	3 (23.1)	1 (16.7)
CRh	7 (9.0)	0	0
CRp	15 (19.2)	1 (7.7)	1 (16.7)
CRi	1 (1.3)	0	1 (16.7)
MLFS	18 (23.1)	1 (7.7)	1 (16.7)
PR	0	1 (7.7)	0
PD	6 (7.7)	1 (7.7)	0
No response	15 (19.2)	6 (46.2)	0
Other[c]	5 (6.4)	0	2 (33.3)
Patients remaining on study, n (%)	24 (30.8)	1 (7.7)	2 (33.3)

- 21 patients proceeded to HSCT while in remission, including 19 with AML and 2 with MPAL
  - As of data cutoff, 9/19 (47.4%) patients with AML who underwent HSCT resumed revumenib treatment after HSCT
- Median (range) duration of treatment[d]
  - AML: 2.6 (0.1–14.9) months
  - ALL: 2.0 (0.2–4.9) months
  - MPAL: 1.7 (0.7–3.9) months

Data cutoff: February 29, 2024. [a]CRc + MLFS + PR. [b]Exact 95% CIs of response rate are 2-sided and calculated using the Clopper-Pearson method. [c]Includes those with unknown or missing status. [d]In the safety population. CI, confidence interval; MLFS, morphologic leukemia-free state.

Efficacy: Response

Parameter	Efficacy population (N = 97)		
	AML (n = 78)	ALL (n = 13)	MPAL (n = 6)
CR + CRh rate, n (%)	18 (23.1)	3 (23.1)	1 (16.7)
95% CI[a]	14.3–34.0	5.0–53.8	0.4–64.1
Duration of response,[b] mo Median (95% CI)	7.7 (3.4–NR)	NR (0.9–NR)	1.8 (NE–NE)
Time to response,[b] mo Median (range)	2.0 (0.9–4.6)	1.9 (0.9–2.8)	3.2 (3.2–3.2)
CRc rate,[c] n (%)	34 (43.6)	4 (30.8)	3 (50.0)
95% CI[a]	32.4–55.3	9.1–61.4	11.8–88.2
MRD-negative status,[d,e] n/N (%)			
CR + CRh	9/14 (64.3)	1/3 (33.3)	1/1 (100)
CRc	18/30 (60.0)	1/4 (25.0)	2/2 (100)

- CR + CRh was achievable and similar across AL subtypes
- MRD negativity, as assessed by investigators, was achievable regardless of AL subtype

Data cutoff: February 29, 2024. [a]Exact 95% CIs of response rate are 2-sided and calculated using the Clopper-Pearson method. [b]Kaplan-Meier method used and 2-sided 95% CI calculated based on the Greenwood method. [c]CR + CRh + CRp + CRi. [d]MRD status percentage based on number of responders with MRD status available. [e]MRD assessment conducted locally by flow cytometry. MRD, measurable residual disease; NE, not estimable; NR, not reached.

Safety: Treatment-emergent AEs

Event in ≥25% of safety population, n (%)	Safety population (N = 116)					
	AML (n = 95)		ALL (n = 15)		MPAL (n = 6)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE[a]	95 (100)	88 (92.6)	15 (100)	12 (80.0)	6 (100)	6 (100)
Hematologic AEs						
Febrile neutropenia	36 (37.9)	35 (36.8)	6 (40.0)	6 (40.0)	4 (66.7)	4 (66.7)
Anemia	27 (28.4)	19 (20.0)	2 (13.3)	2 (13.3)	2 (33.3)	2 (33.3)
Non-hematologic AEs						
Nausea	45 (47.4)	4 (4.2)	6 (40.0)	2 (13.3)	1 (16.7)	0
Vomiting	33 (34.7)	3 (3.2)	7 (46.7)	1 (6.7)	0	0
QTcF prolongation	30 (31.6)	15 (15.8)	3 (20.0)	0	1 (16.7)	0
Diarrhea	29 (30.5)	1 (1.1)	6 (40.0)	2 (13.3)	0	0
Differentiation syndrome	27 (28.4)	14 (14.7)	2 (13.3)	2 (13.3)	2 (33.3)	1 (16.7)
Epistaxis	25 (26.3)	3 (3.2)	4 (26.7)	0	1 (16.7)	0

- Revumenib was well tolerated and no new safety signals were identified across AL subtypes

Data cutoff: February 29, 2024. [a]AEs that started on or after first administration of study drug and within 30 days of last dose. For patients who resumed study drug post HSCT, only AEs from the period prior to HSCT are included.
AE, adverse event; QTcF, Fridericia's corrected QT interval.

Safety: Treatment-related AEs

Event in ≥15% of safety population, n (%)	Safety population (N = 116)					
	AML (n = 95)		ALL (n = 15)		MPAL (n = 6)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any revumenib-related AE[a]	83 (87.4)	55 (57.9)	8 (53.3)	4 (26.7)	5 (83.3)	4 (66.7)
Hematologic AEs						
Anemia[b]	16 (16.8)	13 (13.7)	1 (6.7)	1 (6.7)	2 (33.3)	2 (33.3)
Febrile neutropenia[b]	14 (14.7)	14 (14.7)	2 (13.3)	2 (13.3)	2 (33.3)	2 (33.3)
Non-hematologic AEs						
Nausea[b]	29 (30.5)	2 (2.1)	3 (20.0)[c]	2 (13.3)	0	0
QTcF prolongation[b]	28 (29.5)	15 (15.8)	3 (20.0)	0	1 (16.7)	0
Differentiation syndrome	27 (28.4)	14 (14.7)	2 (13.3)	2 (13.3)	2 (33.3)	1 (16.7)[d]
Vomiting[b]	20 (21.1)	1 (1.1)	5 (33.3)[c]	1 (6.7)	0	0

- DS and QTcF prolongation events were manageable per protocol guidance, without any patients receiving DS prophylaxis
  - Majority of DS and QTcF prolongation events occurred during the first cycle, with a median (range) duration of 12 (3–31) and 1 (1-8) days, respectively
- Low rate of treatment discontinuation due to TRAEs (n = 6; 5.2%)
  - No patients discontinued revumenib due to cytopenias, DS, or QTcF prolongation

Data cutoff: February 29, 2024. [a]Relatedness judged by the investigator as possibly related, probably related, or definitely related to study drug. [b]None were grade 4 or 5. [c]One event led to treatment discontinuation. [d]Grade 4 event.
DS, differentiation syndrome; TRAE, treatment-related AE.

Conclusions

- Revumenib monotherapy provides **clinically meaningful responses** in patients with R/R *KMT2A*r AL **regardless of leukemia type**
  - MRD negativity was achievable in patients achieving CR + CRh across AL subtypes
  - Durable responses were seen in patients who achieved CR + CRh across AL subtypes
- The well-characterized safety profile of revumenib is consistent with prior reports and is similar across AL subtypes
  - Differentiation syndrome was manageable, without any patients having received prophylaxis
  - No patients discontinued treatment due to cytopenias, differentiation syndrome, or QTcF prolongation

These findings continue to support revumenib as an effective treatment option for patients with *KMT2A*r AL, demonstrating its potential to improve outcomes across multiple leukemia types in this difficult-to-treat population

Menin inhibitors: conclusions

- Monotherapy can induce MRD negative remissions in R/R setting allowing patients to proceed to allo HSCT with curative intent
- High response rates in early trials of combination therapy in frontline setting
- Duration of response in generally short (under 6 months) : need for referral for HSCT as soon as possible
- Development of MEN1 resistance mutations common
- Differentiation syndrome can be life threatening and needs close monitoring and immediate intervention

Triplet regimens including targeted agents

- Combinations of FLT3 inhibitors, Menin inhibitors or IDH1/2 inhibitors with backbone of intensive chemo or Ven + aza
- Strongest case for KMT2Ar AML and FLT3rAML
- Current data on IDH inhibitor triplets is retrospective or single arm studies
- Balancing higher response rate and deeper response with additional toxicity
- Randomized trials on going

FLT3 inhibitors with intensive chemotherapy

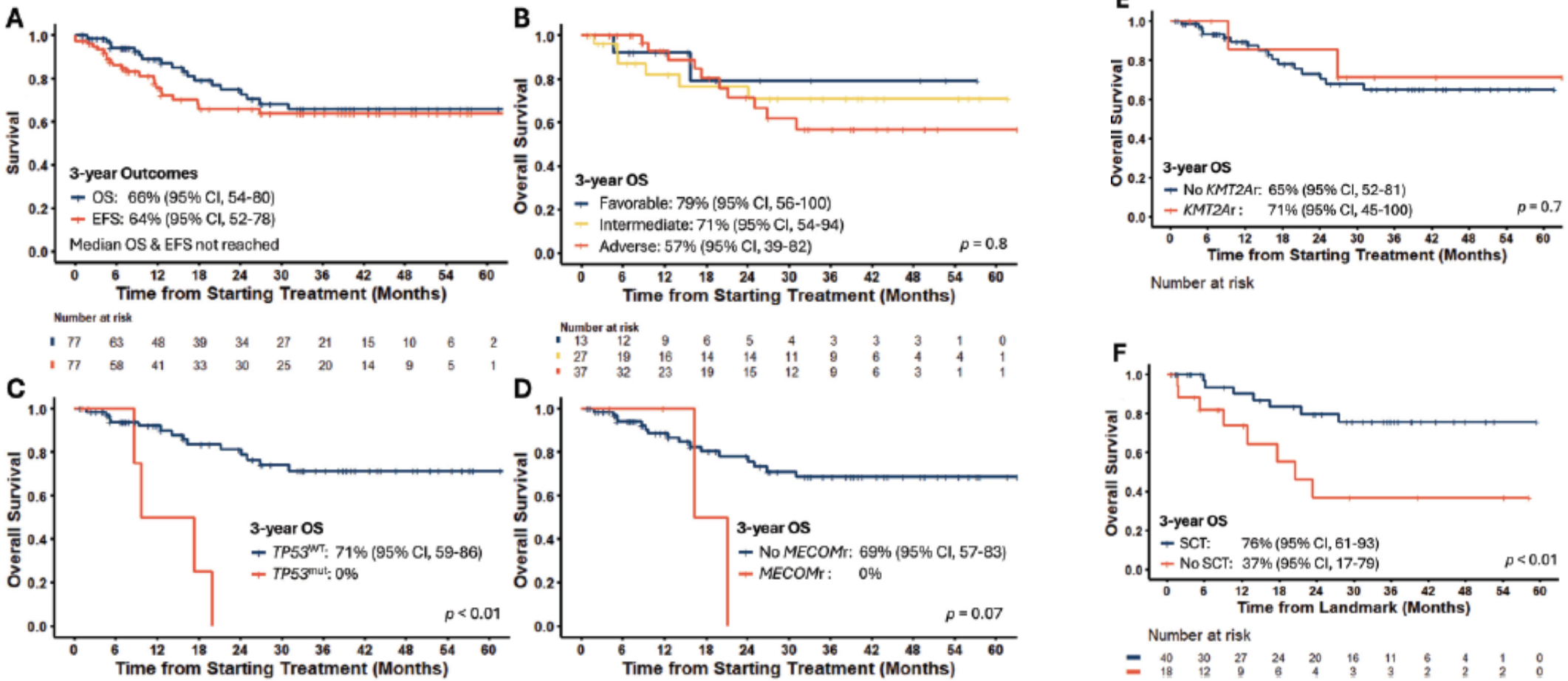
Drug	FDA Approved	Indication	Trial	Outcomes	MRD negativity in responders	Count Recovery (ANC/PLT)	Grade 3 Infection / FN (Drug vs. Control)
Midostaurin (Rydapt) Type 1	2017	ND FLT3-ITD or TKD+ in combination with 7+3. 50mg BID d8-21	RATIFY (phase 3) in 717 pts Age 18-59	**Response**: 66% CRc, 59% CR **OS:** 74 v. 25 mos (placebo)	Not formally reported	ANC: 26 v. 26d PLT 26 v. 25d	No difference in gr 3 infection(50-52%) and FN (82%) in both arms
Gilteritinib (Xospata) Type 1	2018	R/R FLT3-ITD or TKD+ Single agent*	ADMIRAL (phase 3) in 371 pts	**Response:** 34% CR/CRh **OS:** 9.3 v. 5.6 mos (salvage chemo)	~8%	ANC: 34d PLT: 32d	No difference, gilteritinib ~46% FN and 46.7% FN with salvage chemo
Gilteritinib +7+3 v. Midostaurin +7+3	Not approved	-- Tested in ND FLT3m AML	HOVON156 in 777 pts	**Response:** 82% vs. 80% CR/CRi **OS:** no difference	88% vs 83% (flow) 62% vs 55% (molecular)	ANC: 34 v. 32d PLT: 31 v. 28d	Gr 3 FN: 50-55% vs 48-52%
Quizartinib (Vanflyta) Type 2	2023	ND FLT3-ITD only in combination with 7+3, 40mg daily d8-21	QuANTUM-First (phase 3) 539 pts Age 18-75	**Response**: 71.6% CRc, 55% CR **OS:** 31.9 v 15.1 mos (placebo)	42% vs. 38% (molecular)	ANC 34 v. 29d PLT 36 v. 28d	43.4% FN with Quizartinib and 7+3 vs. 41% with placebo +chemo

FLT3 inhibitors with HMA-VEN

Combination	Phase	Setting (n)	CRc Rate	MRD Neg Rate	Median ANC/PLT recovery	Grade 3+ Infection/Grade 3+ FN	Trial number/reference
Gilt + VEN(28)/AZA (gilt d1-28) – 80mg RP2D	1/2	ND (n=30)	96%	93% (flow) 90% (PCR)	37-40d/33d	53%/33% 60d mortality 0%	NCT04140487; Short et al (JCO 2024)
Quiz +VEN(14-21) +DEC	1/2	ND (n= 26)	92%	67% (flow) 71% (PCR)	37-40d/36d	38% PNA/ 24%inf/57% 30d mortality 4%	NCT03661307; Yilmaz et al (EHA 2025)
Gilt + VEN(28)/AZA	1/2	R/R (n=22)	27% (additional 41% with MLFS)	45% (flow) 43% (PCR)	--	71%/45%	NCT04140487; Short et al (JCO 2024)
Quiz+VEN (14-21) +DEC (Quiz 30mg/d RP2D)	1/2	R/R (n=47)	60%	29% (flow) 32% (PCR)	--	72%PNA/ 47%inf/62%	NCT03661307; Yilmaz et al (EHA 2025)
VEN(28)+AZA (control VIALE-A)	3	ND (n=286)	66.4%	23.4% (flow) only after 1 cycle; 41% long term f/u	29d/27d	64%/42%	NCT02993523; Dinardo et al (NEJM 2020)

FLAG ida ven

77 newly diagnosed 61 R/R ORR 97% CRc 95% MRG neg 90%



DiNardo C et al Leukemia 2025; 39: 854-63

B-ALL

- Chemo free approach for Ph+ ALL
- Blinatumomab with chemotherapy and novel bispecifics
- Early consolidation with CART cells

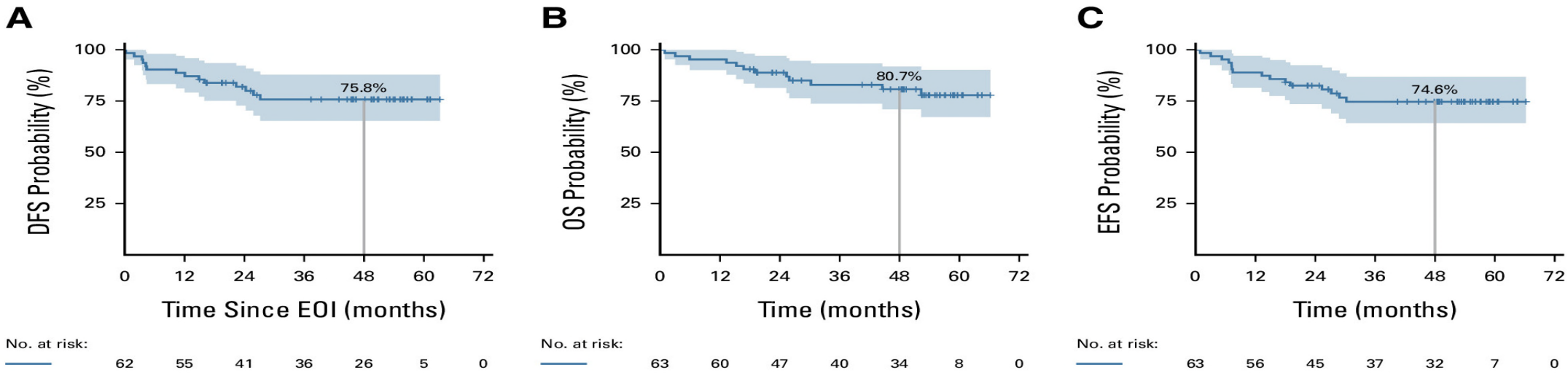
Ph+ ALL : Background

- TKI highly active, obviating need for intensive chemotherapy
- Ponatinib showed superiority over imatinib in PhALL CON trial
- Dasatinib-blinatumomab combo shown to achieve (18 mo OS 95% and DFS 88%) *Foa et al NEJM 2020; 383: 1613-23*
- CNS directed chemotherapy is critical component of regimen

Background

- Ph+ ALL was historically the hematologic malignancy with the worst outcome.
- The scenario has markedly changed first with the introduction of TKIs in induction and then with the addition of blinatumomab in consolidation (targeted treatment plus immunotherapy), opening the way to chemo-free strategies (see *Foà R, NEJM 2025)*.

Long-term results of the GIMEMA LAL2116 D-ALBA study (dasatinib + blinatumomab)

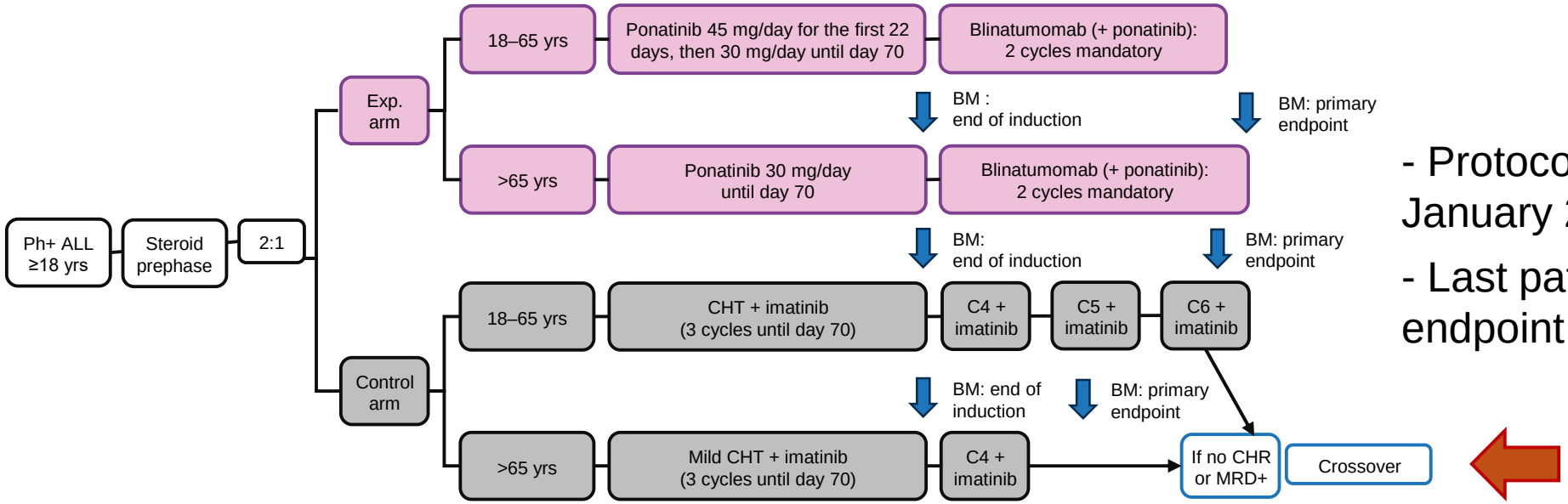


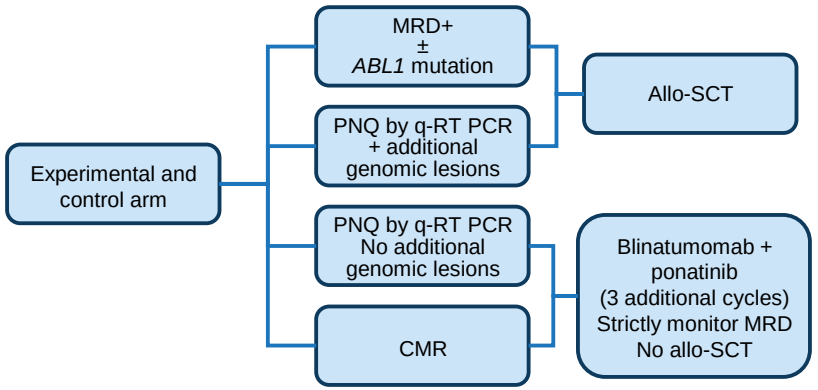
- At a median follow-up of 53 months DFS, OS and EFS are 75.8%, 80.7% and 74.6%, respectively.
- 9 relapses recorded: 5 *IKZF1*^{plus} + T3151I and 4 CNS.

Foà R et al, NEJM 2020 & JCO 2024

GIMEMA ALL2820 Phase III Trial

Frontline treatment of adult Ph+ ALL (≥18 years, no upper age limit) with ponatinib plus steroids followed by blinatumomab compared to chemotherapy with imatinib





- Protocol closed to enrolment in January 2025.
- Last patient reached primary endpoint in June 2025.

- CNS prophylaxis strengthened:
15 triple medicated lumbar punctures
18 if CNS+ at diagnosis.

Chairetti S et al ASH 2025

GIMEMA ALL2820. Patients' features (n=236)

	Experimental arm N=158	Control arm N=78
Age, median (range)	56.5 (19-84)	55 (21-79)
>65 years (%)	44 (28)	21 (27)
Gender: M/F (%)	79/79 (50/50)	48/31(59/41)
WBC $x10^9$/l, median (range)	10.5 (0.1-244)	13.4 (0.7-231)
≥$30x10^9$/l (%)	43 (27)	27 (31)
≥$70x10^9$/l (%)	16 (10)	7 (9.3)
CNS+	15 (9.9)	11(15)
p190 (%)	111 (70)	49 (64)
p210, p190/210 (%)	41 (26), 6 (4)	24 (31.7), 4 (5.2)
IKZF1^{plus} (%)	52 (34)	19 (26)

GIMEMA ALL2820. Hematologic responses

End of induction (d +70)	Experimental arm (n=158)	Control arm (n=78)	p
CHR	149 **(94.3%)**	62 **(79.4%)**	**0.004**
Deaths	4 **(2.5%)**	8 **(10.2%)**	
Refractory	-	1 **(1.3%)**	
Off-treatment	5 **(2.8%)**	7 **(8.9%)**	

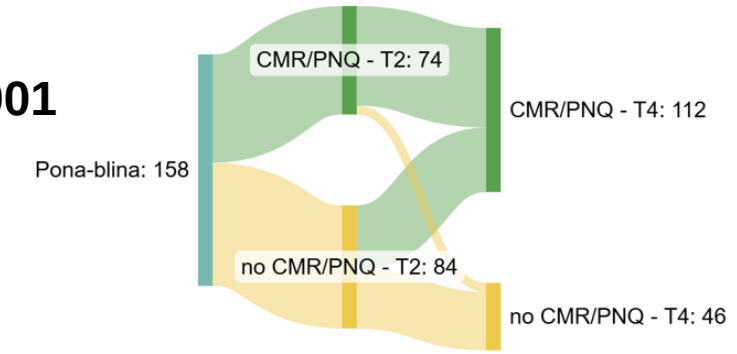
GIMEMA ALL2820. Molecular responses by ITT

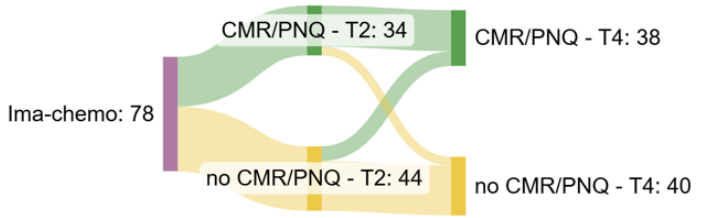
Experimenal arm (n=158)	No molecular responses (%)	CMR	PNQ	Overall molecular responses (%)	D-ALBA (n=63):	Overall molecular responses (%)
End of induction	84 (53.2)	48 (30.4)	26 (16.5)	**74 (46.8)**	End of induction	**17 (26.9)**
After 2 blina cycles	46 (29.1)	82 (51.9)	30 (19)	**112 (70.9)**	After 2 blina cycles	**33 (52.4)**
Control arm (n=78)						
End of induction	44 (56.4)	28 (35.9)	6 (7.7)	**34 (43.6)**		
After 4/6 CHT cycles*	40 (51.3)	29 (37.2)	9 (11.5)	**38 (48.7)**		

*Depending on age

***p*= ns**

***p*= <0.001**





GIMEMA ALL2820. Crossover to blinatumomab + ponatinib

31 patients underwent the crossover:

- 1 for refractoriness
- 3 early during consolidation for mutations development early during phases

20 patients achieved a MRD negativity (15 after the 1st and 5 after the 2nd cycle)

A single death due to general conditions deterioration recorded in a 74-year old patient

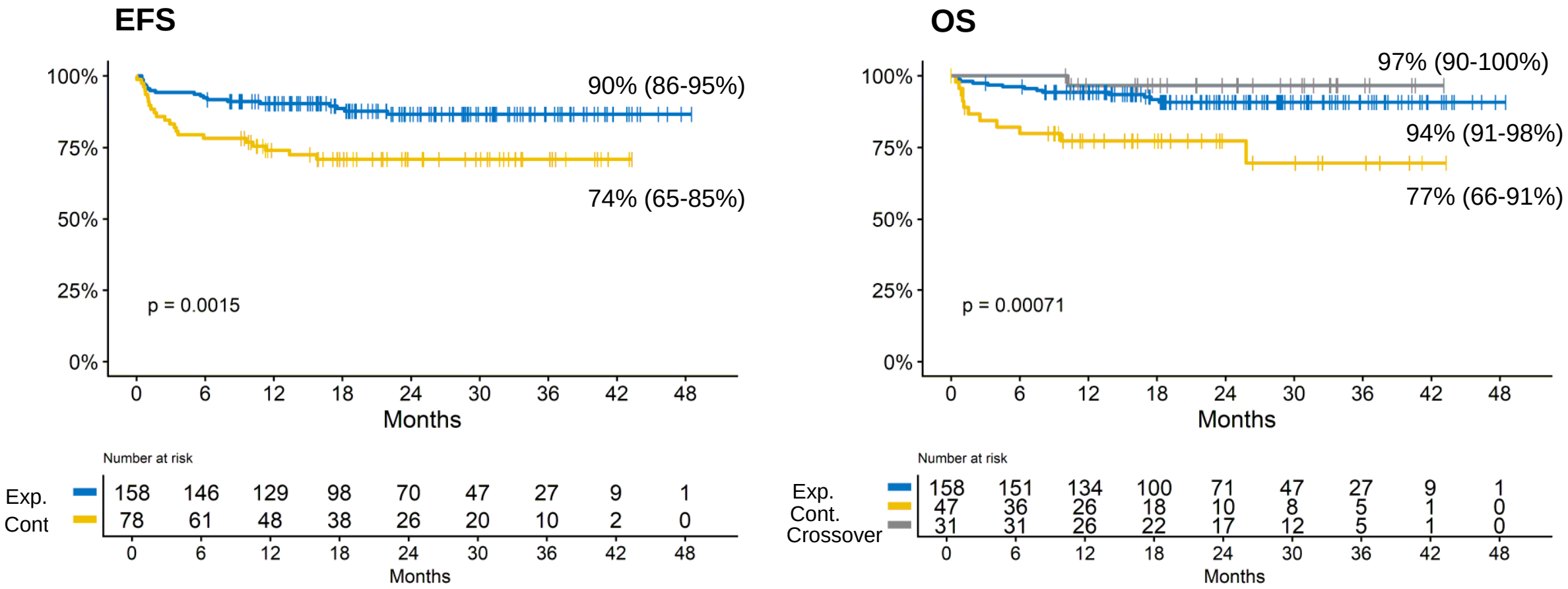
14 patients underwent a subsequent allo-SCT

- Median age (range): 51 (20.5-75.9), 7 >65 years)
- Median WBC: 18.9 $x10^9$/l
- p190/p210: 17/14
- *IKZF1*^{plus}: 9 (29%)

GIMEMA ALL2820. Transplant

	Experimental arm (n=30)	Control arm (n=15)
Ist CHR	30	12
IInd CHR	-	3
Median age (range)	49 (20-66)	47.07 (20-62)
Median WBC x 10^9/l (range)	25.2 (1-244)	18.7 (2.8-73)
IKZF1^{plus}	15	6
EOI MRD+	24	8
After 2 blina cycles MRD+	18	10
IKZF1^{plus}+ MRD+ at both time points	6	3

GIMEMA ALL2820. EFS and OS



Median follow-up: 23.4 months (0.1- 48.5)

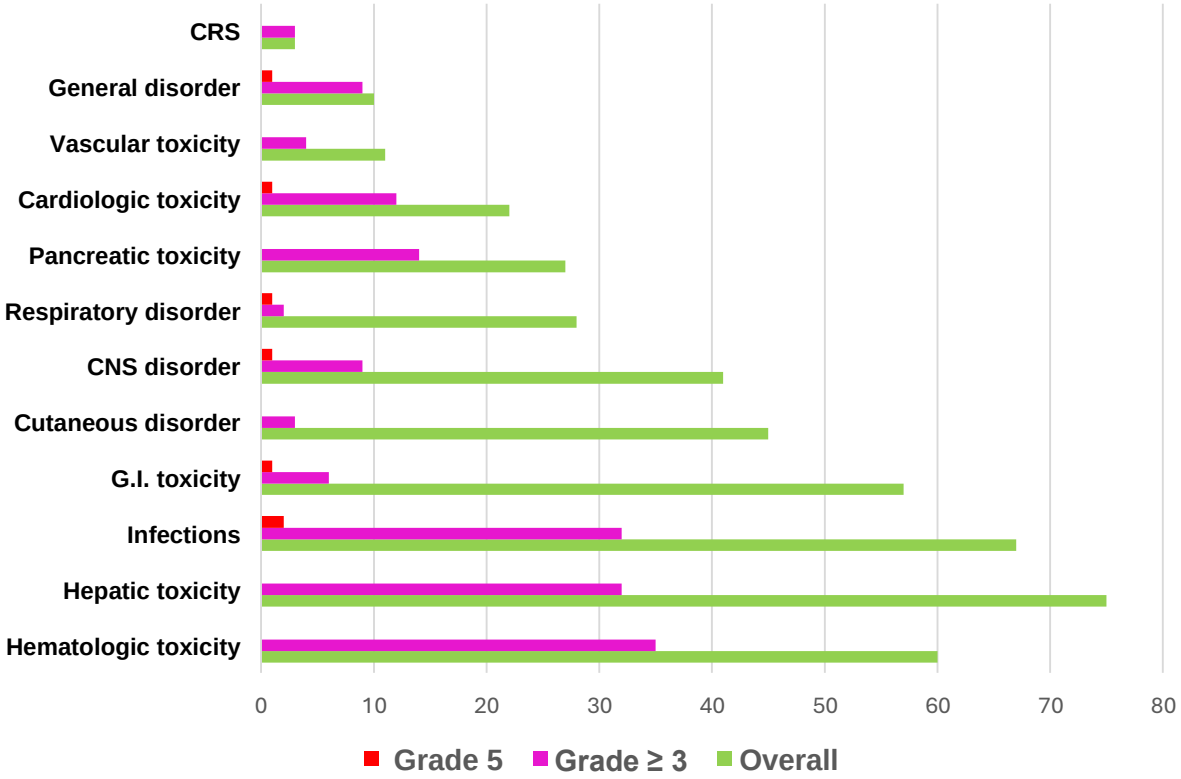
GIMEMA ALL2820. Toxicity

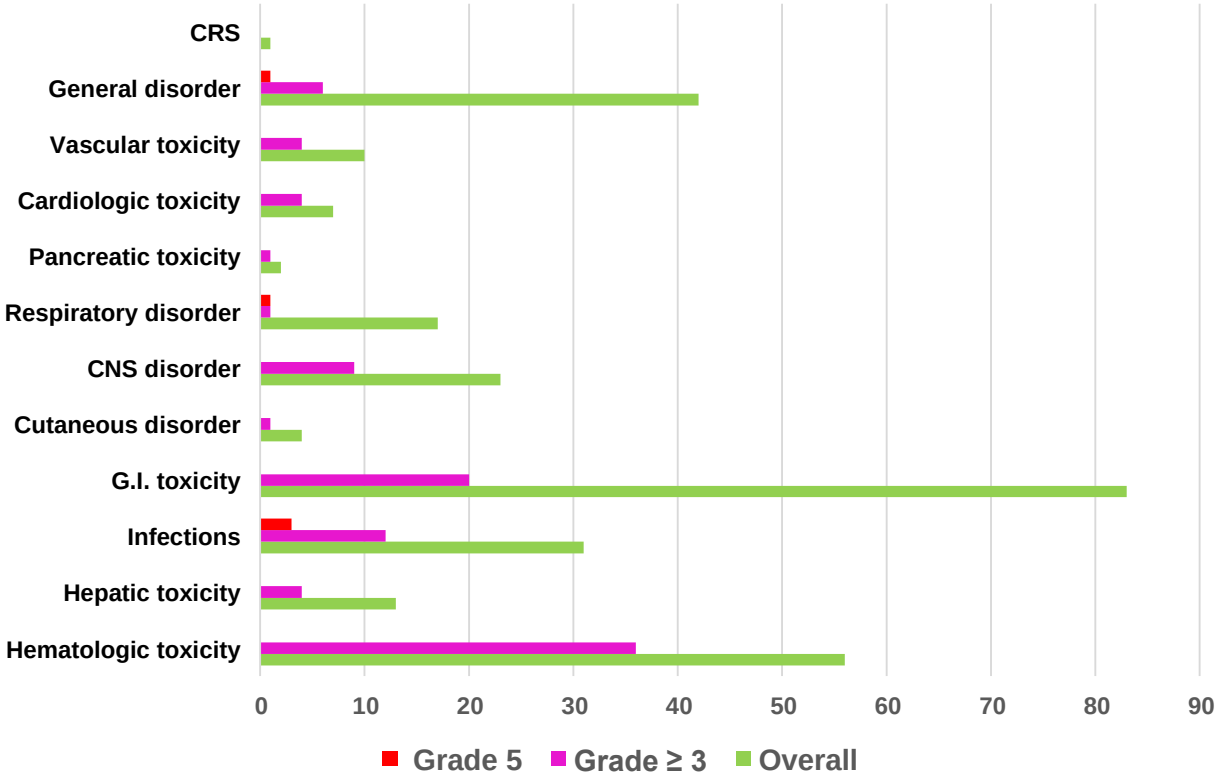
Experimental arm (n=158)

590 AEs overall in 109 pts (68.9%), 171 of grade ≥3 in 85 pts (53.8%); 96 SAEs in 49 pts (27.5%)

Control arm (n=78)

354 AEs overall in 53 pts (67.9%),121 grade ≥3 in 44 pts (56.4%); 54 SAEs in 34 pts (50%)





GIMEMA ALL2820. Conclusions

- The first results of the phase III GIMEMA ALL2820 trial show for the first time, in a head-to-head comparison, a significant advantage of a chemo-free, targeted/immunotherapeutic based approach over a TKI/chemotherapy strategy, with higher CHR and MRD responses, fewer deaths and improved EFS and OS.

- An increase in MRD negativity and less relapses have so far been observed compared to the D-ALBA trial.

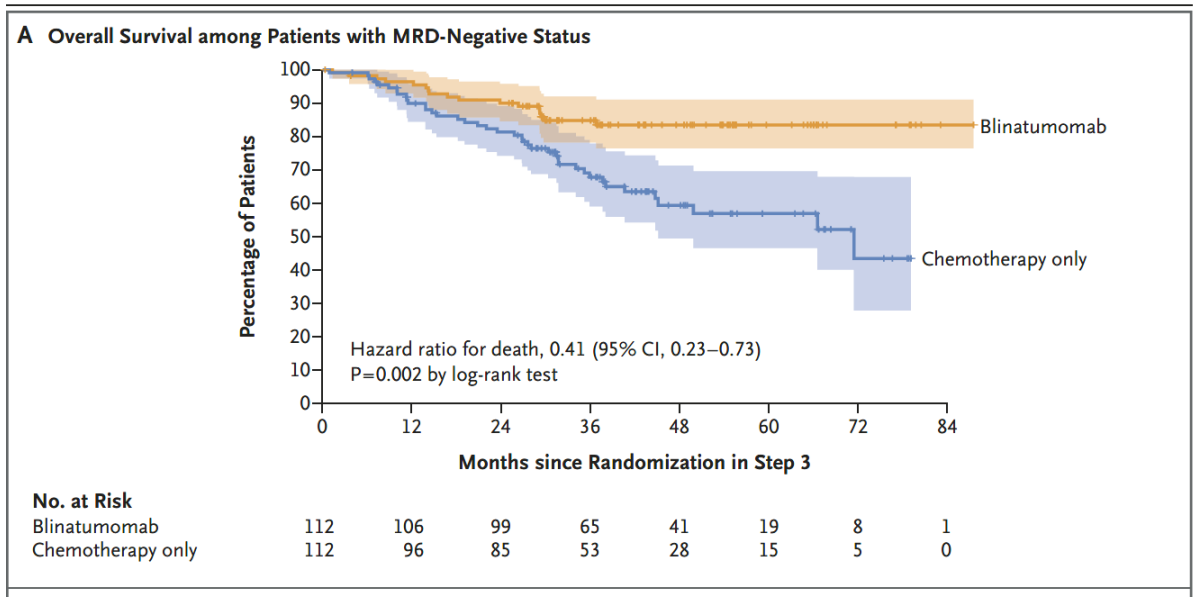
- A crossover is capable of rescuing MRD+ patients in the control arm.

- A biology-driven transplant allocation strategy appears to be feasible and effective.

ORIGINAL ARTICLE

Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults

M.R. Litzow, Z. Sun, R.J. Mattison, E.M. Paietta, K.G. Roberts, Y. Zhang, J. Racevskis, H.M. Lazarus, J.M. Rowe, D.A. Arber, M.J. Wieduwilt, M. Liedtke, J. Bergeron, B.L. Wood, Y. Zhao, G. Wu, T.-C. Chang, W. Zhang, K.W. Pratz, S.N. Dinner, N. Frey, S.D. Gore, B. Bhatnagar, E.L. Atallah, G.L. Uy, D. Jeyakumar, T.L. Lin, C.L. Willman, D.J. DeAngelo, S.B. Patel, M.A. Elliott, A.S. Advani, D. Tzachanis, P. Vachhani, R.R. Bhave, E. Sharon, R.F. Little, H.P. Erba, R.M. Stone, S.M. Luger, C.G. Mullighan, and M.S. Tallman

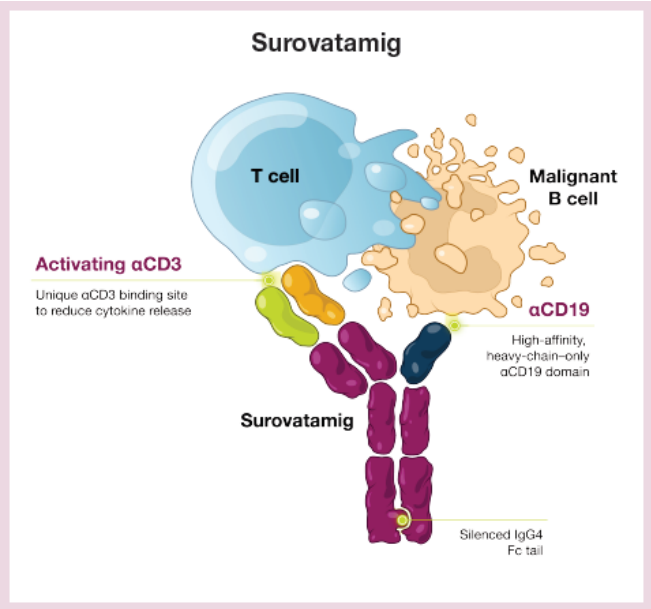


B Subgroup Analysis

Subgroup	Blinatumomab (no. of deaths/total no.)	Chemotherapy Only (no. of deaths/total no.)	Hazard Ratio for Death (95% CI)
All MRD-negative patients	17/112	40/112	0.41 (0.23–0.73)
Age			
<55 yr	4/66	21/65	0.16 (0.05–0.47)
≥55 yr	13/46	19/47	0.66 (0.33–1.35)
Combined molecular risk			
Favorable	0/19	6/28	0.00
Intermediate	2/22	5/19	0.32 (0.06–1.65)
Unfavorable	12/50	24/45	0.39 (0.19–0.78)
BCR::ABL1–like genotype			
BCR::ABL1–like	2/16	7/15	0.28 (0.06–1.36)
Not *BCR::ABL1*–like	15/96	33/97	0.40 (0.22–0.74)
Transplantation intended			
Yes	6/36	13/35	0.40 (0.15–1.05)
No	11/76	27/77	0.37 (0.18–0.75)
CD20 status			
Positive	7/45	16/46	0.43 (0.18–1.04)
Negative	1/26	7/26	0.13 (0.02–1.05)
Rituximab use			

Our practice is to incorporate blinatumomab in between cycles of C10403 regimen for 4 cycles (Tinajero J et al BJH 2025; 207: 426-31)

Safety and Efficacy of Surovatamig (AZD0486) in Adolescent and Adult Patients With Relapsed or Refractory (R/R) B-Cell Acute Lymphoblastic Leukemia (B-ALL): Updated Results From thePhase 1/2 SYRUS



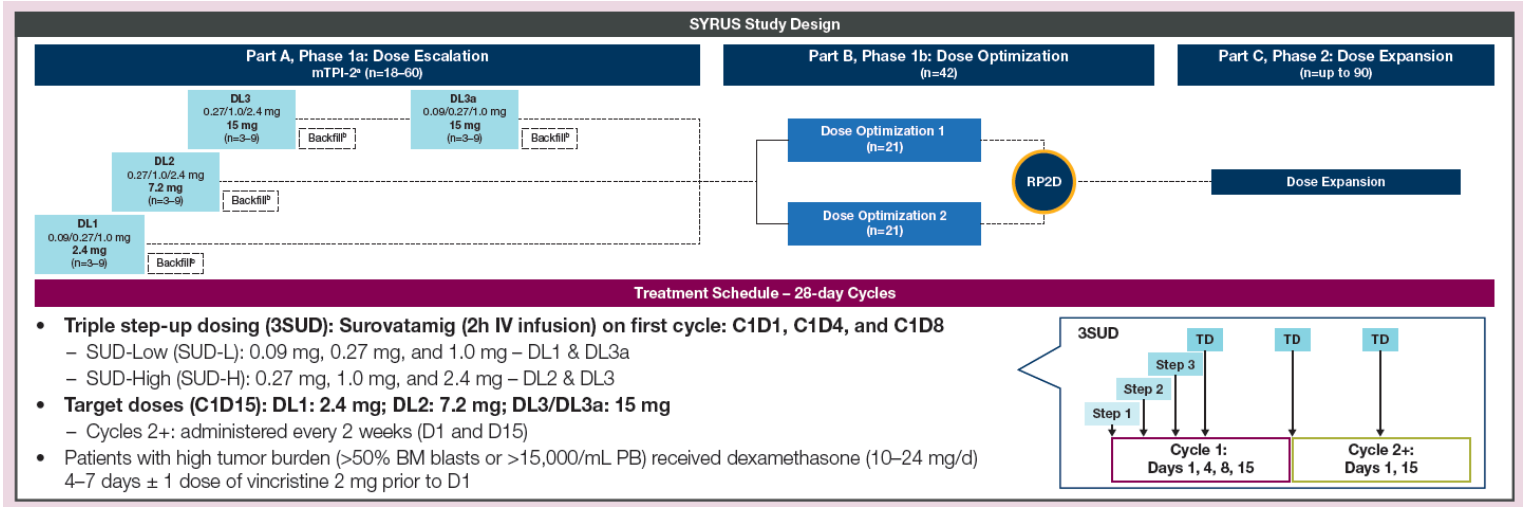


Table 3. Safety Summary

	All Patients (N=42)	
Any TEAEs	42 (100)	
Any related TEAEs	33 (79)	
AEs leading to dose interruption	11 (26)	
G3+ TEAEs	30 (71)	
G3+ related TEAEs	9 (21)	
TEAEs leading to death	4 (10)[a]	
Related TEAEs leading to death	0	
Any serious TEAEs	25 (60)	
Any related serious TEAEs	9 (21)	
Most Common AEs (≥15%)	**Any Grade**	**Grade 3+**
CRS	30 (71)	1 (2)
Neutropenia	14 (33)[b]	10 (24)[b]
ALT increased	12 (29)	3 (7)
Thrombocytopenia	11 (26)[b]	7 (17)[b]
Anemia	10 (24)[b]	6 (14)[b]
Leukopenia	8 (19)[b]	5 (12)[b]
AST increased	8 (19)	2 (5)
Pyrexia	8 (19)	0
Headache	7 (17)	1 (2)
ICANS	7 (17)	1 (2)

[a]Deaths were caused by sepsis (n=2), septic shock (n=1), and COVID-19 (n=1).
[b]Grouped terms reported.

Table 1. Demographics and Baseline Characteristics

Characteristic	Total (N=42)
Age, median (range), y	50 (17–77)
Female	17 (40.5)
Ph(+)	7 (17)
Median (range) prior therapies	3 (1–9)
Prior CD19 targeted therapy exposure	
Blinatumomab-exposed	22 (52)
CAR-T-exposed	17 (40)
Double-exposed[a]	13 (31)
Triple-exposed[b]	11 (26)
Prior allo-SCT	18 (43)
Mean (range) BM blasts, %	55 (3–97)
>50% BM blasts	25 (60)
Extramedullary disease	11 (26)

Values are n (%) unless otherwise specified.
[a]Resistant and/or exposed to blinatumomab and CAR-T therapy.
[b]Resistant and/or exposed to blinatumomab, CAR-T, and inotuzumab ozogamicin.

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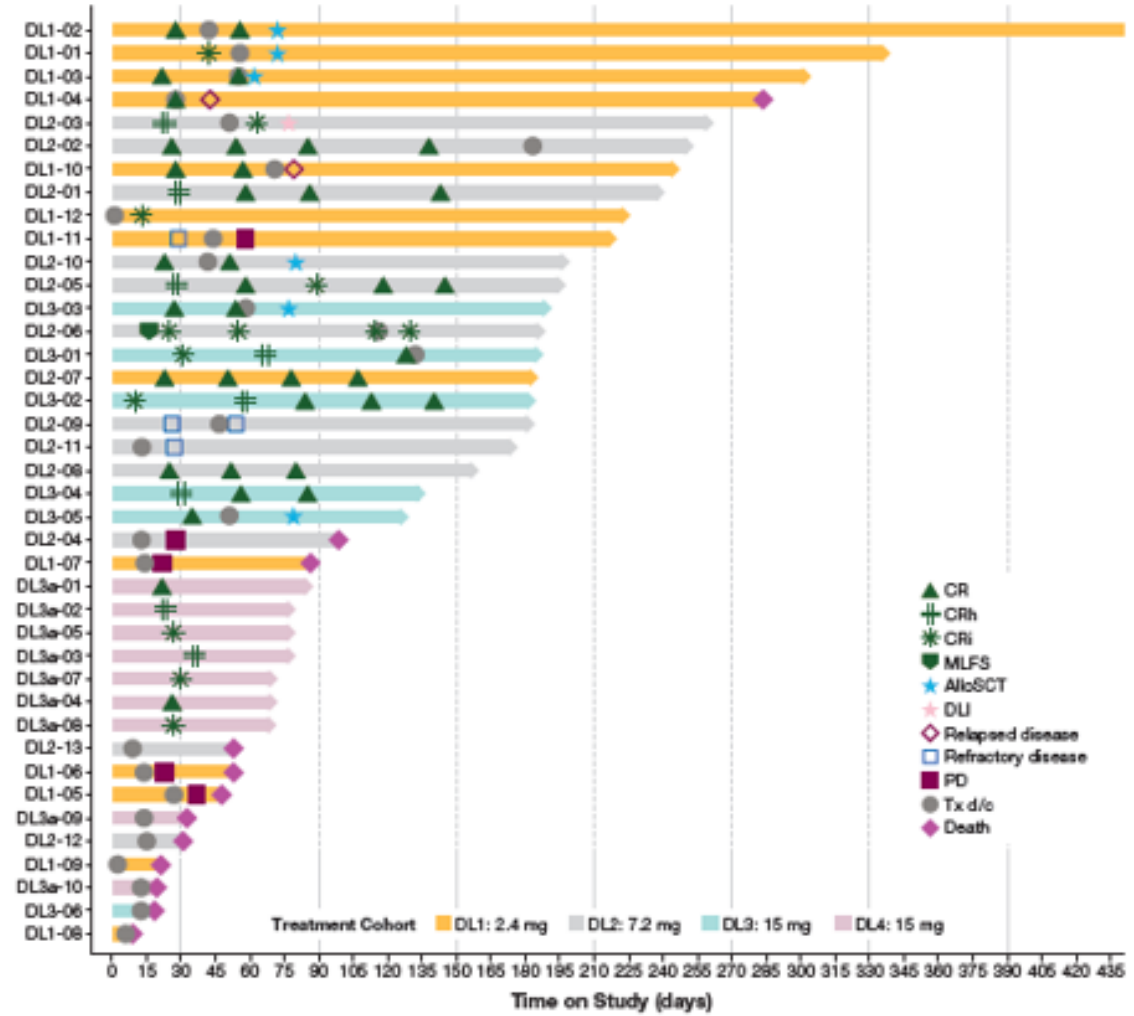
Table 2. Summary of ORR, Overall and by Prior Therapy

Response, n/N (%)	TD: 2.4 mg (n=13)	TD: 7.2 mg (n=12)	TD: 15 mg (n=17)
ORR[a] (CR/CRh/CRi) (ITT)	7/13 (54)	7/12 (58)	14/17 (82)
CR/CRh/CRi MRDneg (local flow 10^{-4})	5/6 (83)	7/7 (100)	13/14 (93)
Disease relapse[a]	3/6 (50)	0/7 (0)	0/14 (0)
ORR[a] by prior therapy subgroup[b,c]			
Blinatumomab-exposed	4/9 (44)	1/4 (25)	7/9 (78)
CAR-T-exposed	1/3 (33)	2/3 (67)	8/11 (73)
Double-exposed	1/3 (33)	1/2 (50)	6/8 (75)
Triple-exposed (+inotuzumab)	0/2 (0)	1/2 (50)	6/7 (86)
ORR[a] in patients with EMD	2/2 (100)	2/2 (100)	5/5 (100)
ORR[a] in patients with Ph+ disease	2/2 (100)	1/2 (50)	3/3 (100)

[a]Among patients with CR/CRh/CRi within 3 cycles.
[b]Median follow-up: 97 days (range 35–401).
[c]Prior therapy subgroups are not mutually exclusive.

Figure 1. Swimmer Plot of Response to Surovatamig (All Patients)



443 CD19-CAR T cell therapy as a definitive consolidation in older adults with B-ALL in CR1 is safe and induces durable MRD- remission

Ibrahim Aldoss, Xiuli Wang, Jianying Zhang, Min Guan, Ruby Espinosa, Mary C Clark, Vaibhav Agrawal, Andrew Artz, Neguine Sanani, Lior Goldberg, Cashmir Gephart, Stephanie Kasten, Dileshni Tilakawardane, Jamie R Wagner, Jinny Paul, Paul Koller, L Elizabeth Budde, Anthony S. Stein, Vinod Pullarkat, Amandeep Salhotra, Ahmed Aribi, Guido Marcucci and Stephen J. Forman

Study Design

- Safety lead-in = 6 pts at RP2D (200M)
- If DLT ≤ 1/6, then the expansion cohort opens with additional 12 pts
- Ph+ pts are allowed to receive post CAR-T TKI maintenance starting day 60
- A minimum of 4 IT chemo is required pre-LD as post CAR T IT chemo was prohibited

Eligibility

- CD19+ B-ALL
- ≥ 55 years old
- ECOG <2
- Achieved CR1

➢ No immediate plans for HCT

Exclusion

- Relapsed disease
- CNS pathology
- Active infection
- Steroids and IS

Primary objectives

- Safety
- RP2D

Secondary objectives

- Feasibility
- EFS,OS
- QOL
- T cell persistence
- Immunogenicity

Patient and Disease Characteristics

Enrolled patients = 18

	Number (%)
Median age (range), years	**64 (55-79)**
Gender	
Male	11 (61)
Female	7 (39)
Race	
White	8
Hispanic	6
African American	1
Asian	3
Median time from ALL diagnosis to Leuk (range), months	4.7 (2.4- 9)
Median number of pre-LD IT chemo (range)	7 (5-10)
Negative pre-LD MRD status	18 (100)
Disease genetics	
Ph+	6
NOS	5
Hypodiploidy/*TP53*m	2
Ph-like	2
KMT2Ar	1
ZNF384::EP300	1
TCF3::PBX1	1
Prior blinatumomab	**15 (83)**
Prior inotuzumab	2 (11)

Treatment Emergent Adverse Events

(n= 18)

Most common TEAEs any grade ≥ 20%

AEs	N	%
Neutropenia	18	100
Lymphopenia	17	94.4
Leukopenia	17	94.4
Anemia	15	83.3
CRS	**13**	**72.2**
Anorexia	13	72.2
Nausea	13	72.2
Thrombocytopenia	11	61.1
Fatigue	11	61.1
Fever	11	61.1
HyperTG	5	27.8
Chills	5	27.8

TEAEs grade ≥ 3

AEs	N	%
Neutropenia	18	100
Lymphopenia	17	94.4
Leukopenia	17	94.4
Anemia	7	38.9
Thrombocytopenia	5	27.8
Febrile neutropenia	2	11.1

CAR T-Cell Therapy Demonstrates a Favorable Safety Profile in Older Adults in MRD- CR1

- No DLT was observed
- Grade 1 CRS= 13 (72%)
- **Grade ≥2 CRS= 0**
- **Any grade ICANS= 0**

R/R B-ALL study (same product/dose)
- **CRS grade ≥2 = 70%**
  - G3= 7%
- **Neurotoxicity (any grade) = 78%**
  - G≥3= 17%

- **Cytopenia**
  - Median time for ANC ≥1000 K/uL post CAR was 11 (6-86) days
  - Median time for platelet > 100 K/uL post CAR was 5 (0-461) days

- **No death on the study has been reported as the date of data cut off**

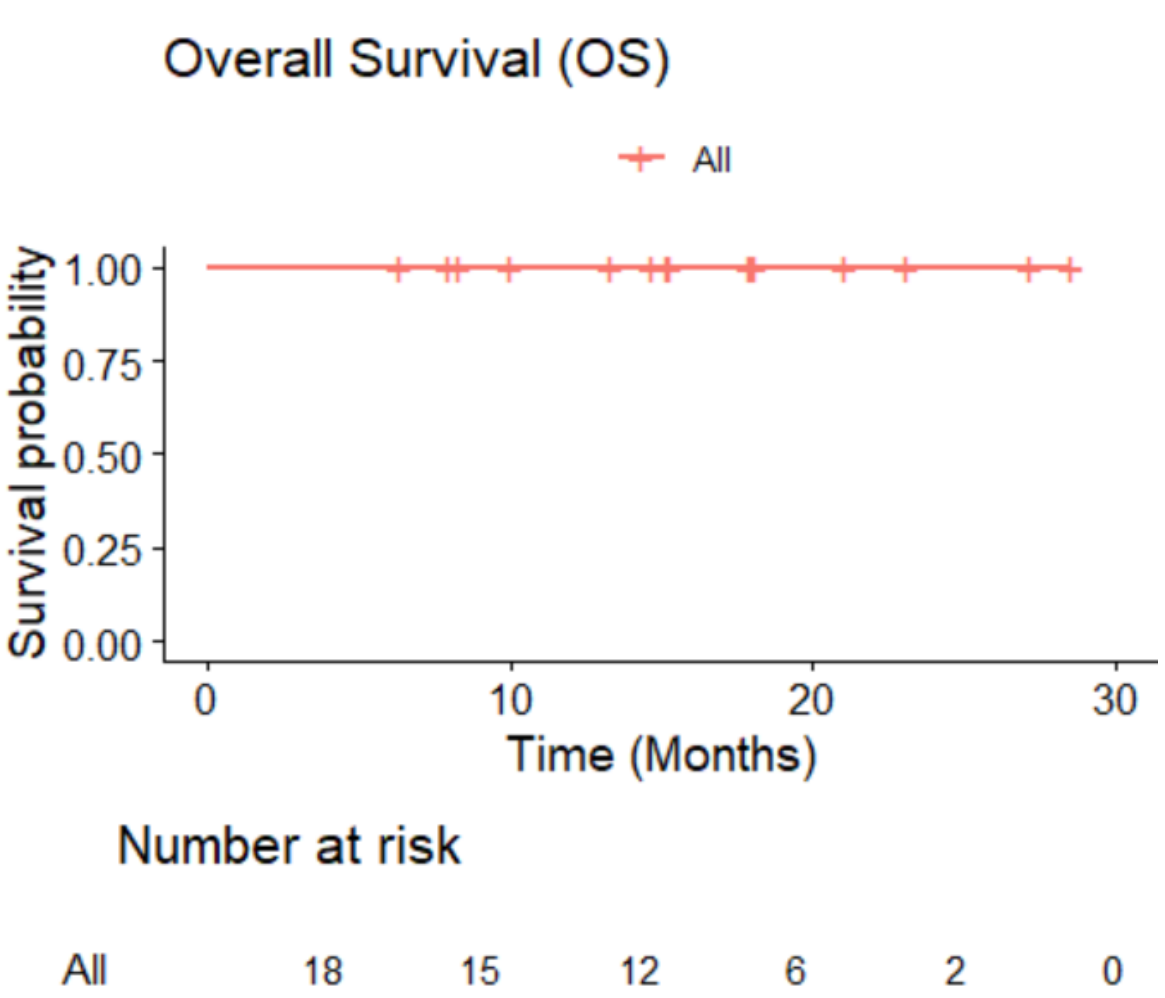
Aldoss I et al. Clin Cancer Res. 2023

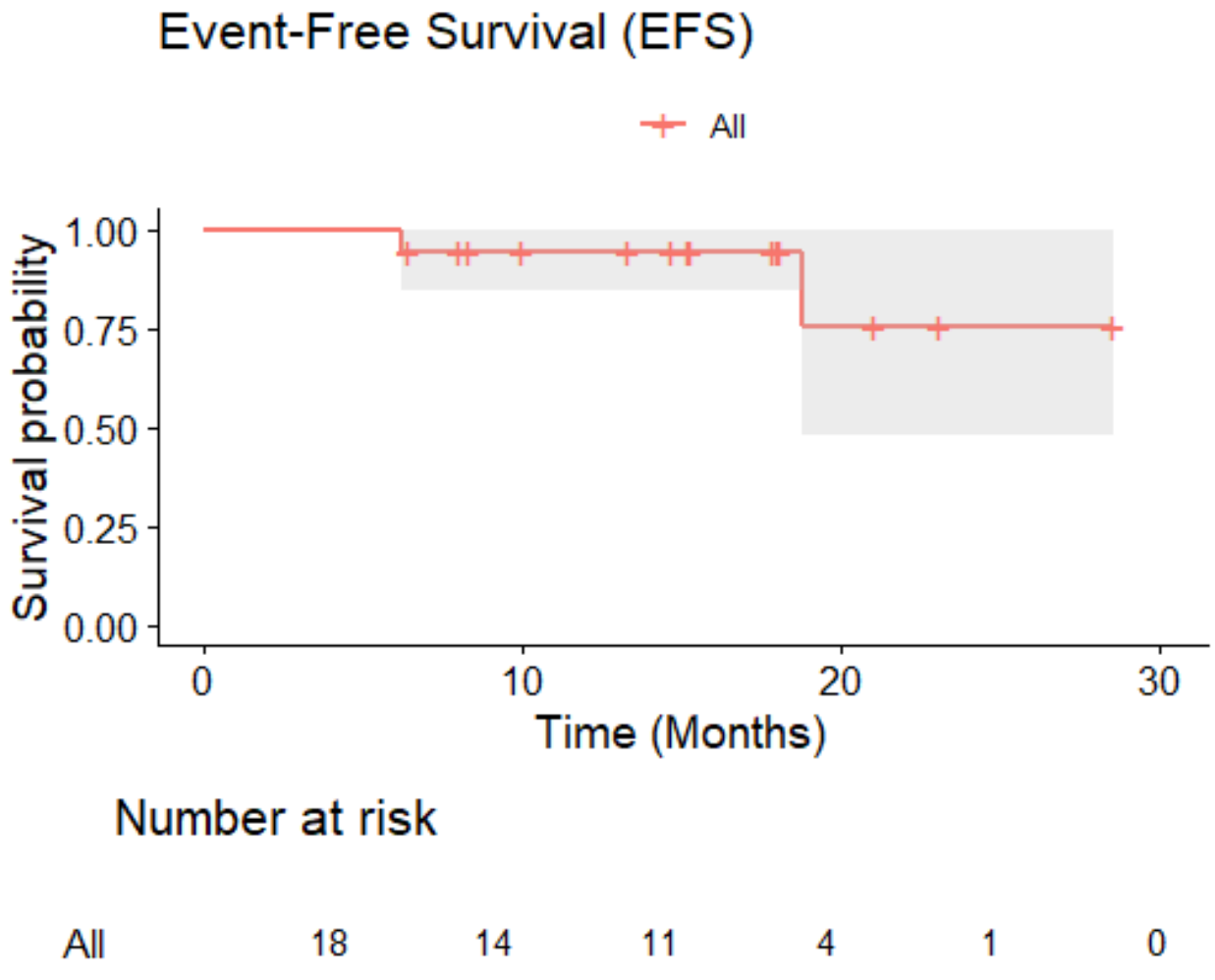
CAR T Cells Produced Durable MRD- Remissions

- **Median follow up= 18 months** (range: 6.4-28.6)
  - **1-year EFS= 94% (84%-100%)**
  - **1-year OS= 100%**

- The first patient with Ph- ALL is >2.5 years post CAR and remain in MRD-CR1 without intervention as of last follow up

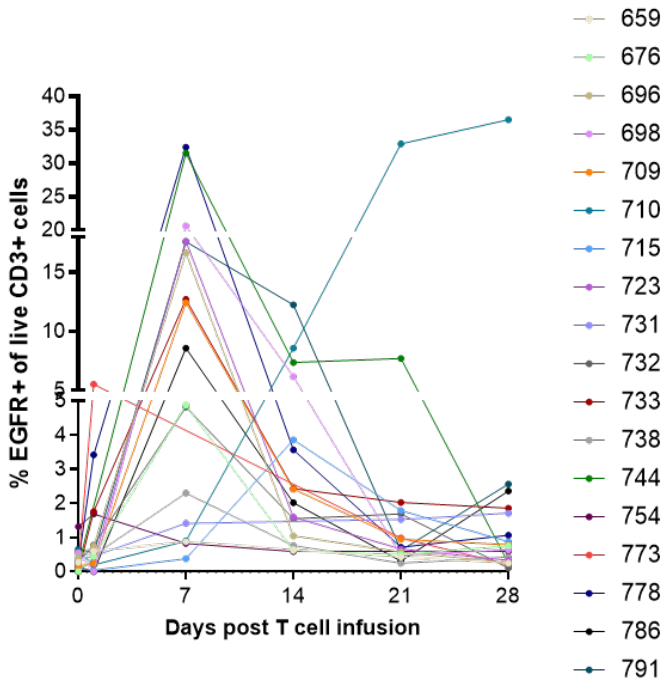
Survival outcomes



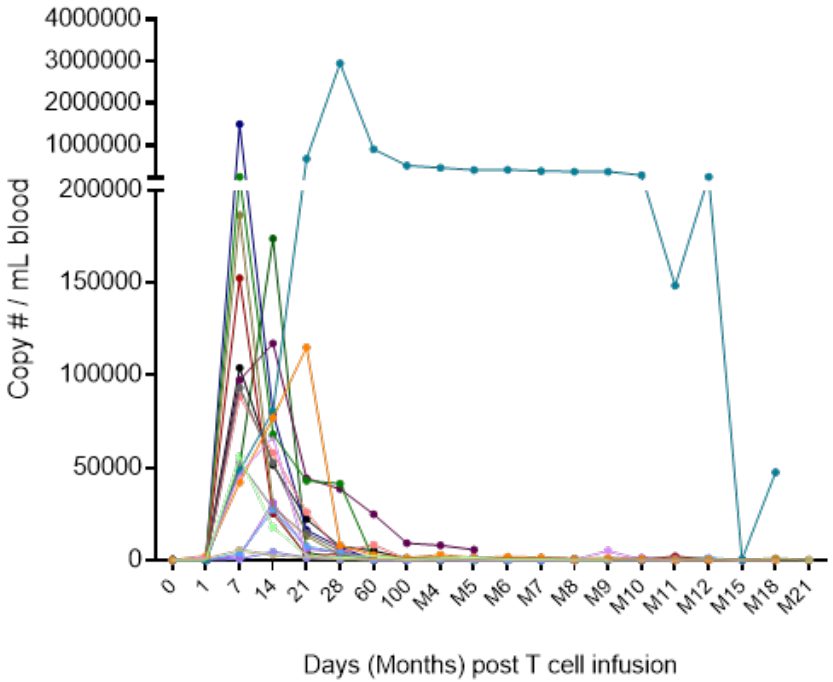


CAR T Cells Demonstrate Sufficient Expansion in the Low-Antigen Setting (MRD-)

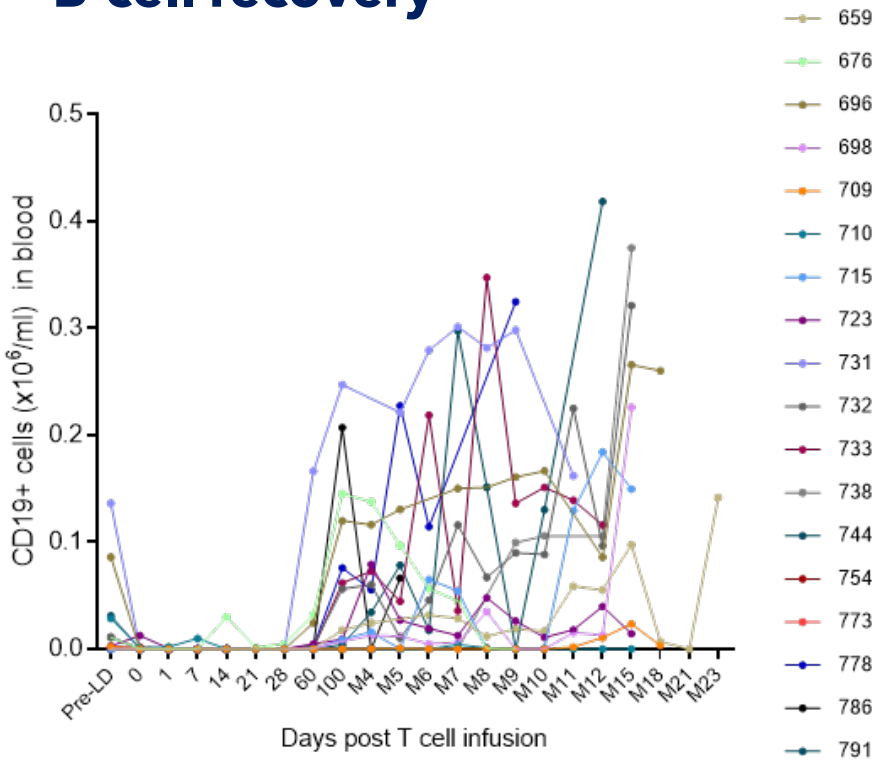
CAR T cell expansion



CAR T cell persistence



B-cell recovery



Conclusions

- CAR T cells administered to older adults with B-ALL in MRD- CR1 is safe
  - No ICANS or grade ≥2 CRS
- CAR T cells expanded sufficiently in low antigen setting (clonoSEQ-state, B-cell aplasia)
  - CAR T cells were detected in the CSF
- Preliminary results indicate ongoing MRD- remission post infusion in the majority of patients
  - Short follow up

ALL Key practice points

- **Lite induction only for Ph positive ALL (TKI, steroid, VCR)**
- **Incorporate blinatumomab in frontline regimens**
- **Optimize asparaginase for age, BMI and ideally monitor level**
- **Follow MRD kinetics to determine need for HSCT (preferably by clonoseq)**
- **Refer early for HSCT/CART (CD19 negative relapses can occur with blinatumomab use in the R/R setting)**

Thank You

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