



LAL e LAM : DAY

Stato dell'arte delle Leucemie Acute

ED. CENTRO

31 marzo 2026 Roma

ALL Ph'-negativa DALLA DIAGNOSI ALLA MALATTIA REFRATTARIA

Sara Galimberti – Ematologia Pisa

Where?

Special Report

Diagnosis, prognostic factors, and assessment of ALL in adults: 2024 ELN recommendations from a European expert panel

Nicola Gökbuget,¹ Nicolas Boissel,² Sabina Chiaretti,³ Hervé Dombret,⁴ Michael Doubek,⁵ Adele Fielding,⁶ Robin Foà,³ Sebastian Giebel,⁷ Dieter Hoelzer,¹ Mathilde Hunault,⁸ David I. Marks,⁹ Giovanni Martinelli,¹⁰ Oliver Ottmann,¹¹ Anita Rijneveld,¹² Philippe Rousselot,¹³ Josep Ribera,¹⁴ and Renato Bassan¹⁵

Special Report

Management of ALL in adults: 2024 ELN recommendations from a European expert panel

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Adult Acute Lymphoblastic Leukemia: 2025 Update on Diagnosis, Therapy, and Monitoring

Hagop Kantarjian
Elias Jabbour



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Acute Lymphoblastic Leukemia

Version 2.2025 — June 27, 2025

How I Treat Series

ACUTE LYMPHOBLASTIC LEUKEMIA

How I treat older patients with Ph/BCR-ABL–negative acute lymphoblastic leukemia

Nicola Gökbuget and Björn Steffen

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31 marzo 2026 **Roma**

AGENDA

1.Diagnosis: new entities

2.First line therapy

3.R/R pts: Antibodies & CAR-T: efficacy, adverse events and economic burden

4.The future



LAL e LAM : DAY

Stato dell'arte delle Leucemie Acute

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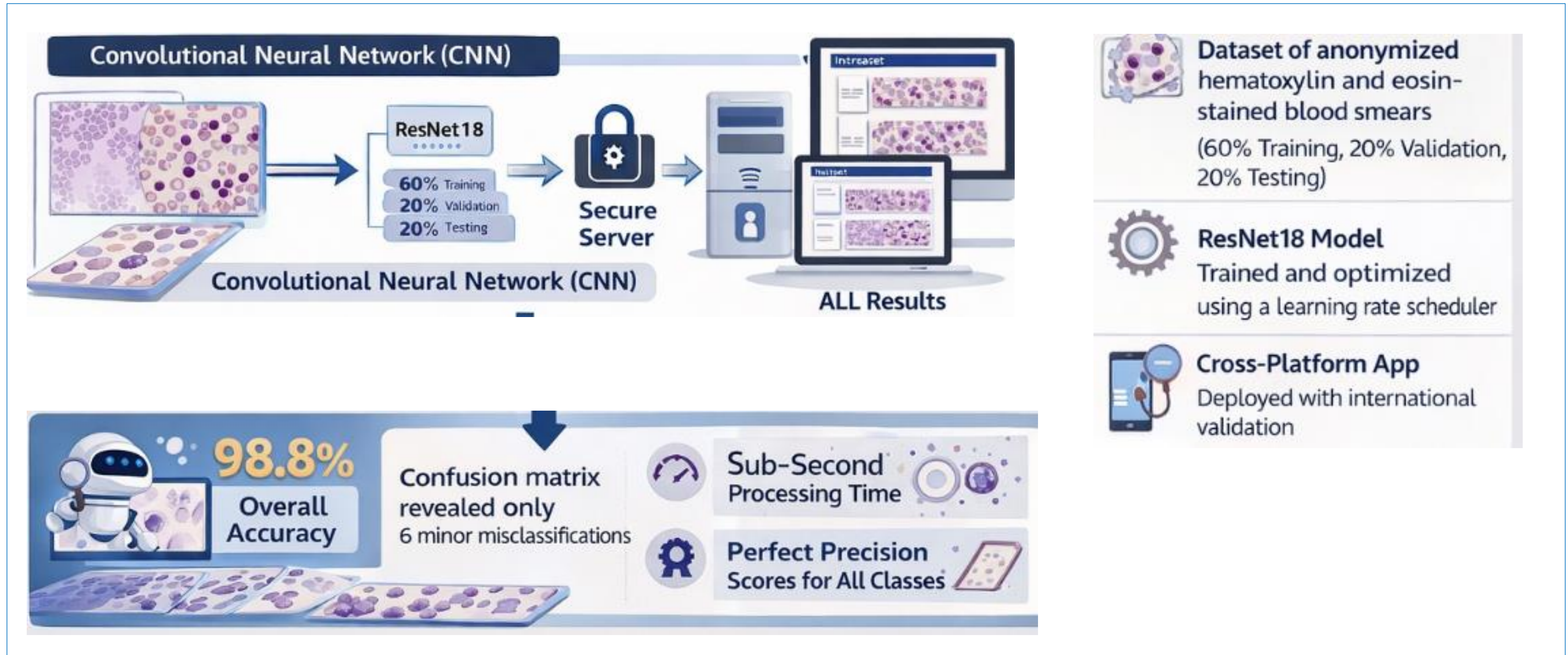
31 marzo 2026 Roma

1. DIAGNOSIS

ELN guidelines 2024

	Recommendation	Outputs
Morphology	Mandatory	Defines infiltration (>25% required for a diagnosis of ALL vs lymphoblastic lymphoma) Allows a differential diagnosis with AML (MPO ⁻ vs + MPO ⁺) Recognizes L3 (Burkitt-type) subsets
Flow cytometry	Mandatory	Allows a differential diagnosis with AML Permits to define the cell of origin Permits to define the stage of differentiation
MPO*	Mandatory	Allows a differential diagnosis with AML.
B-lineage ALL*: CD19, cCD79a, c/sCD22 (minimal requirement), TdT, CD10, CD20, clgM, slg (kappa or lambda)	Mandatory	Pro-B: CD19/CD79a/cCD22 ⁺ /CD10 ⁻ (B-I), NG2 Common: CD10 ⁺ /clgM ⁻ (B-II) Pre-B: clgM ⁺ /slg ⁻ (B-III) Mature: slg ⁺ (B-IV), CD20 ⁺
T-lineage ALL*: c/sCD3, CD7 (minimal requirement), TdT, CD1a, CD2, CD5, CD4, CD8, TCR α/β or γ/δ	Mandatory	Pro-T: cCD3/CD7 ⁺ (T-I) Pre-T: CD2/CD5 ⁺ (T-II) Cortical-T: CD1a ⁺ (T-III) Mature-T: sCD3 ⁺ /CD1a ⁻ (T-IV)

DIAGNOSIS: the use of AI



DIAGNOSIS: the use of AI

➤ **Develop EfficientNetB1 AI Model**

➤ **Classify ALL subtypes:**

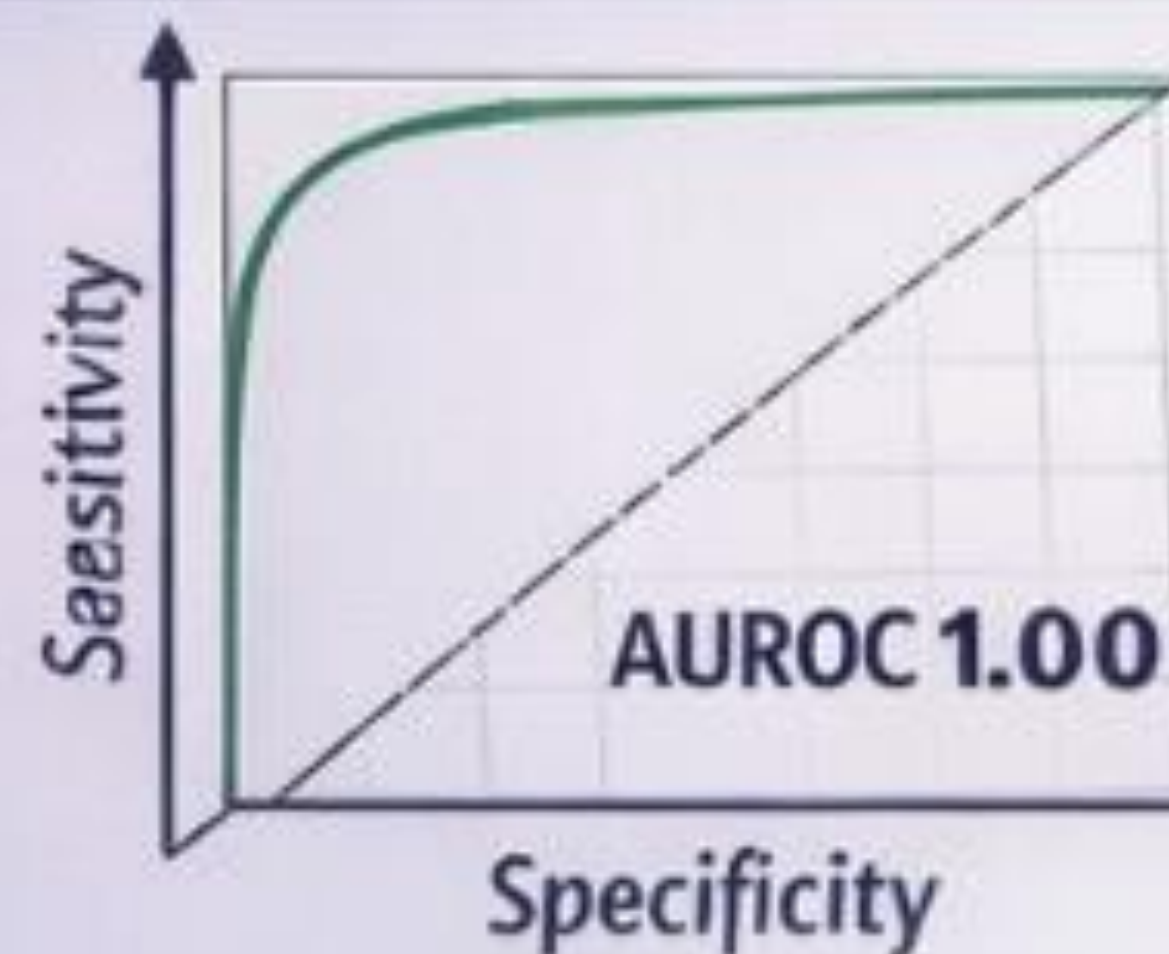
Early Pre-B,
Pre-B, Pro-B



- **Instant & Reliable Results**
- **Eliminates Observer Bias**
- **Point-of-Care Diagnostics**

Perfect Accuracy

100% (2,436 / 2,436) ✓



ELN guidelines 2024

Molecular genetics	Mandatory	t(9;22)/Ph ⁺ /BCR::ABL1 t(4;11) ⁺ /KMT2Ar t(1;19) ⁺ /TCF3::PBX1 Other high-risk cytogenetics
MRD (molecular or MFC)	Mandatory	Individual MRD assay for further follow-up
Extended genomics (GEP, CNA, WES, WGS, NGS)	In clinical trials and for research purposes	Identification of novel subgroups with prognostic/biologic significance Identification of molecular targets for targeted therapies

NCCN guidelines 2025

MOLECULAR CHARACTERIZATION

- Cytogenetic and molecular prognostic risk stratification for B-cell ALL (B-ALL) ([ALL-2](#))
- Optimal risk stratification and treatment planning require testing marrow or peripheral blood lymphoblasts for specific recurrent genetic abnormalities using:
 - ▶ Interphase fluorescence in situ hybridization (FISH) testing, including probes capable of detecting the major recurrent genetic abnormalities
 - ▶ Reverse transcriptase polymerase chain reaction (RT-PCR) testing for *BCR::ABL1* in B-ALL, including determination of transcript size (ie, p190 vs. p210)
 - ▶ Comprehensive testing by next-generation sequencing (NGS) for gene fusions and pathogenic mutations is recommended.
- Additional optional tests include:
 - ▶ Assessment with chromosomal microarray (CMA)/array comparative genomic hybridization (cGH) in cases of aneuploidy or inadequate karyotype.

CLASSIFICATION

Together, these studies allow determination of the World Health Organization (WHO) and International Consensus Classification (ICC) ALL subtypes and cytogenetic and clinical risk groups.

WHO classification 2022

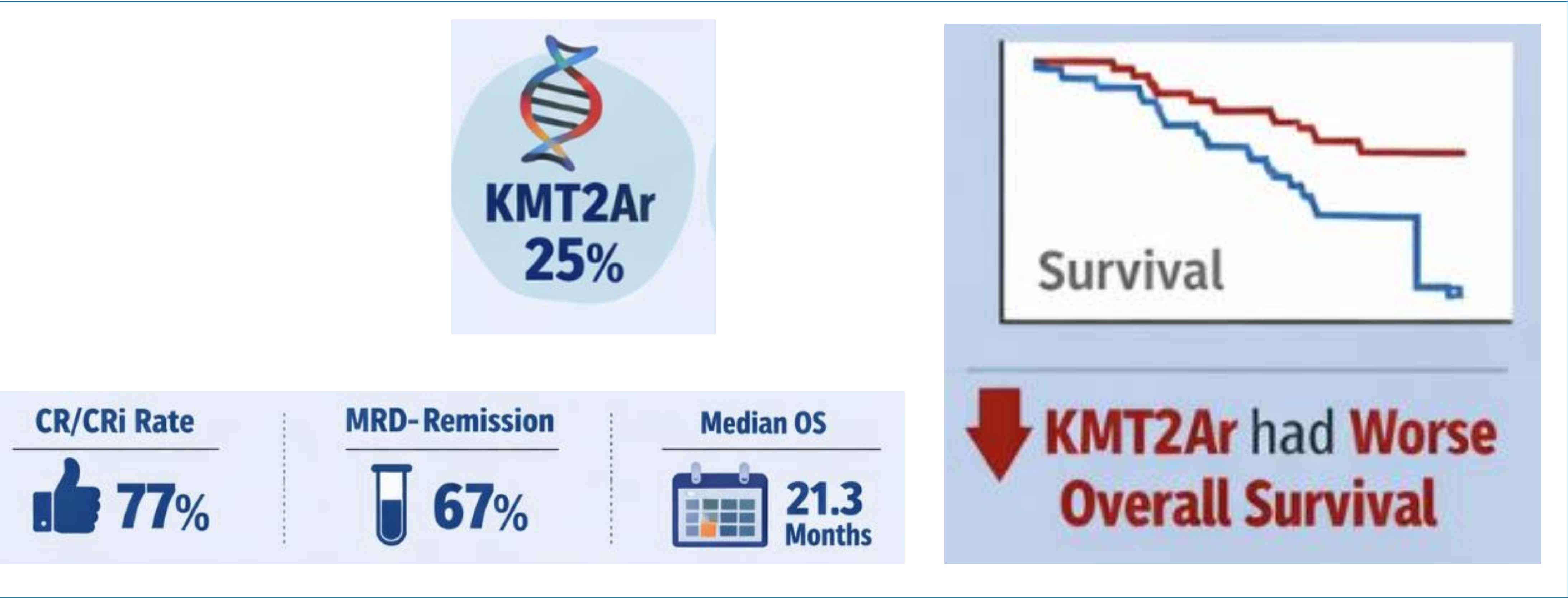
Precursor B-cell neoplasms	
<i>B-cell lymphoblastic leukaemias/lymphomas</i>	
B-lymphoblastic leukaemia/lymphoma, NOS	(Same)
B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy	B-lymphoblastic leukaemia/lymphoma with hyperdiploidy
B-lymphoblastic leukaemia/lymphoma with hypodiploidy	(Same)
B-lymphoblastic leukaemia/lymphoma with iAMP21	(Same)
B-lymphoblastic leukaemia/lymphoma with <i>BCR::ABL1</i> fusion	B-lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); <i>BCR-ABL1</i>
B-lymphoblastic leukaemia/lymphoma with <i>BCR::ABL1</i> -like features	B-lymphoblastic leukaemia/lymphoma, <i>BCR-ABL1</i> -like
B-lymphoblastic leukaemia/lymphoma with <i>KMT2A</i> rearrangement	B-lymphoblastic leukaemia/lymphoma with t(v;11q23.3); <i>KMT2A</i> -rearranged
B-lymphoblastic leukaemia/lymphoma with <i>ETV6::RUNX1</i> fusion	B-lymphoblastic leukaemia/lymphoma with t(12;21)(p13.2;q22.1); <i>ETV6-RUNX1</i>
B-lymphoblastic leukaemia/lymphoma with <i>ETV6::RUNX1</i> -like features	<i>Not previously included</i>
B-lymphoblastic leukaemia/lymphoma with <i>TCF3::PBX1</i> fusion	B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); <i>TCF3-PBX1</i>
B-lymphoblastic leukaemia/lymphoma with <i>IGH::IL3</i> fusion	B-lymphoblastic leukaemia/lymphoma with t(5;14)(q31.1;q32.1); <i>IGH/IL3</i>
B-lymphoblastic leukaemia/lymphoma with <i>TCF3::HLF</i> fusion	<i>Not previously included</i>
B-lymphoblastic leukaemia/lymphoma with other defined genetic abnormalities	(Same)

NCCN guidelines & prognosis

CYTOGENETIC AND MOLECULAR PROGNOSTIC RISK STRATIFICATION FOR B-ALL^h

RISK GROUPS	CYTOGENETIC AND MOLECULAR ALTERATIONS
Standard risk	• Hyperdiploidy (51–65 chromosomes) ▶ Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome • t(12;21)(p13;q22): <i>ETV6::RUNX1</i>ⁱ • t(1;19)(q23;p13.3): <i>TCF3::PBX1</i> • <i>DUX4</i> rearranged • <i>PAX5</i> P80R • t(9;22)(q34;q11.2): <i>BCR::ABL1</i>^j without <i>IKZF1</i> plus^k and without antecedent chronic myeloid leukemia (CML)
Poor risk	• Hypodiploidy^{l,m} (<44 chromosomes) • Low hypodiploidy (30–39 chromosomes) • Near triploidy (60–78 chromosomes) • <i>TP53</i> mutationⁿ • <i>KMT2A</i> rearranged (t[4;11] or others) • <i>IgH</i> rearranged^o • <i>HLF</i> rearranged • <i>ZNF384</i> rearranged • <i>MEF2D</i> rearranged • <i>MYC</i> rearranged • <i>BCR::ABL1</i>-like (Philadelphia chromosome [Ph]-like) ALL ▶ JAK-STAT (<i>CRLF2</i>r,^p <i>EPOR</i>r, <i>JAK1/2/3</i>r, <i>TYK2</i>r, mutations of <i>SH2B3</i>, <i>IL7R</i>, <i>JAK1/2/3</i>) ▶ ABL class (rearrangements of <i>ABL1</i>, <i>ABL2</i>, <i>PDGFRA</i>, <i>PDGFRB</i>, <i>FGFR</i>) ▶ Other (<i>NTRK</i>r, <i>FLT3</i>r, <i>LYN</i>r, <i>PTK2B</i>r) • <i>PAX5alt</i> • t(9;22)(q34;q11.2): <i>BCR::ABL1</i>^j with <i>IKZF1</i> plus^k and/or antecedent CML • Intrachromosomal amplification of chromosome 21 (iAMP21) • Alterations of <i>IKZF1</i>^{k,q,r} • Complex karyotype (5 or more chromosomal abnormalities)

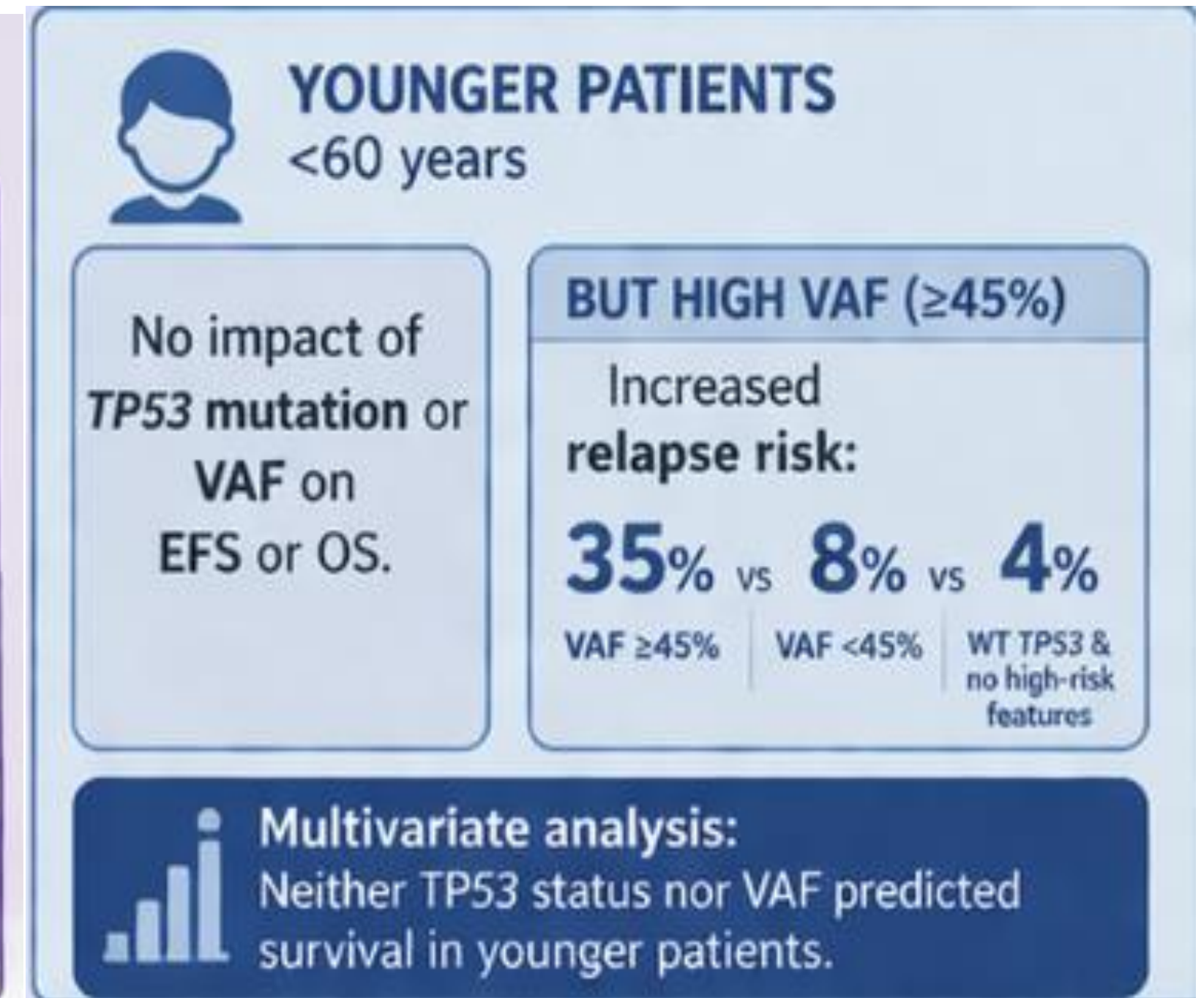
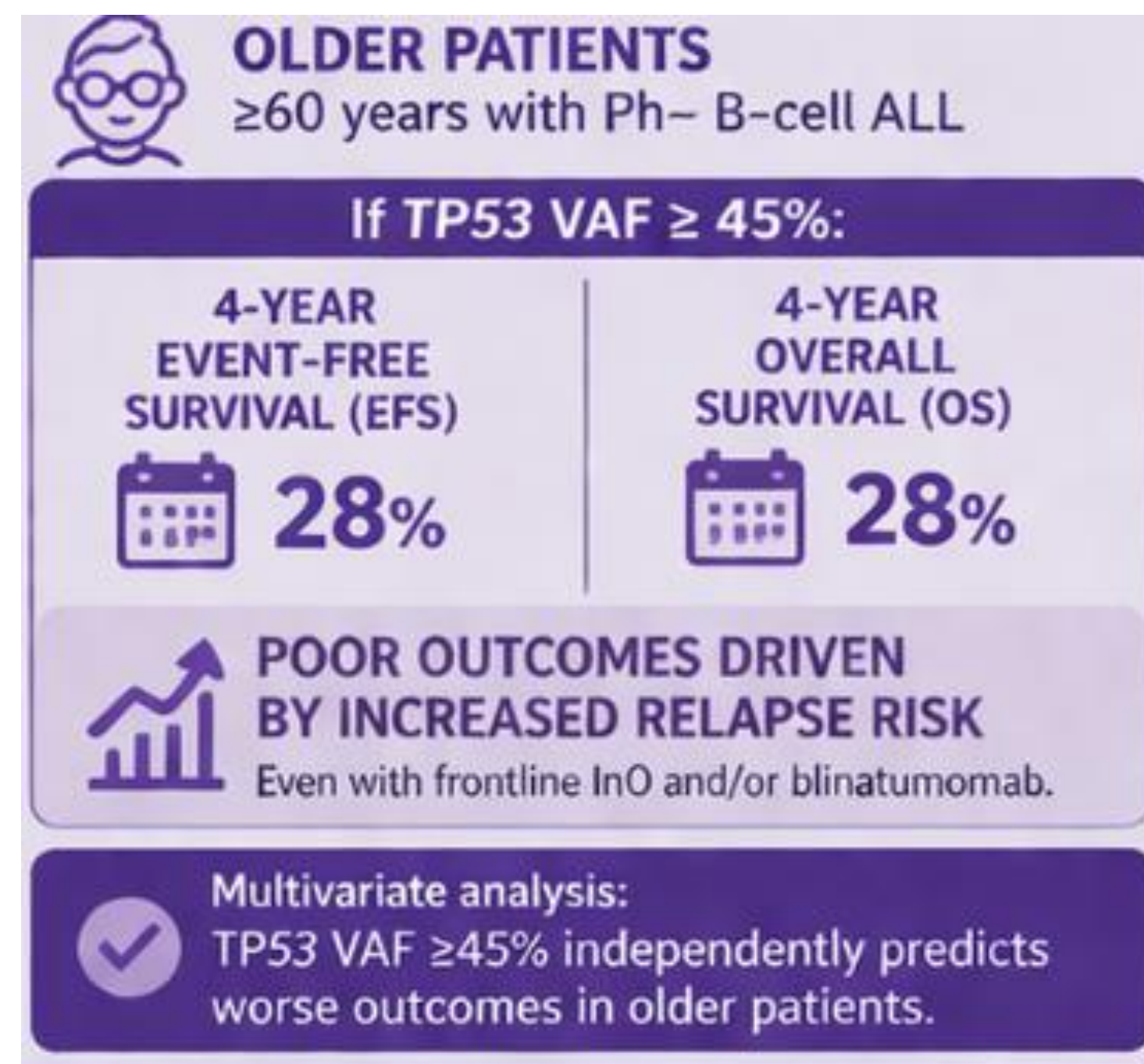
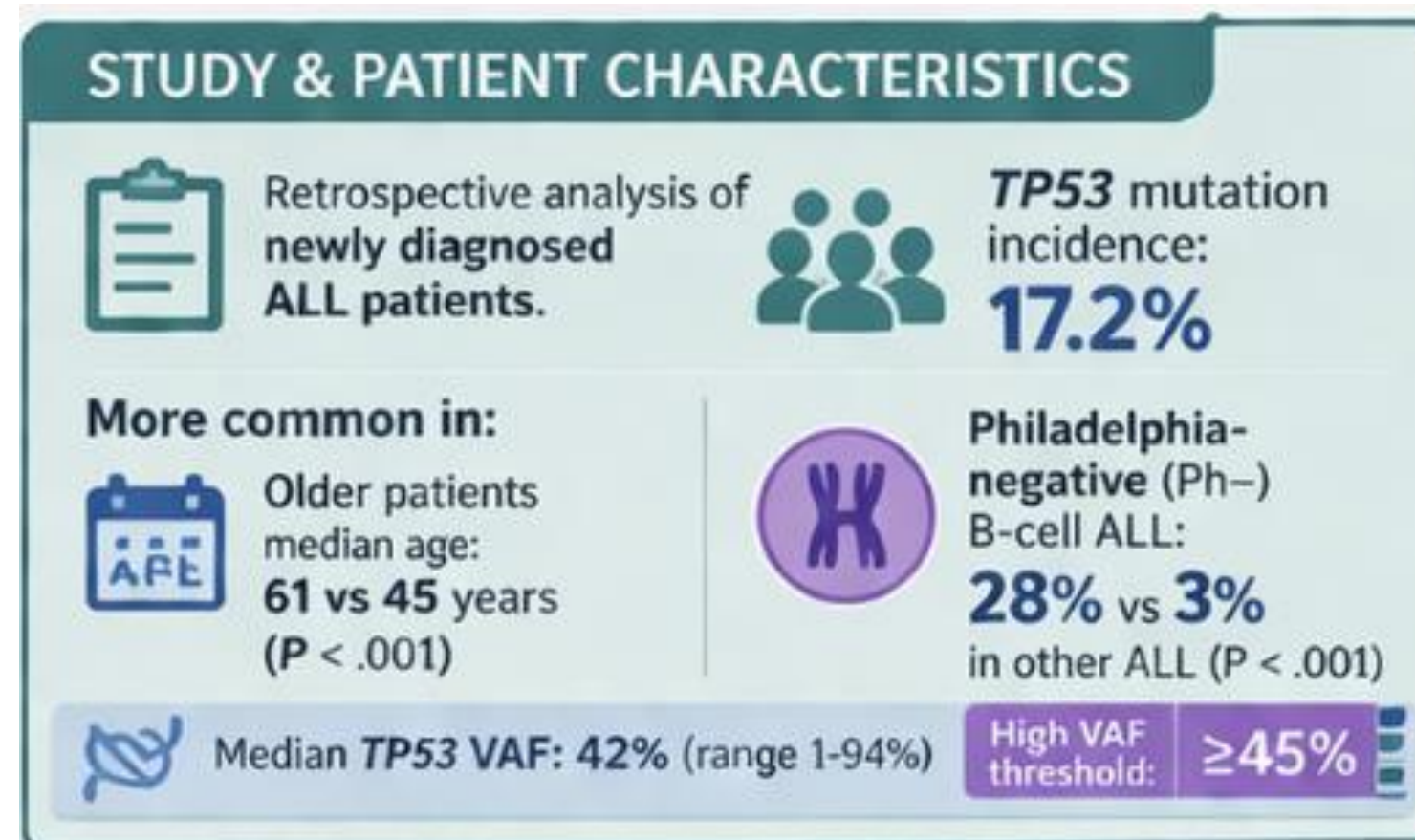
KMT2A rearrangements



Even with CAR-T

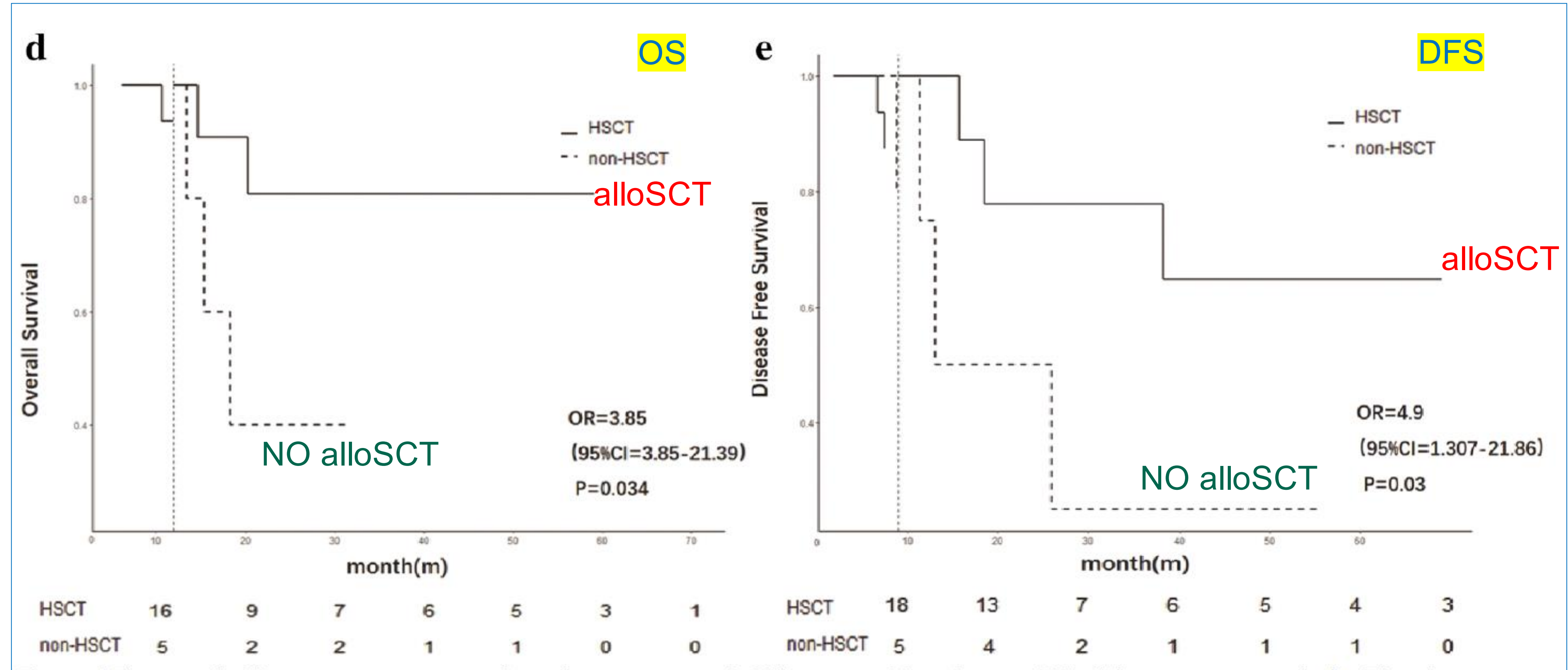
TP53 mutations

A great problem!



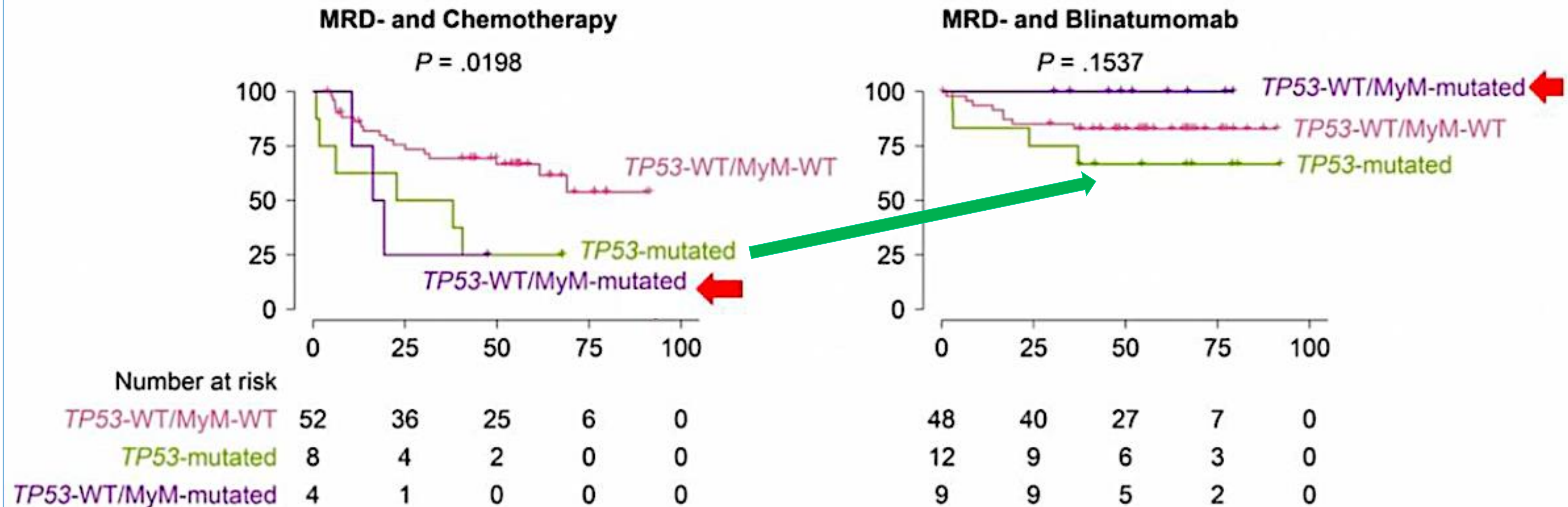
TP53 mutations

17%, associated with hypodiploidy and myeloid mutations



TP53 mutations & BLINATUMUMAB

Outcome is associated with MyM/TP53 status



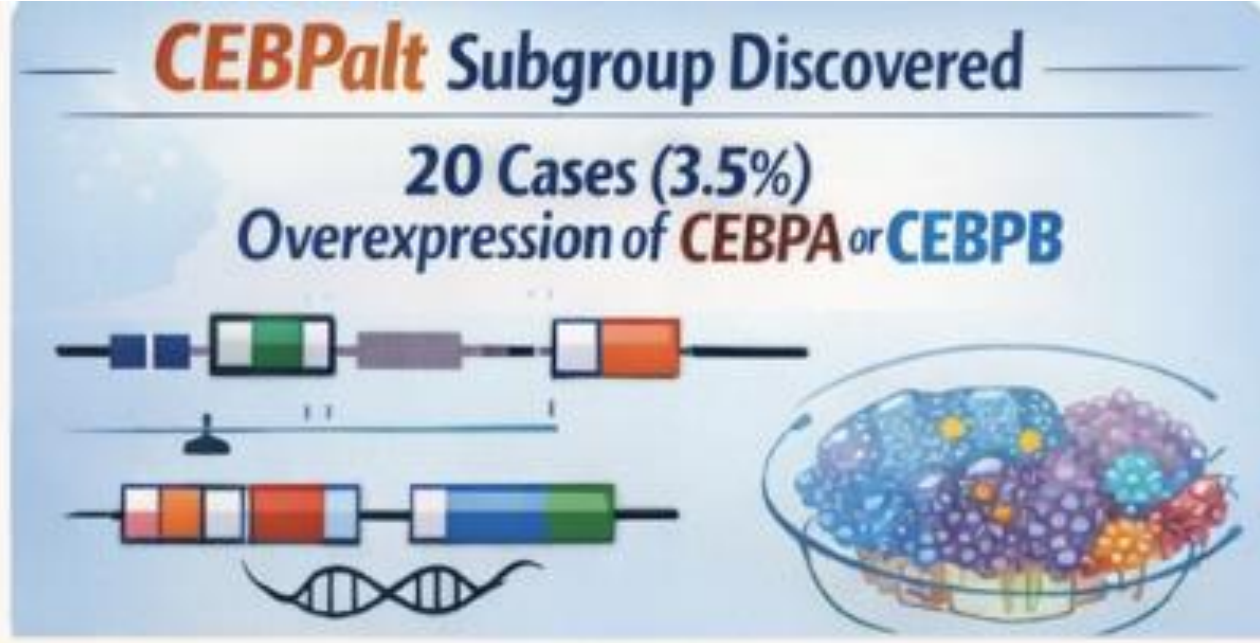
DIAGNOSIS: NEW entities

CEBP abnormalities

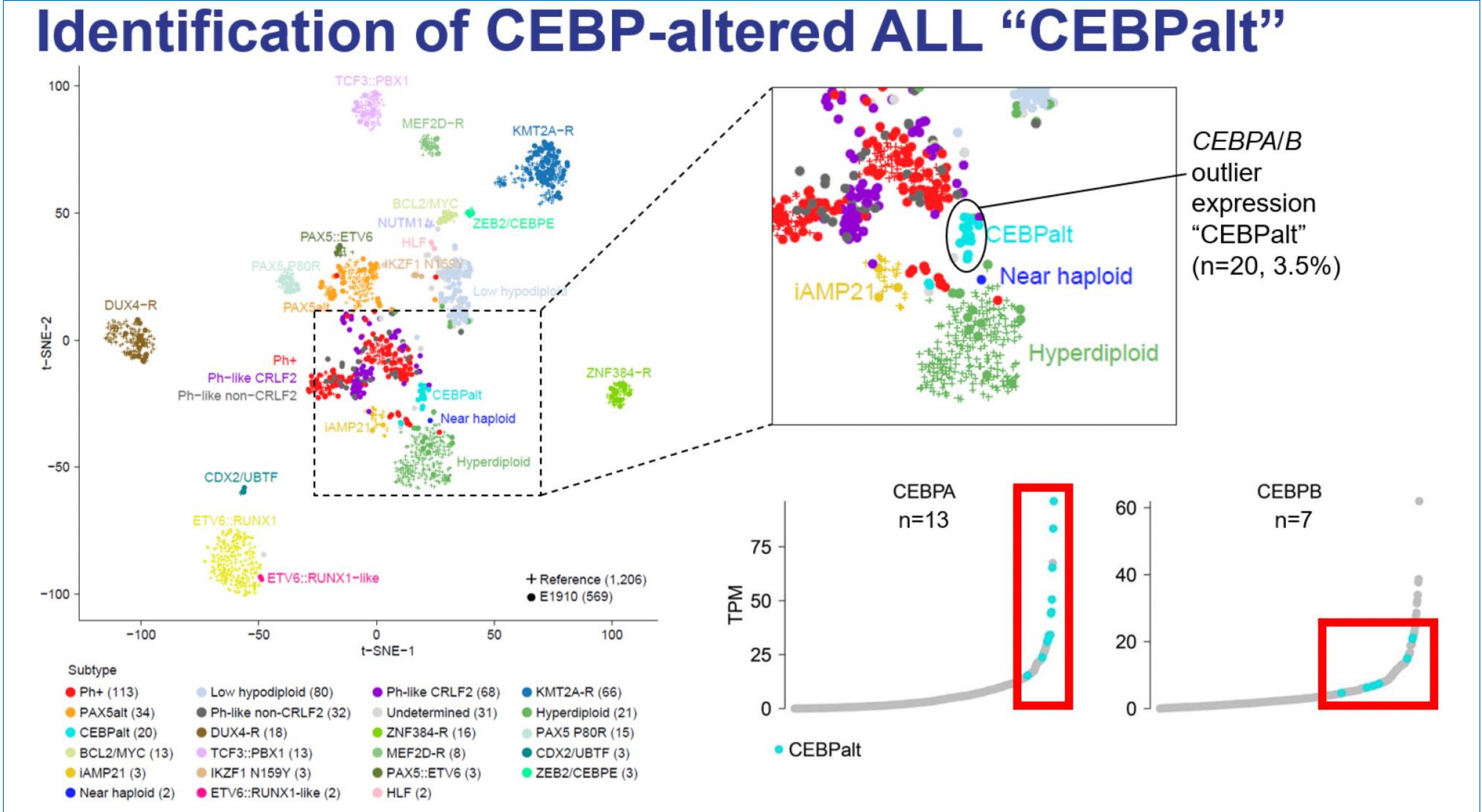
FLT3 mutations

IDH1/IDH2 mutations

CEBP-altered group

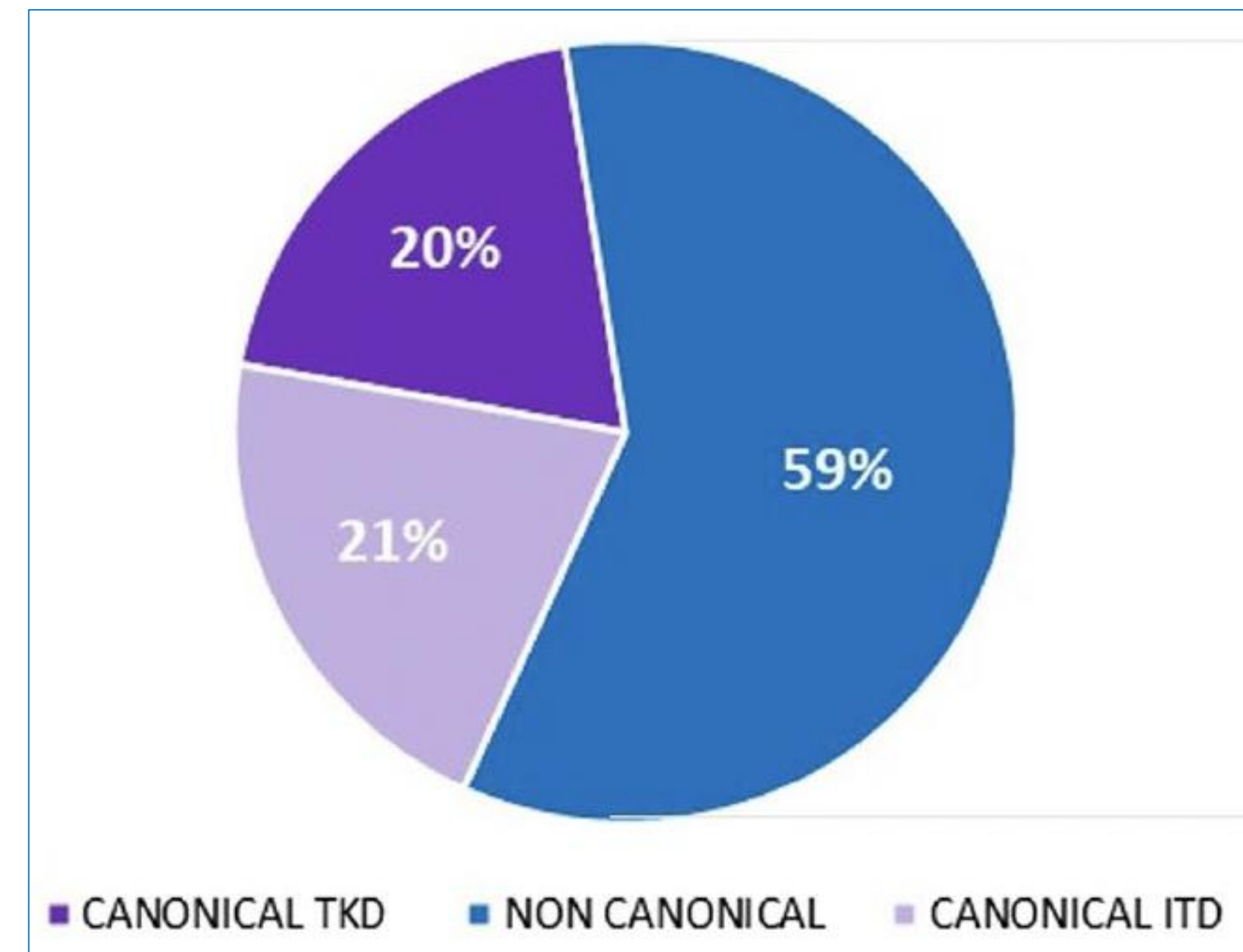
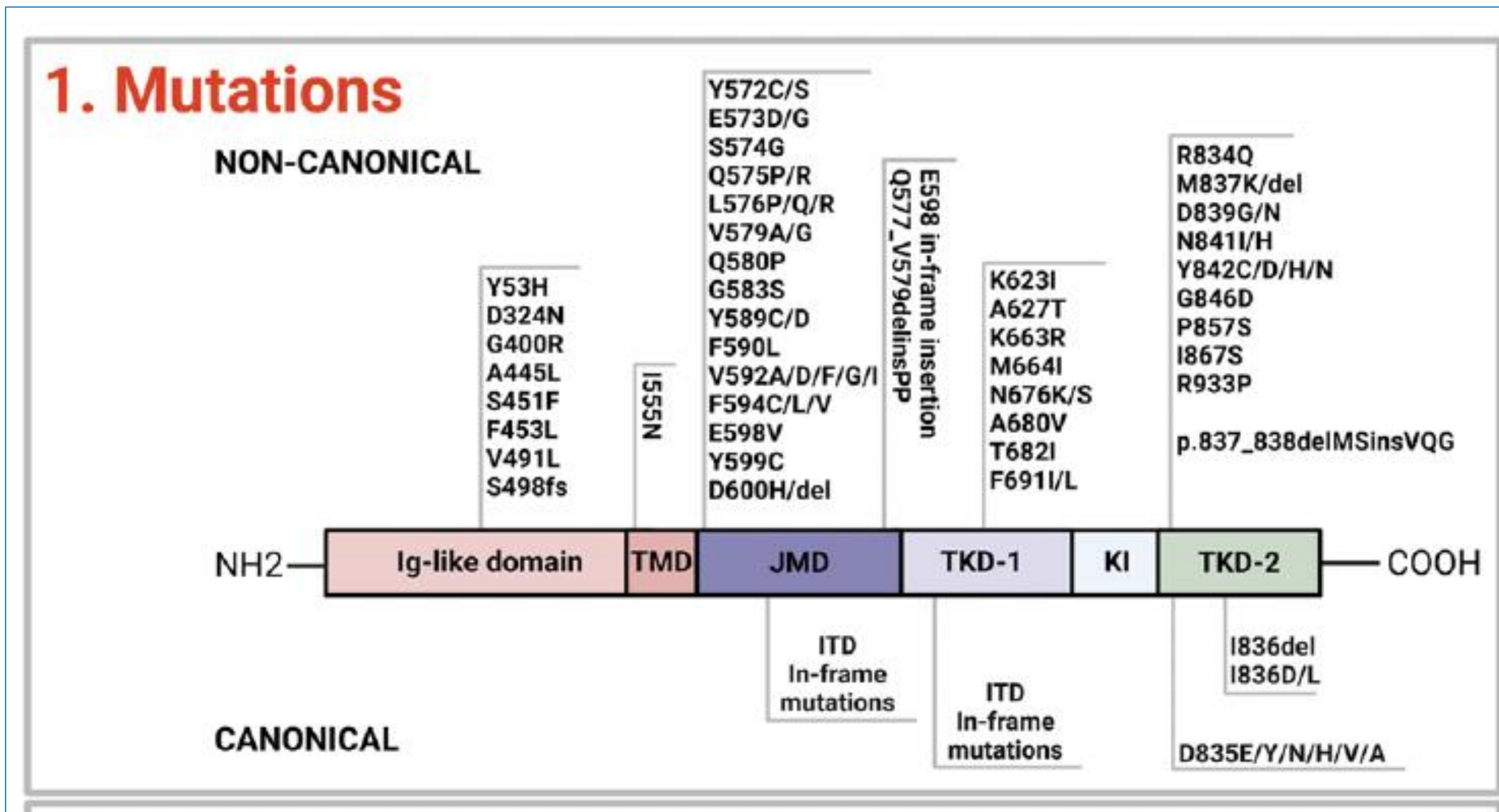


Prognostic impact?



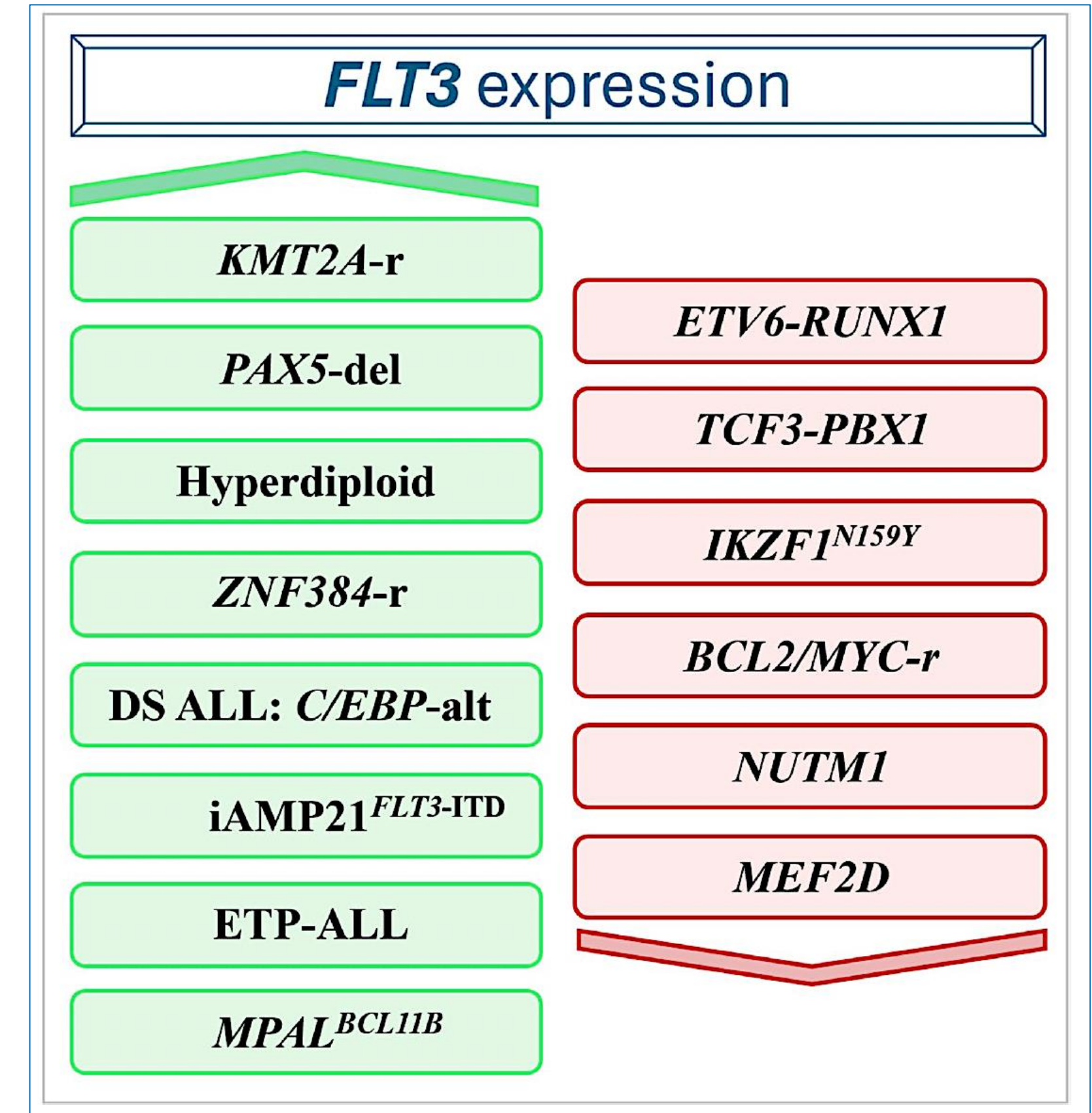
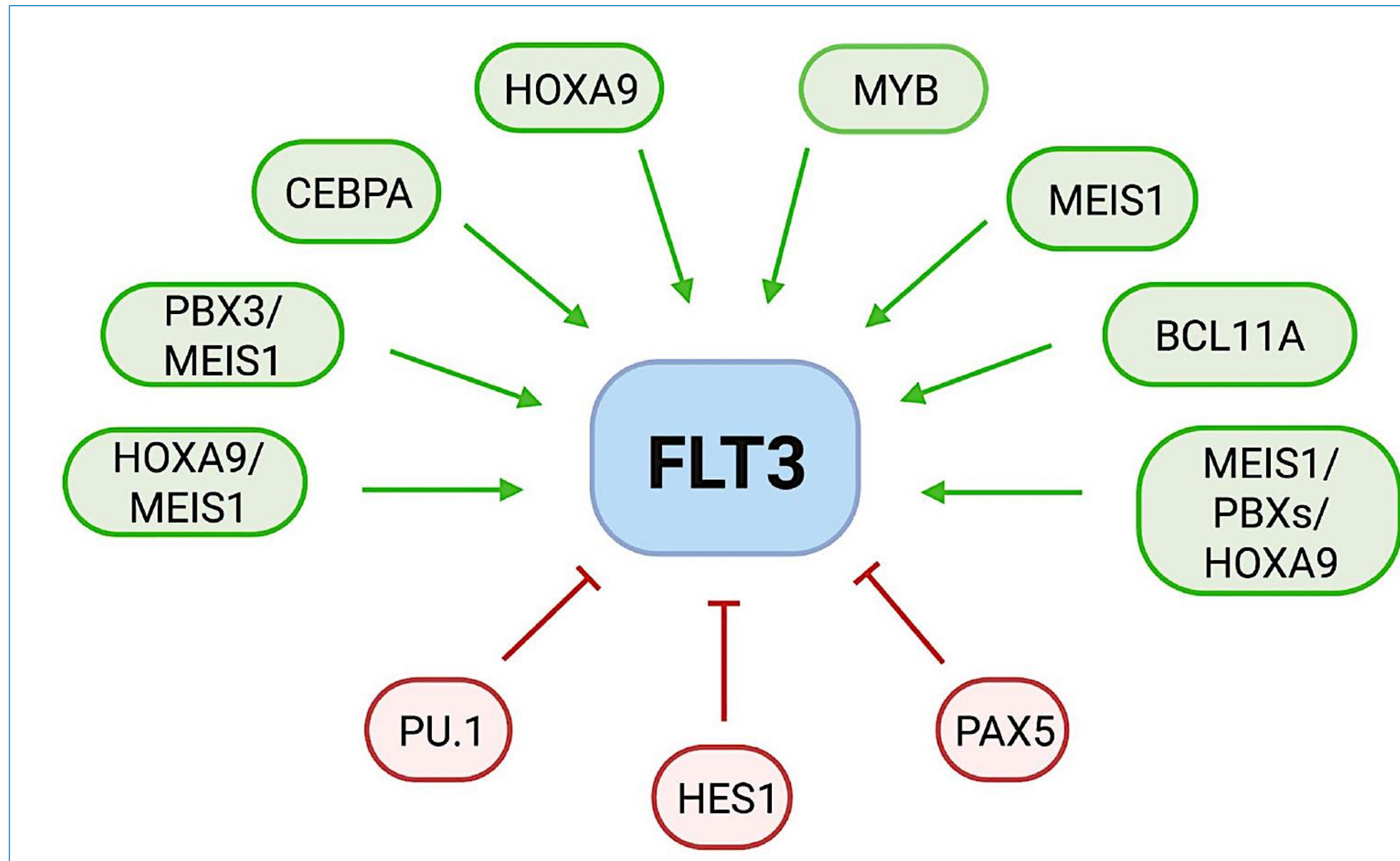
FLT3 mutations

FLT3 mutations/over-expression are detectable in 5% of ALL (mostly in T-ALL)



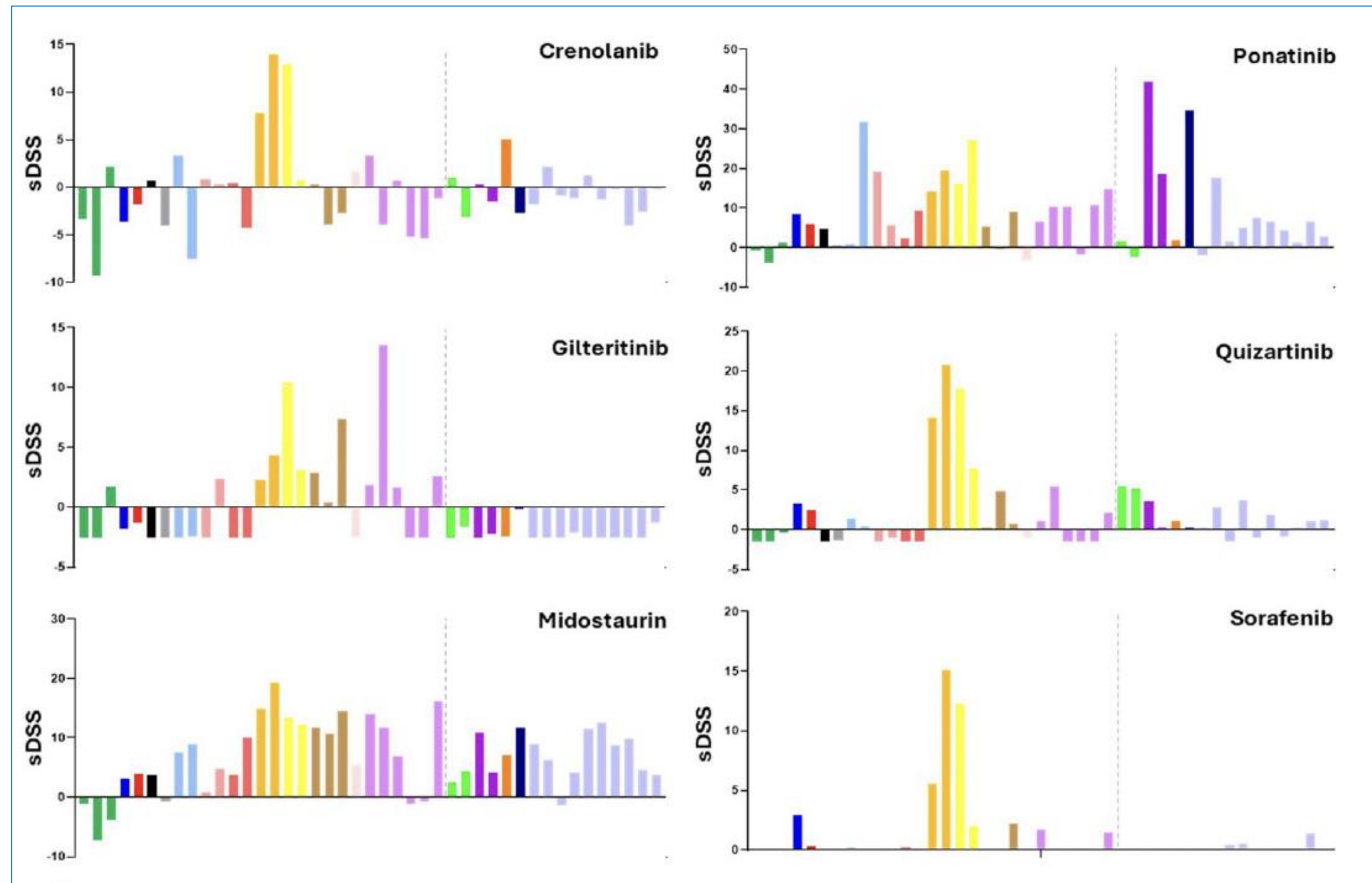
FLT3 mutations

Different mechanisms activate FLT3



FLT3 mutations

FLT3 inhibitors could be useful



IDH1 & IDH2 mutations

IDH1 or IDH2 Mutations

- **B-ALL: 3% (n=11)**
- **T-ALL: 12% (n=10)**

Common Co-Mutations



DNMT3A
35%



NOTCH1
30% (T-ALL)



NRAS
25%

Older Age
Median: 50 years

Lower WBC
 $3.4 \times 10^9/L$

Event-Free Survival



- **Median EFS: 16 months**
- **3-Year EFS: 28%**

Overall Survival



- **Median OS: 33 months**
- **3-Year OS: 43%**



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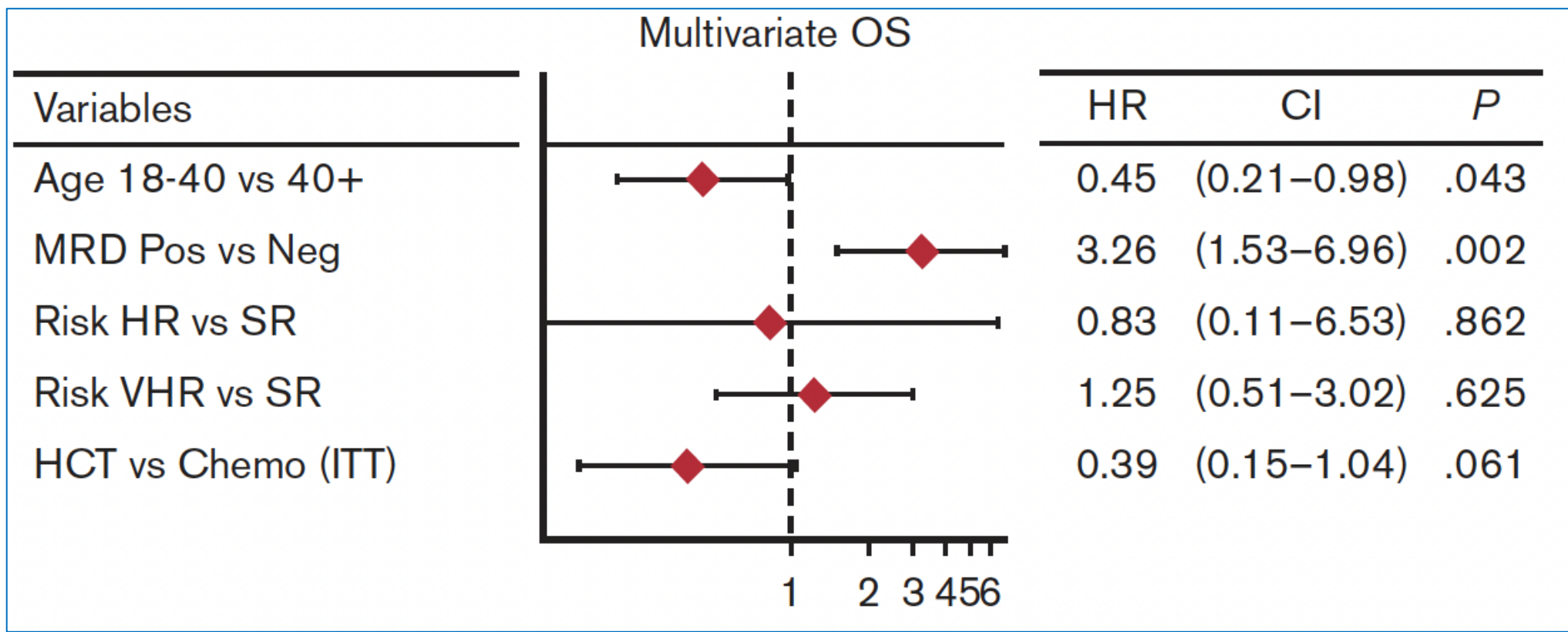
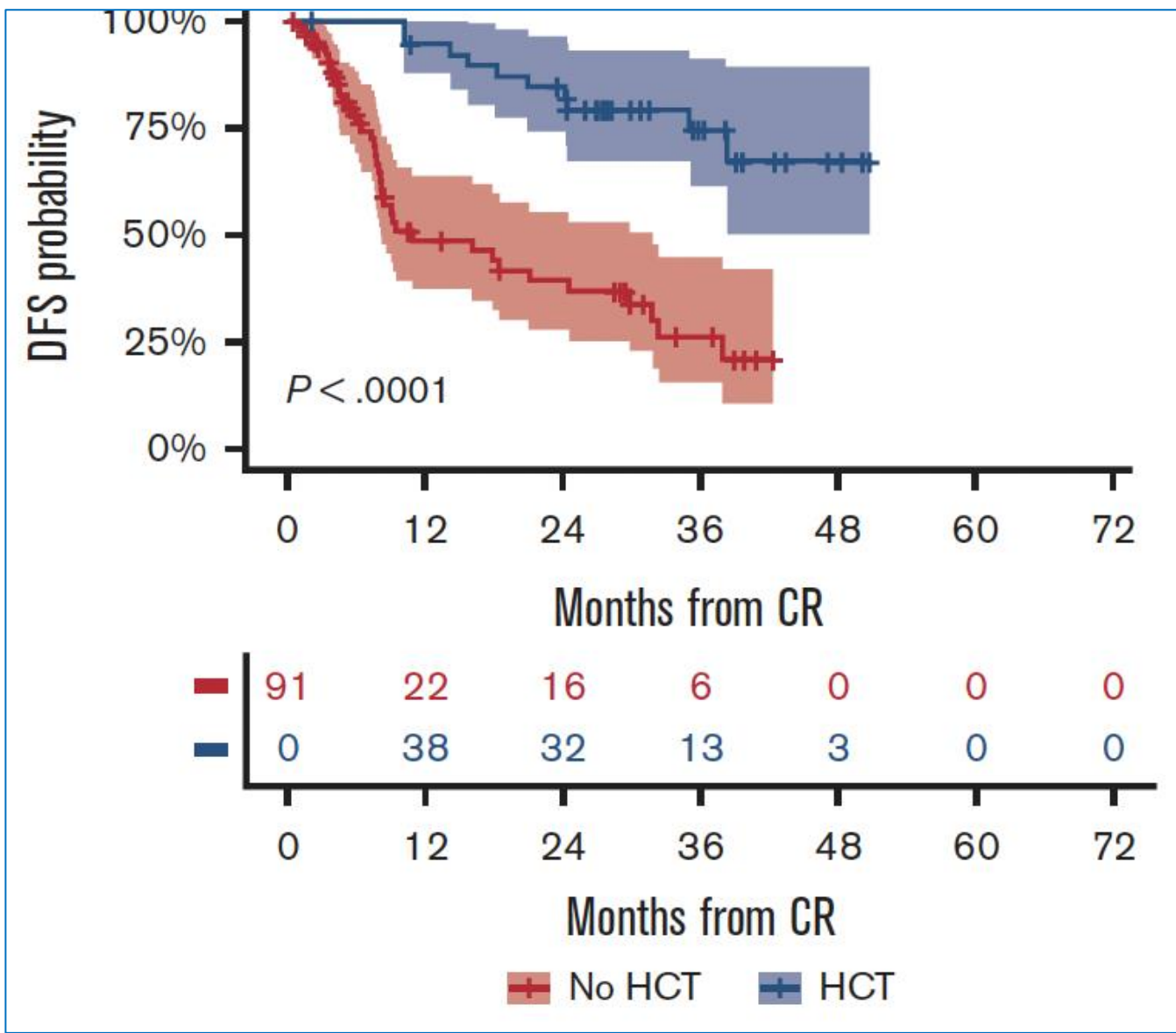
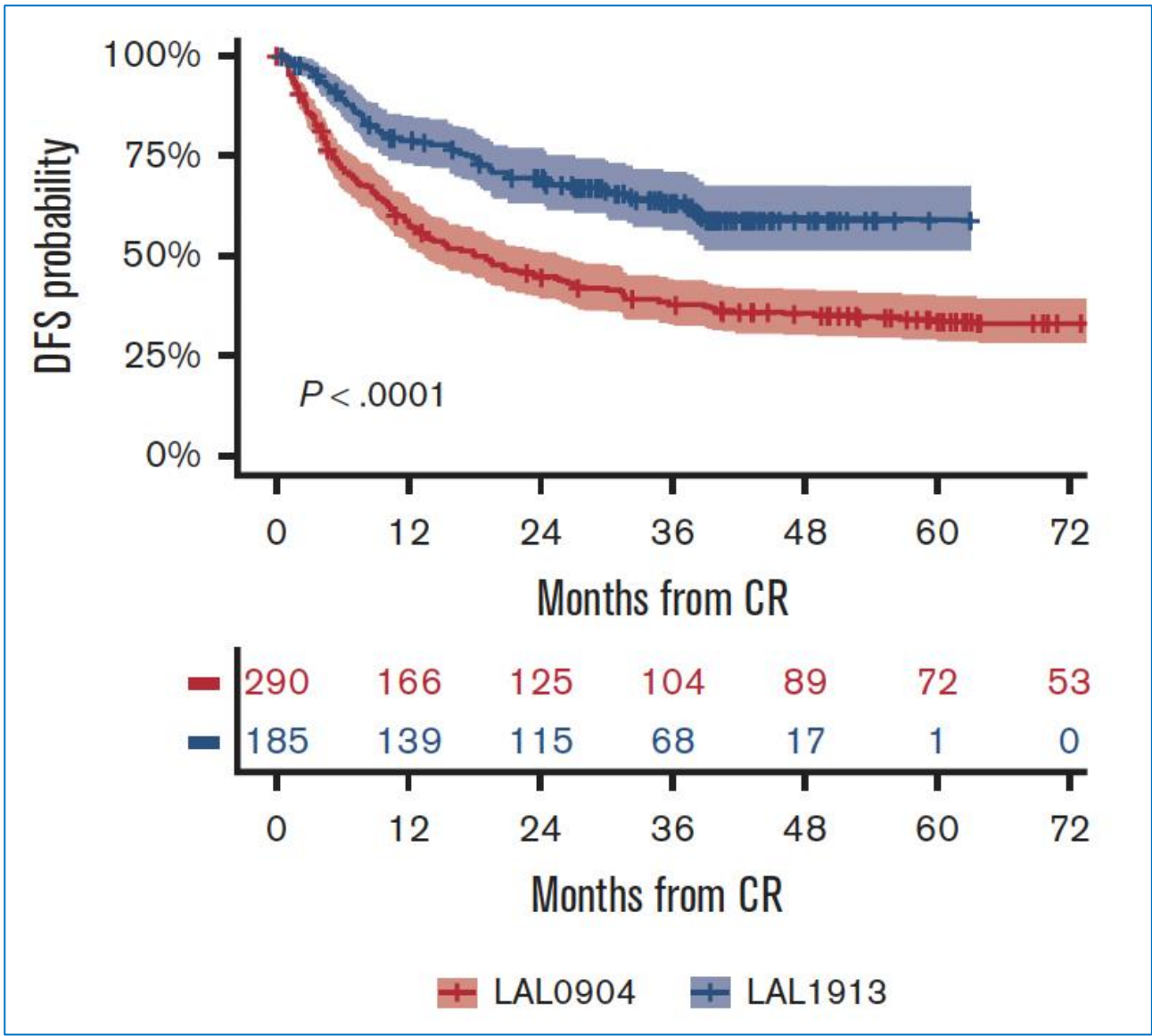
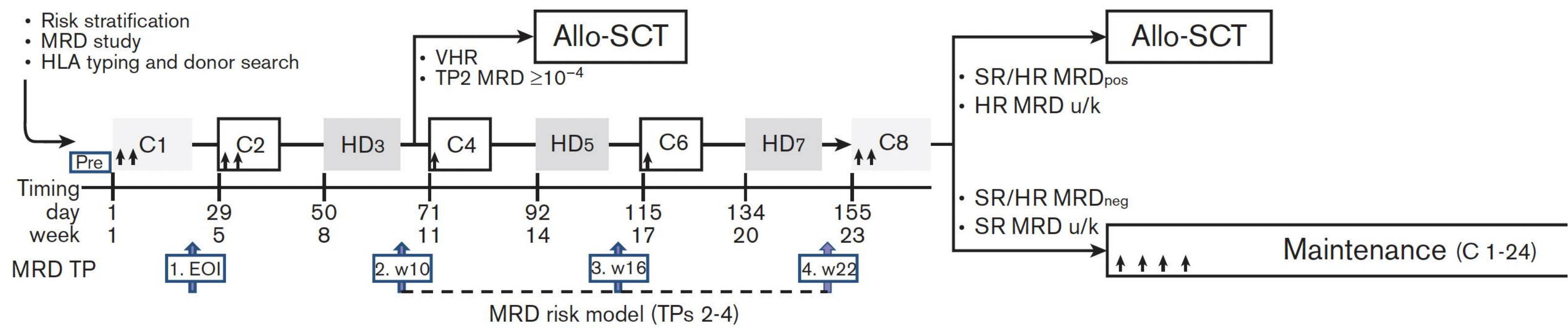
2. THE FIRST LINE TREATMENT

PEDIATRIC-INSPIRED THERAPIES

Study (reference)	ALL subset	Combination treatment	Age (y)	No.	CR (%)	CRD/ RFS (%)	OS (%)	EFS (%)	FUP	Annotations
Rituximab/ofatumumab (anti-CD20 antibody)	MDACC ²⁷	Hyper-CVAD + R ×8 in cycles 1-4, ×4 in maintenance cycles 6, 18	≤60	68	100	70	75	—	3 y	Better outcome vs no R patients ($P < .001$ for CRD, $P = .003$ for OS); outcome not improved by R in patients aged 60+
	GMALL ²⁸	GMALL 07/2003 + R ×8 (SR), ×3 (HR) in induction/consolidation	15-55	117	94	64	75	—	3 y	Better outcome vs no R patients ($P < .009$ for CRD), with better/faster MRD clearing (MRD < 0.01% 60% at day 21)
	GRAALL-2003 ²⁹	A: SOC B: SOC + R ×16-18 during induction/consolidation	40 (24-53)	105 104	94 92	—	50 61	43 55	4 y	Better outcome vs no R patients ($P < .04$ for EFS, $P = .02$ for relapse incidence)
	UKALL 14 ³⁰	A: SOC B: SOC + R ×4 in induction	25-65	288 289	92 94	—	—	42 48	3 y	No overall benefit from R ($P = .28$), better outcome with R after MAC SCT (EFS 72% vs 50%, $P = .03$)
	MDACC ³¹	Hyper-CVAD + ofatumumab ×8 in induction/consolidation	41 (18-71)	46 CD20 ⁺ 23 CD20 ⁻	93	—	66 70	61 65	4 y	CD20 ⁺ : EFS and OS with R 43% ($P = .119$) and 48% ($P = .123$); CD20 ⁻ : EFS and OS with R 50% ($P = .89$) and 62% ($P = .61$)

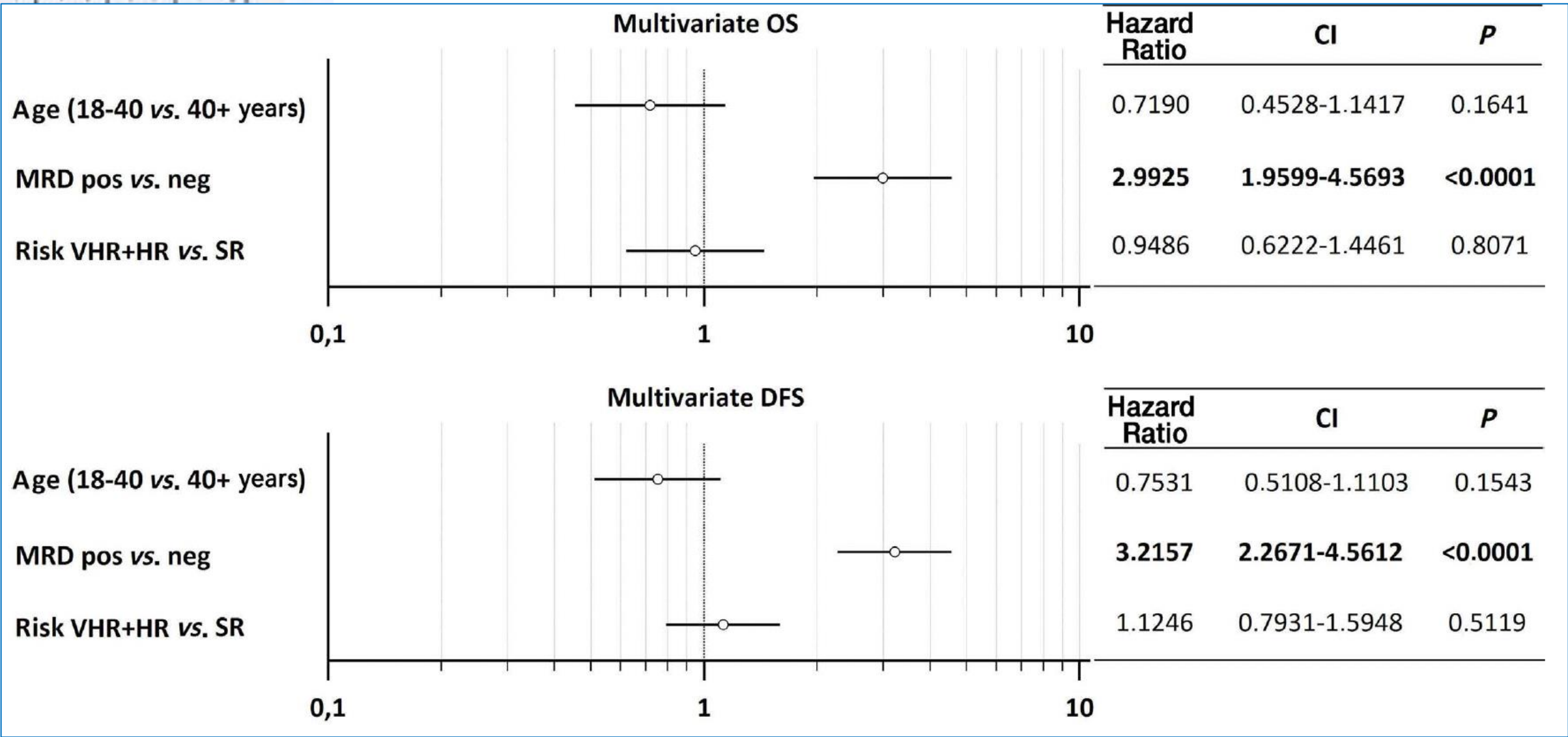
I LINE THERAPIES

The GIMEMA 1913 trial



I LINE THERAPY

Pts treated according to GIMEMA 1913 trial: the real-life





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3. MRD

MRD & techniques

	Flow Cytometry	ASO-PCR	NGS
Sensitivity	10^{-4} (to 10^{-5})	10^{-4} to 10^{-5}	10^{-6}
Samples	Fresh	Fresh or Frozen	Fresh or Frozen
Availability	Widely available*	Not widely available	Universally via centralized reference lab
Customization	Not required [†]	Patient-specific probes and primers	Not required
Cost	Expensive	Expensive	Expensive

technique?

sensitivity?

where?

when?

NCCN guidelines



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NCCN Guidelines Version 2.2025 Acute Lymphoblastic Leukemia

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[Discussion](#)

MEASURABLE (MINIMAL) RESIDUAL DISEASE ASSESSMENT

- MRD refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods or standard immunophenotyping.
- MRD quantification is an essential component of patient evaluation over the course of sequential ALL therapy.
- Studies in children and adults with ALL have demonstrated a strong correlation between the presence of MRD during remission and risk for relapse, as well as the prognostic significance of MRD measurements after induction and consolidation therapy.¹
- The prognostic significance of MRD positivity may be regimen-, ALL subtype-, and/or ALL risk-dependent. MRD timepoints and levels prompting allogeneic HCT should be guided by the specific treatment protocol being used. Referral to or consultation with a center with expertise is recommended due to the complexity of MRD assessment and monitoring.
- The preferred sample for MRD assessment is the first small volume (of up to 3 mL) pull of the bone marrow aspirate, if feasible.
- If validated MRD assessment technology with appropriate sensitivity (at least 10^{-4}) is not available locally, there are commercially available tests.
- The most frequently used methods for MRD quantification include an FDA-approved NGS-based assay to detect fusion genes or clonal rearrangements in Ig and T-cell receptor (TCR) loci (does not require patient-specific primers) (preferred), flow cytometry assays^{2,3} specifically designed to detect abnormal MRD immunophenotypes at low frequency, real-time quantitative PCR (RQ-PCR) assays (eg, clonally rearranged Ig, TCR genes), and quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) assays (eg, *BCR::ABL1*).
- High-sensitivity flow cytometry with validated analysis algorithms or PCR methods can quantify leukemic cells at a sensitivity threshold of 1×10^{-4} (0.01%) bone marrow mononuclear cells (MNCs).^{2,3} NGS and some PCR methods can detect leukemic cells at a sensitivity threshold of 1×10^{-6} (0.0001%) MNCs.^{4,5}
- If MRD is negative by flow cytometry, an FDA-approved NGS assay should be considered to confirm negativity.
- For flow cytometric quantification of MRD, notify laboratory performing the assay if the patient has received immunotherapy (such as monoclonal antibodies, bispecific antibodies, or CAR T cells) or HCT as these treatments can affect interpretation. Such testing should be performed in a laboratory with experience performing MRD testing in this clinical setting.
- For MRD assessment of *BCR::ABL1*, RT-qPCR is sensitive but in some cases lacks specificity, possibly due to multilineage involvement. Other MRD techniques, including flow cytometry and NGS, may be more specific.
- Timing of MRD assessment:
 - ▶ Upon completion of initial induction.
 - ▶ End of consolidation
 - ▶ Additional time points should be guided by the regimen used and risk features.
 - ▶ Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden.
 - ▶ For some techniques, a baseline sample (ie, prior to treatment) is needed to characterize the leukemic clone for subsequent MRD assessment.

MRD: where?

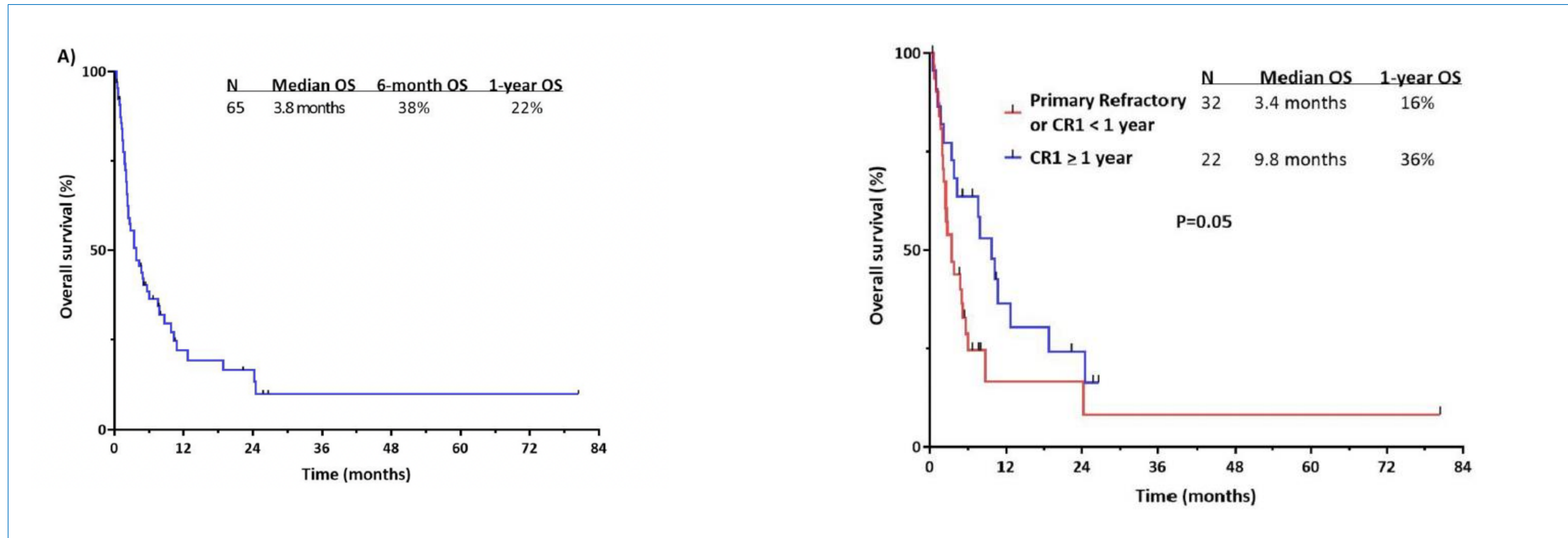
The cfDNA & ddPCR

With Active Leukemia (n=10 Samples)	Without Active Leukemia (n=7 Samples)
 9/10 ddPCR Positive	 6/7 ddPCR Negative
PB Flow Positive: 1/10 PB NGS Positive: 7/9	PB Flow Negative: 7/7 PB NGS Negative: 7/7

4. RELAPSED/REFRACTORY PTS

R/R pts: A GREAT PROBLEM

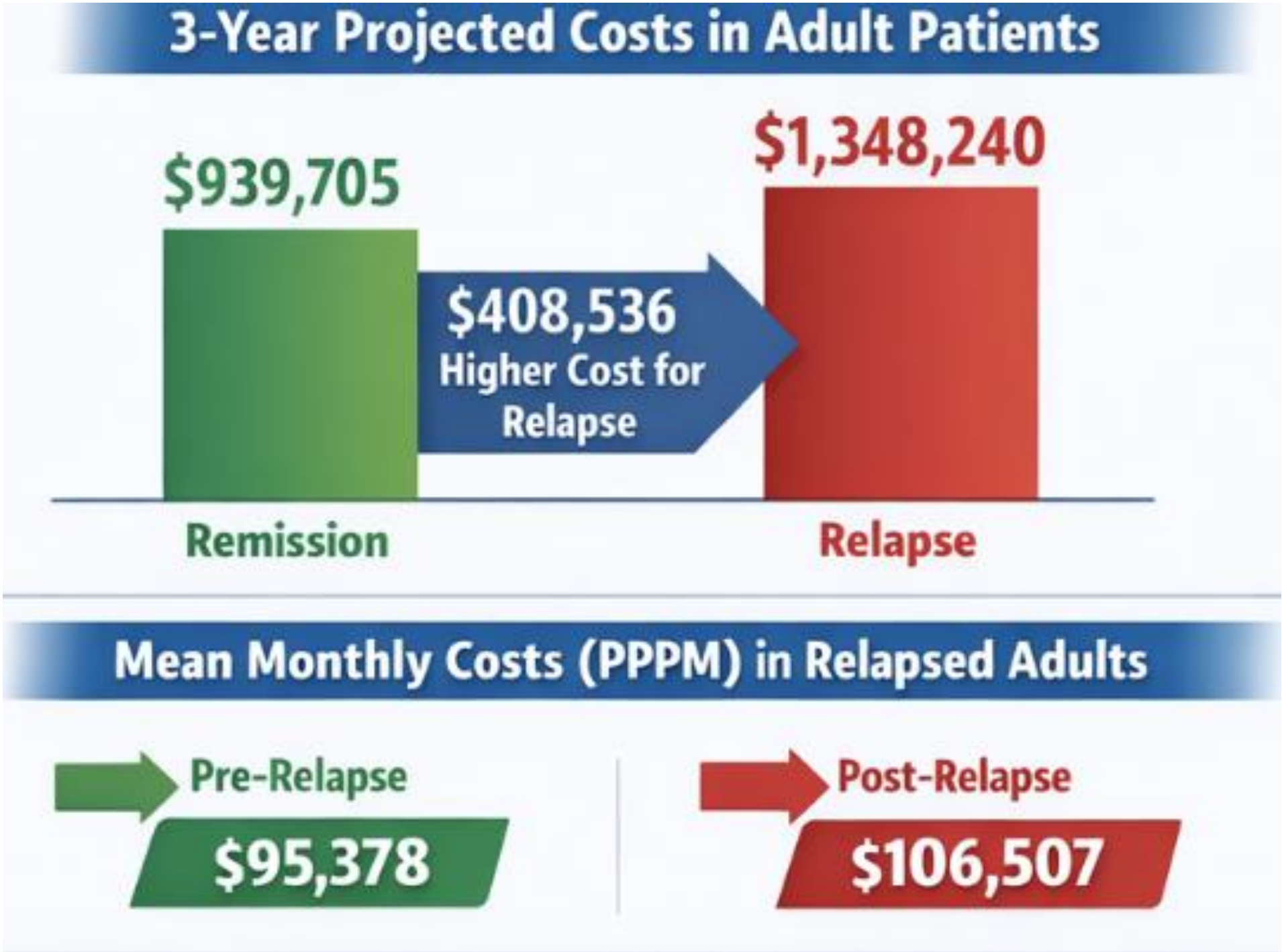
Pts not responder to blina or ino



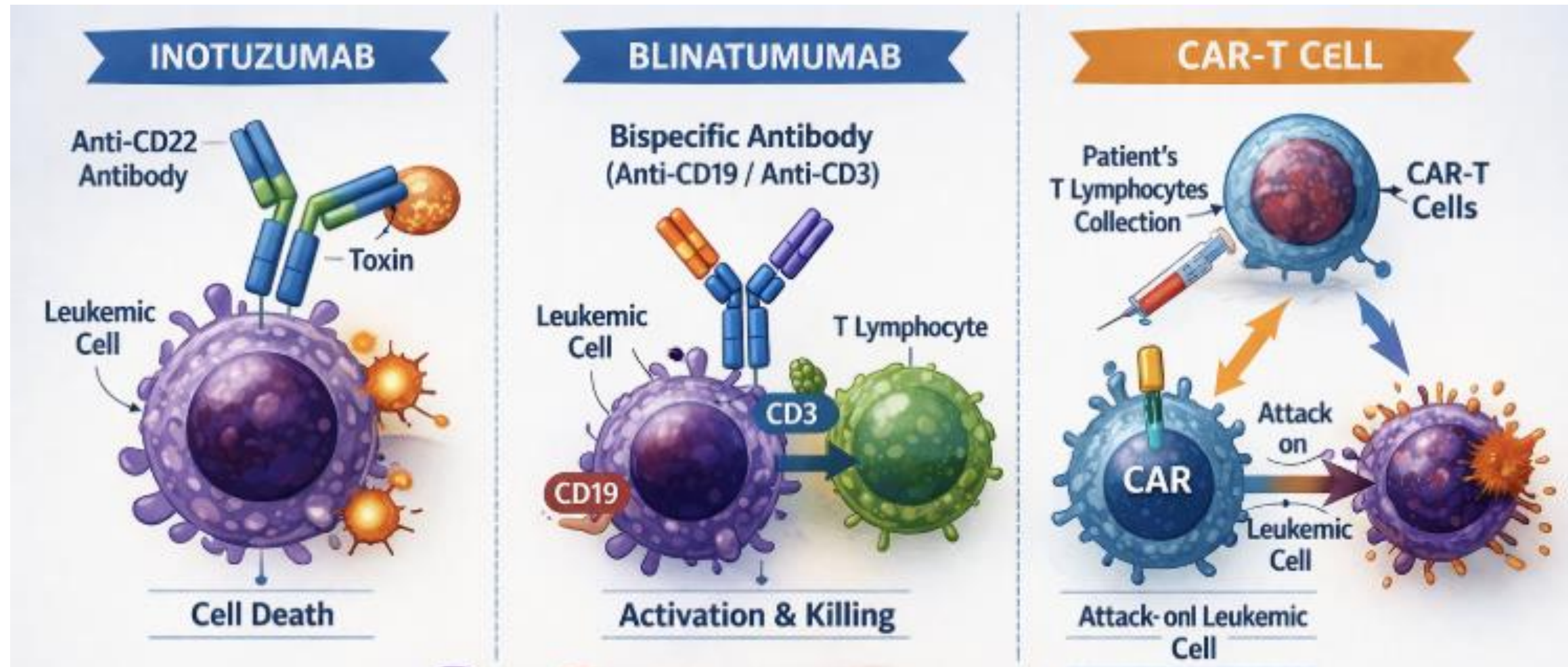
R/R ALL: Economic burden

Costs are related to hospitalization:
by 3 years, progressed pts are hospitalized 4 times more

Effective treatments for
R/R pts are needed



IMMUNOTHERAPIES



adult patients with relapsed or refractory CD22+ B-ALL

adult patients with relapsed or refractory CD19+ B-ALL
or
I or II CR MRD+ (>0.1%)

BREXUCEL: pts ≥ 26 y with relapsed or refractory CD19+ B-ALL (III line or after alloSCT)

TISACEL: pts <25y with relapsed or refractory CD19+ B-ALL

ANTIBODIES

Reference	Study	Eligibility	Patients, N	Median age (y)	Prior alloHSCt	ORR	Molecular response	Bridge to alloHSCt	OS estimate or median
Multicenter antibody-based studies									
Kantarjian et al, 2016 ¹²²	INO phase 3 (INO-VATE)	≥18 years R/R CD22 ⁺ ALL	109 (67% salvage 1)	47	16%	81%	63%	40%	7.7 mo
Topp et al, 2015 ¹⁹¹	Blinatumomab phase 2	≥18 years Ph-neg R/R ALL CR1 <12 months	189 (61% salvage 1)	36	34%	43%	35%	40%	6.1 months
Kantarjian et al, 2017 ¹⁹²	Blinatumomab phase 3 (TOWER)	≥18 years Ph-neg R/R ALL CR1 <12 months	271 (42% salvage 1)	37	35%	44%	36%	14%	7.7 months
Gokbuget et al, 2018 ⁶⁷	Blinatumomab phase 2 (BLAST)	≥18 years ALL in HCR MRD ≥ 0.1%	116 (65% CR1)	45	NR	NR	80% complete MRD response	67%	36.5 months
Brown et al, 2021 ¹⁹³	Blinatumomab COG AALL1331	1-30 years HR/IR ALL in first relapse	105 (all salvage 1)	9	NR	NR	79%	73%	79% at 24 months

CAR-T: efficacy & toxicities

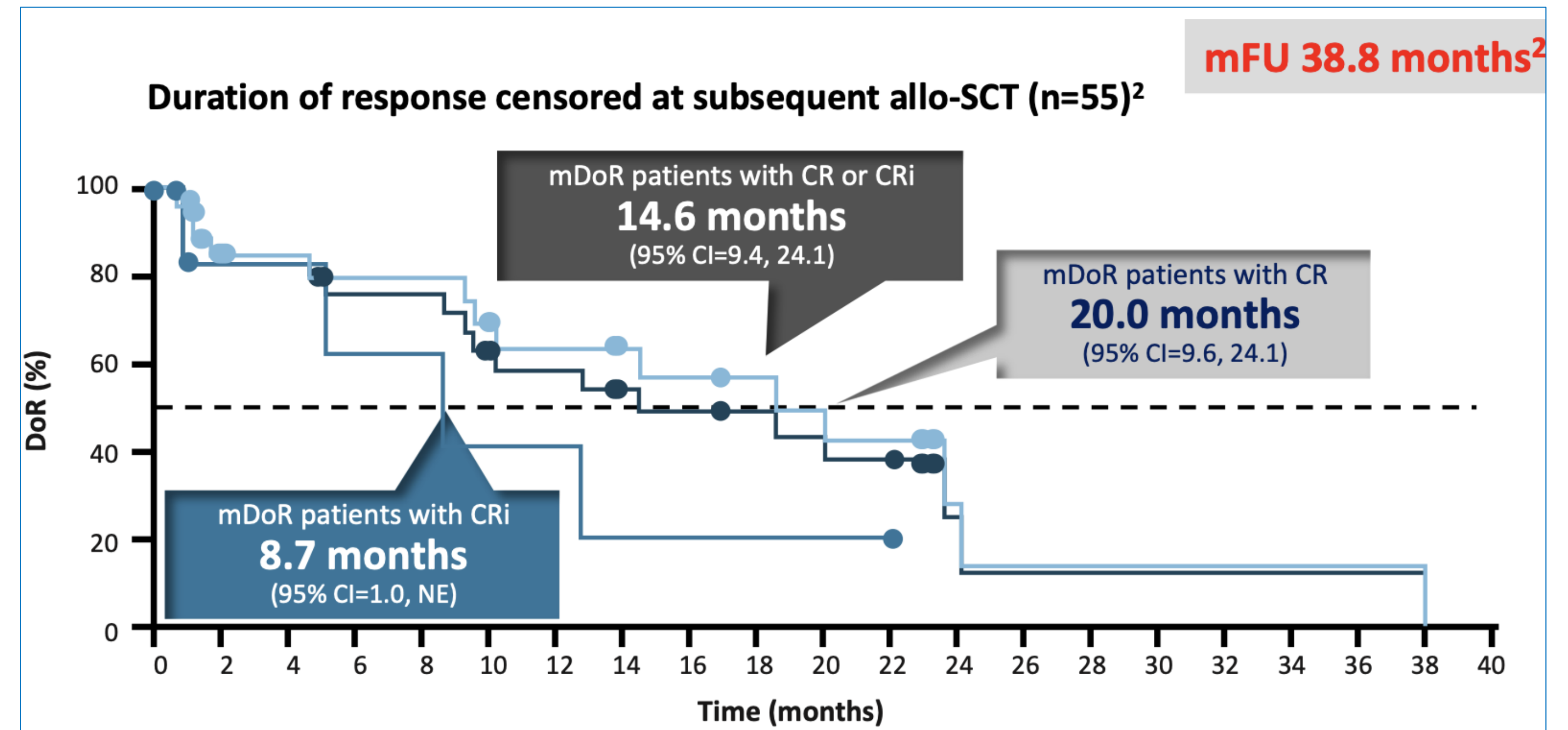
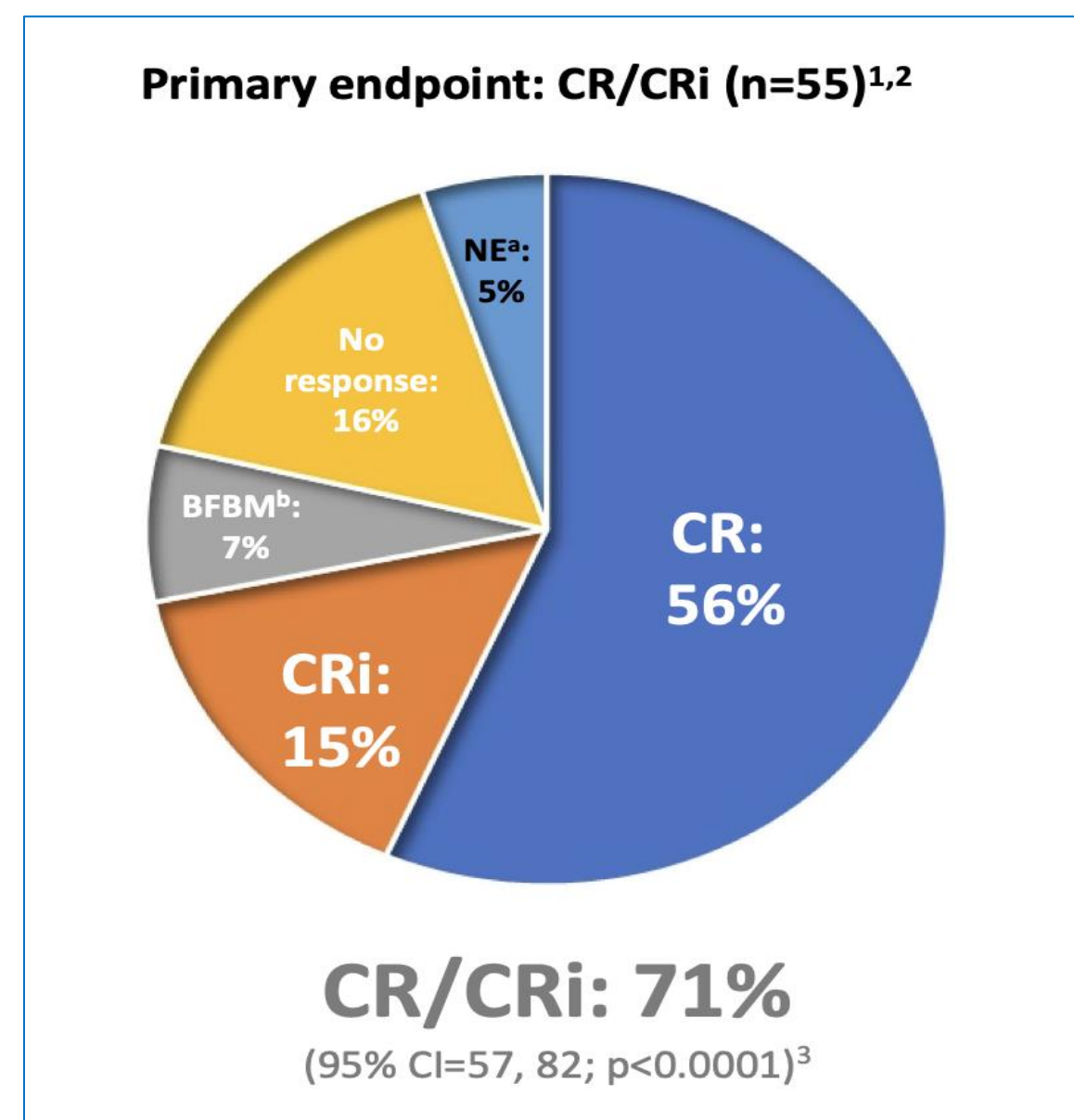
CD19 Chimeric Antigen Receptor (CAR)-T cells in ALL

	Tisagenlecleucel ^{202,215,216}		Brexucabtagene Autoleucel ^{190,203}		Obecabtagene Autoleucel ^{206,207}
Co-stimulatory domain	4-1BB		CD28		4-1BB
Number of patients infused	79	255	55	189	127
Median age (range), <i>years</i>	11 (3–24)	13 (0.4–26)	40 (28–52)	46 (18–81)	47 (20–81)
CR/CRi (%)	82	86	73	90	78
MRD negative rate (%)	98	99	100	79	94
Grade ≥3 CRS/ Grade ≥3 ICANS (%)	48/21	16/9	24/25	11/31	3/8
Median follow up (months)	38.8	13.4	54	11.4	14.1
Median survival (months)	Not reached	NA 12-month OS rate: 77%	26 (16.2–60.4)	Not reached	23.8 (12.9-NR)

CAR-T

	Any grade	Grade 3/4	Grade 5
Any adverse event	43 (100)	32 (74)	9 (21)
Pyrexia	42 (98)	15 (35)	0 (0)
Hypotension	27 (63)	14 (33)	0 (0)
Anemia	22 (51)	21 (49)	0 (0)
Nausea	17 (40)	0 (0)	0 (0)
Sinus tachycardia	15 (35)	3 (7)	0 (0)
Headache	15 (35)	0 (0)	0 (0)
Chills	12 (28)	0 (0)	0 (0)
Platelet count decreased	13 (30)	12 (28)	0 (0)
Hypoxia	13 (30)	8 (19)	0 (0)
Fatigue	13 (30)	0 (0)	0 (0)
Hypokalemia	11 (26)	3 (7)	0 (0)
Hypophosphatemia	11 (26)	8 (19)	0 (0)
Neutrophil count decreased	12 (28)	12 (28)	0 (0)
Tremor	11 (26)	1 (2)	0 (0)
White blood cell count decreased	11 (26)	10 (23)	0 (0)
Confusional state	10 (23)	1 (2)	0 (0)
Diarrhea	10 (23)	2 (5)	0 (0)
Hypomagnesemia	10 (23)	0 (0)	0 (0)
Tachycardia	9 (21)	0 (0)	0 (0)
Encephalopathy	9 (21)	3 (7)	0 (0)
Cytokine release syndrome ^a	37 (86)	10 (23)	0 (0)
Neurological events ^b	25 (58)	8 (19)	1 (2)

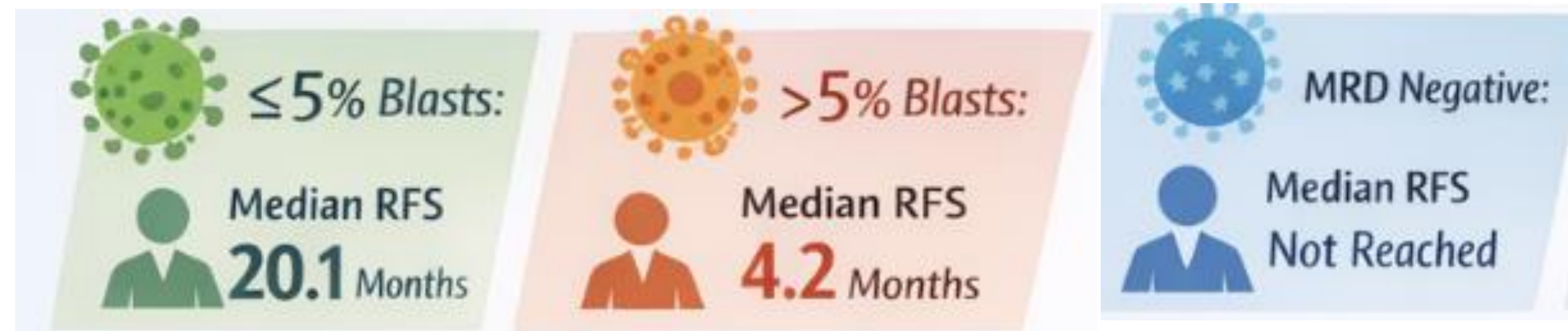
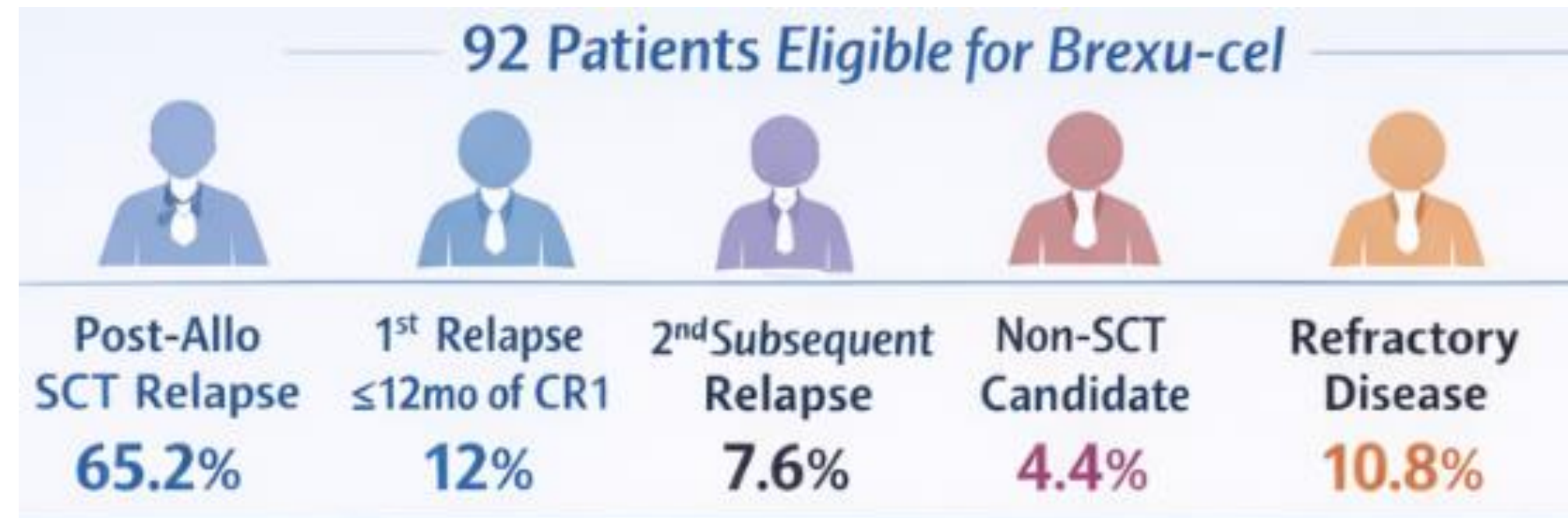
CAR-T: ZUMA 3



Median time to first CR/CRi was 1.1 months (IQR 1.0–1.9);
97% of patients achieving CR or CRi were MRD negative^{3,c}

CAR-T

UK experience



CAR-T: ZUMA 3

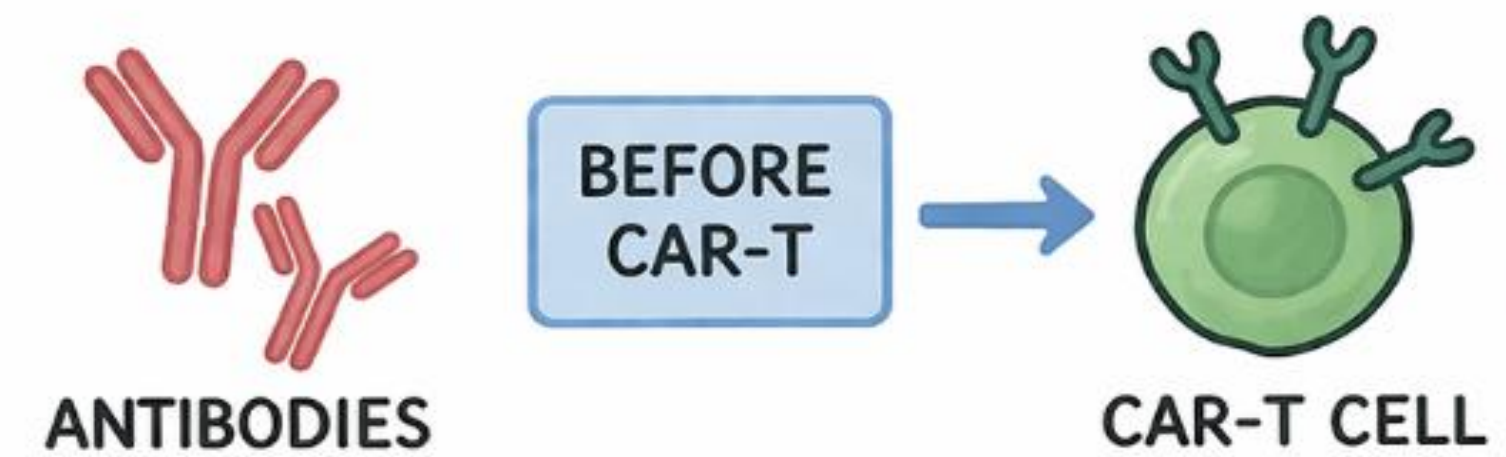
Baseline characteristics ^{1,2}	Patients treated with brexucabtagene autoleucel (n=55) ¹
Age, median (range), years	40 (19–84) ²
Male, n (%)	33 (60)
ECOG PS of 1, n (%)	39 (71)
Philadelphia chromosome positive, n (%)	15 (27)
CNS-1 disease at baseline, n (%) ^a	55 (100)
Number of prior therapies, median (range)	2 (1–8) ²
≥3 prior lines of therapy, n (%)	26 (47)
Prior blinatumomab, n (%)	25 (45)
Prior inotuzumab ozogamicin, n (%)	12 (22)
Prior allo-SCT, n (%)	23 (42)
Primary refractory, n (%)	18 (33)
R/R to ≥2 prior systemic therapy lines, n (%)	43 (78)
First relapse with remission ≤12 months, n (%)	16 (29)
R/R post allo-SCT, ^b n (%)	24 (44)
BM blasts at screening, median (range), %	65 (5–100)²
BM blasts at preconditioning after bridging chemotherapy, median (range), %^c	59 (0–98)²

CAR-T: question

1 DOES TRANSPLANT HAVE
A ROLE AFTER CAR-T?

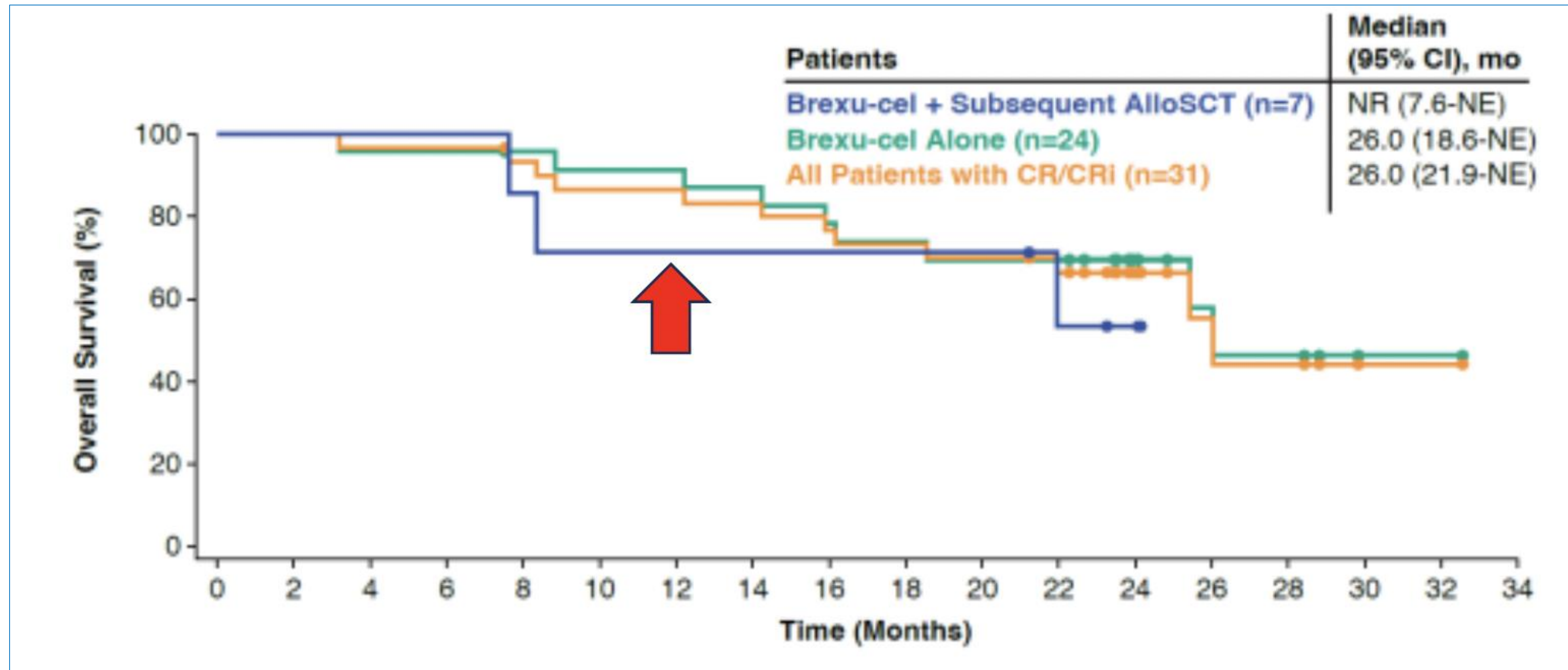


2 CAN ANTIBODIES BEFORE CAR-T
HAVE A NEGATIVE IMPACT?



alloSCT after CAR-T

Role of the alloSCT?



alloSCT after CAR-T

Role of the alloSCT in pts in CR/MRD- after CAR-T: never? Before? After?

near-world, multicenter retrospective analysis



Patients

234 adults with r/r Philadelphia-negative B-ALL treated with Brexu-cel (2021–2023)



Median follow-up

12.4 months



Allo-HCT

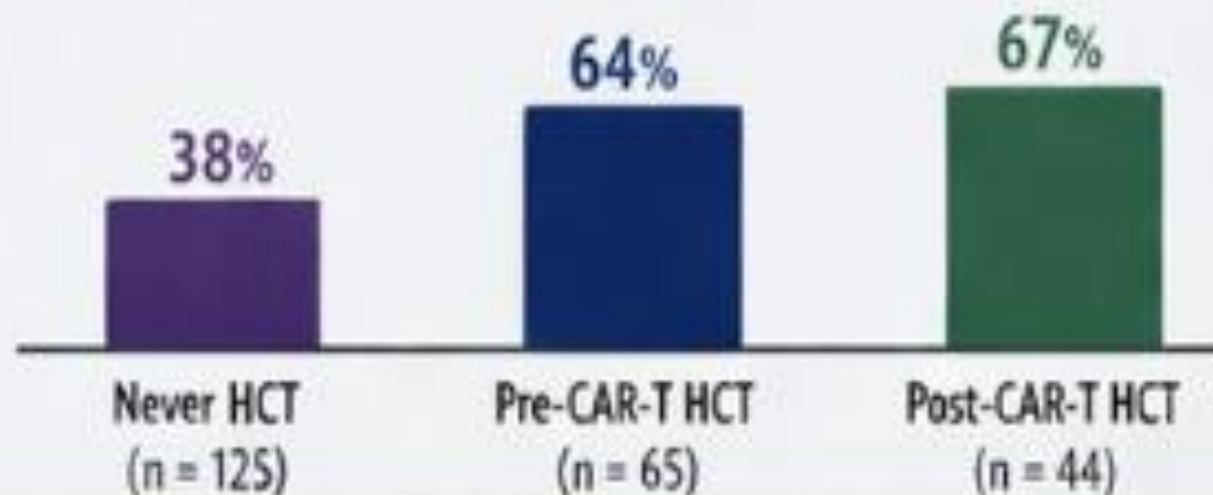
109 patients (46.6%) proceeded to allogeneic hematopoietic cell transplant

DETAILED SURVIVAL BY TRANSPLANT GROUP

RELAPSE-FREE SURVIVAL (RFS)

Median RFS: 260 days in Never HCT group;
Not reached in Pre- and Post-CAR HCT groups ($p = 0.002$)

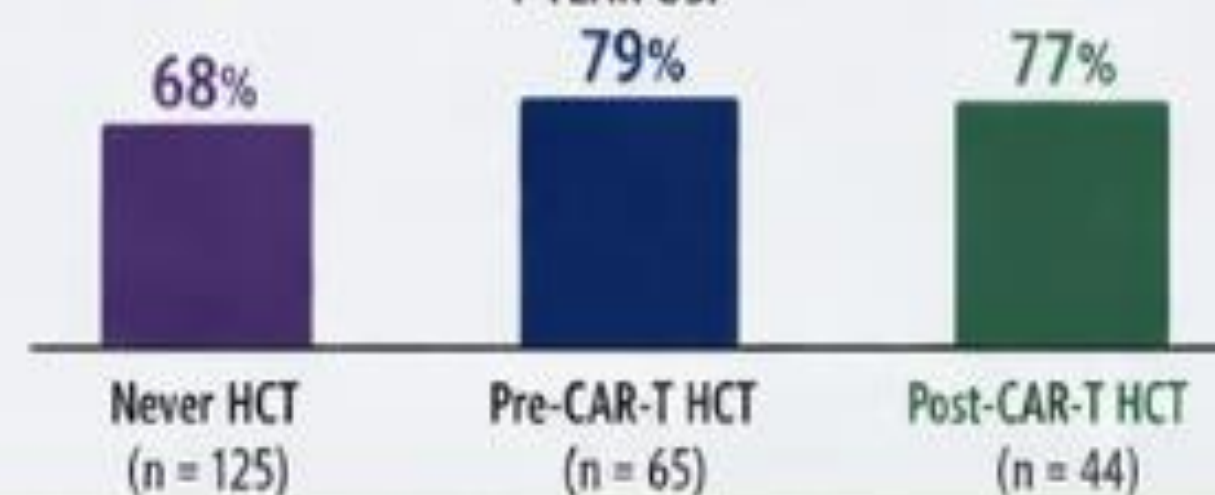
1-YEAR RFS:



OVERALL SURVIVAL (OS)

Median OS: Not reached in any group
($p = 0.13$)

1-YEAR OS:



➔ Allo-HCT (pre or post) associated with superior RFS; OS similar across groups at 1 year.

TIMING OF TRANSPLANT MATTERS

Post-CAR-T allo-HCT group:



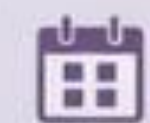
≤3 months
after CAR-T

12-month RFS:



>3 months
after CAR-T

12-month RFS:

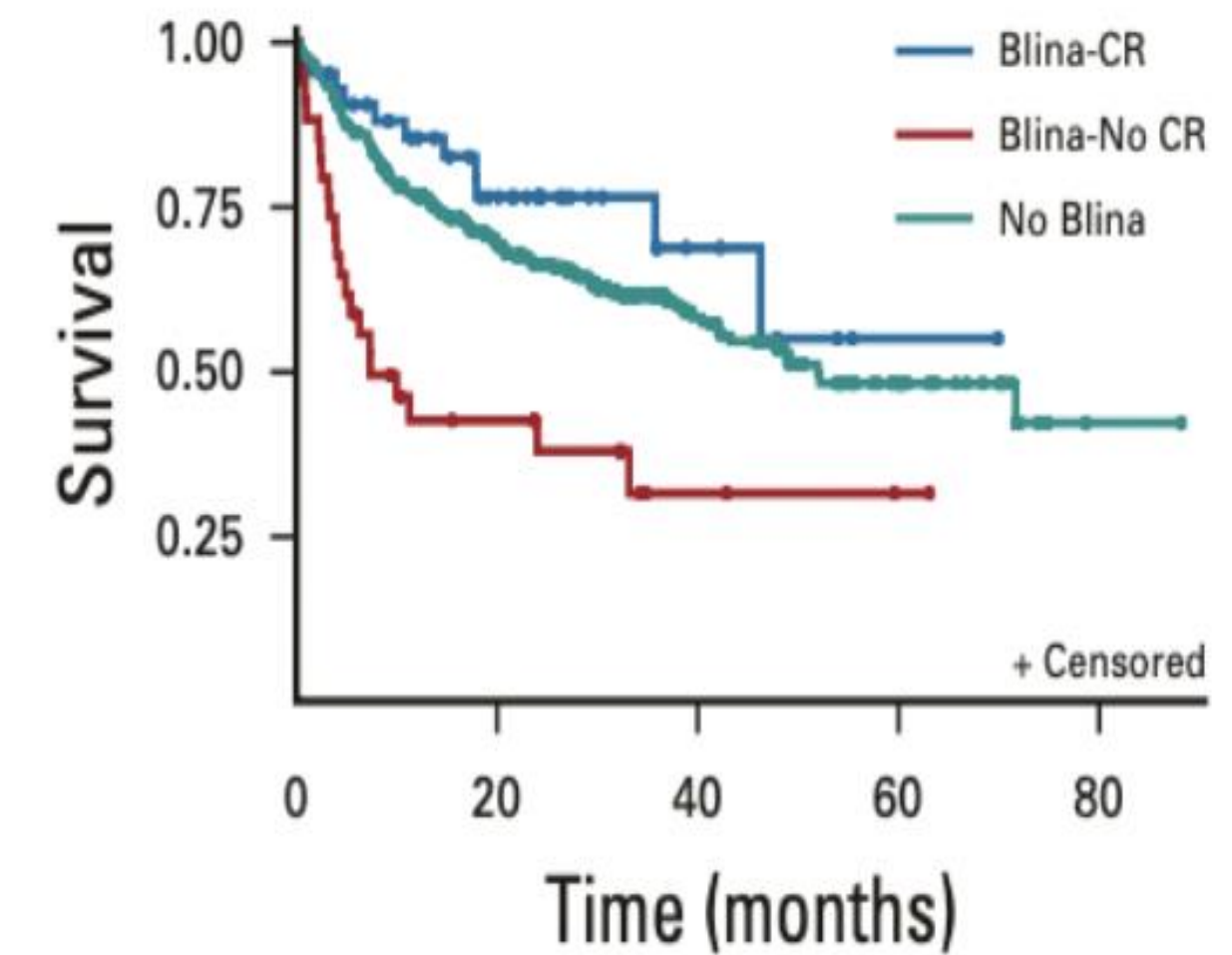
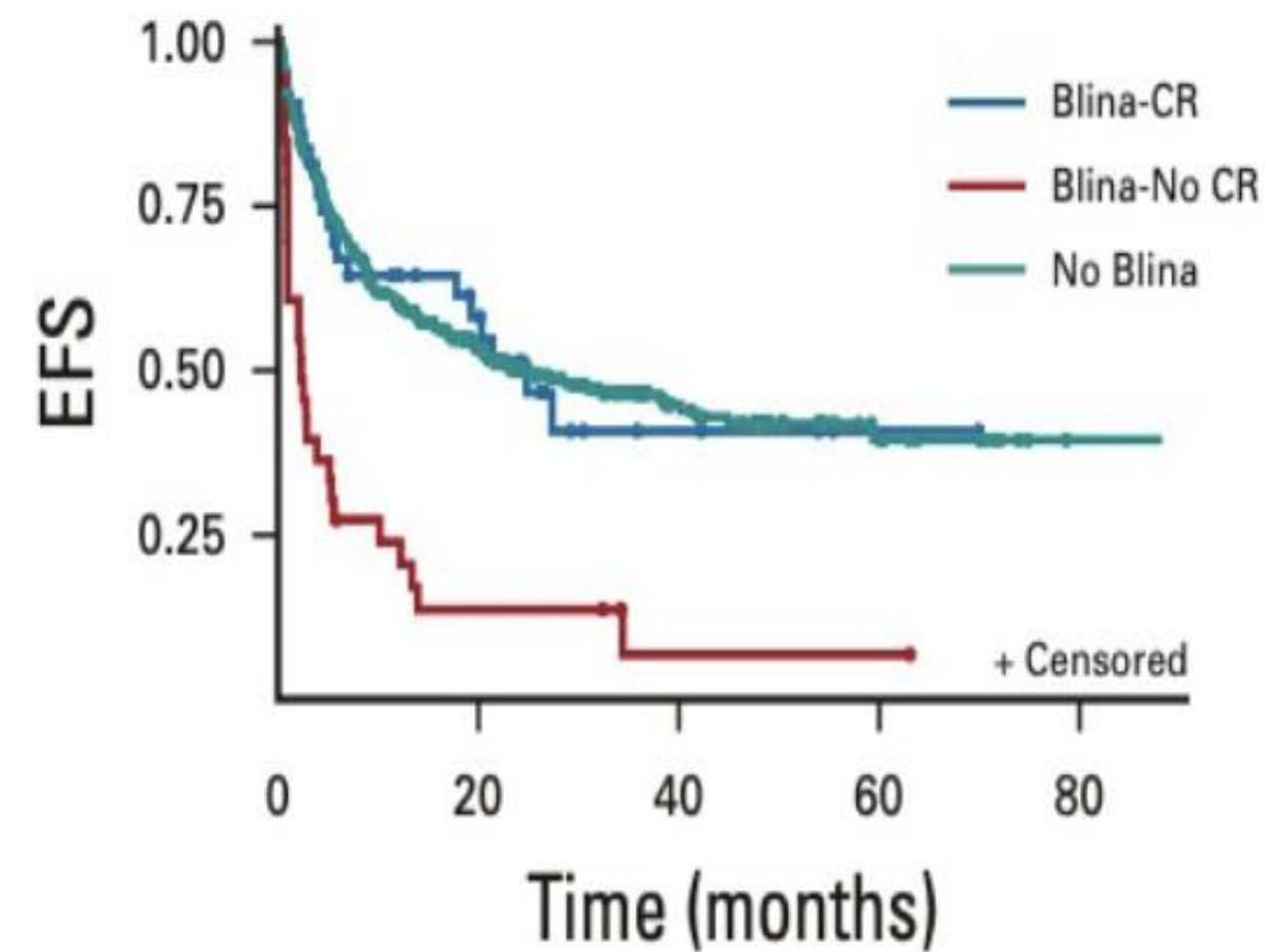
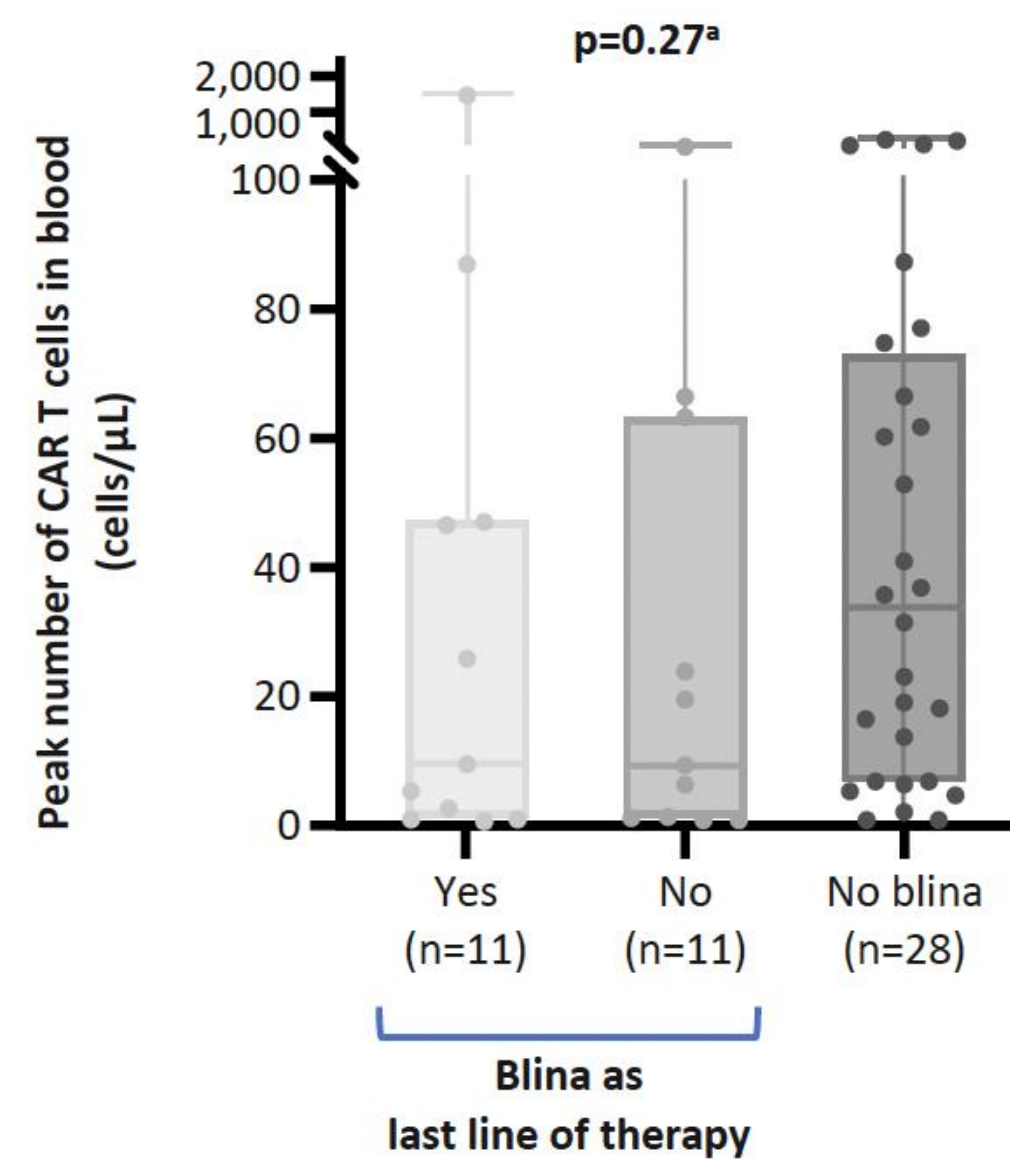


Earlier transplant (≤3 months) linked to improved relapse-free survival

CAR-T: ZUMA 3

CAR-T expansion

Peak and AUC CAR T-cell levels by last prior therapy as blinatumomab in Phase 2-treated patients (N=55)



Median peak CAR T-cell expansion trended lower in patients with prior blinatumomab exposure vs. those without; differences were not statistically significant, potentially due to small sample size

BLINATUMUMAB as consolidation

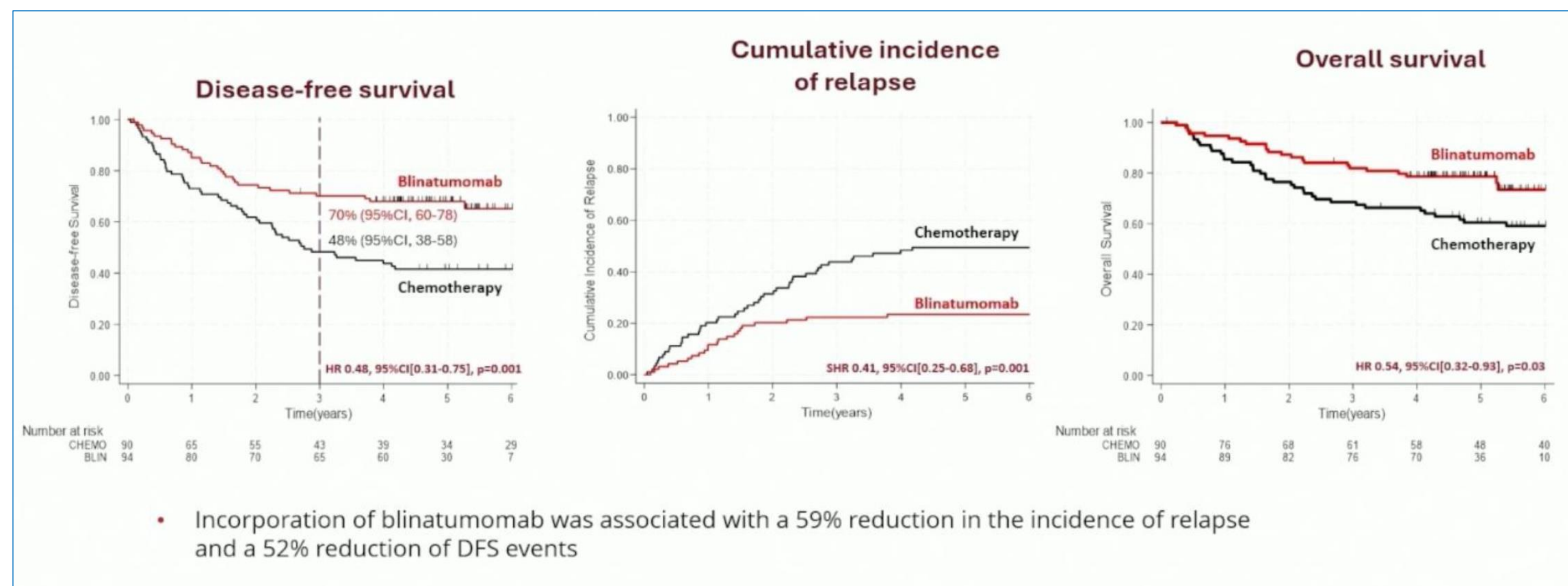
The "QUEST" trial

GRAALL-2014/B-QUEST substudy

if High-Risk criteria:

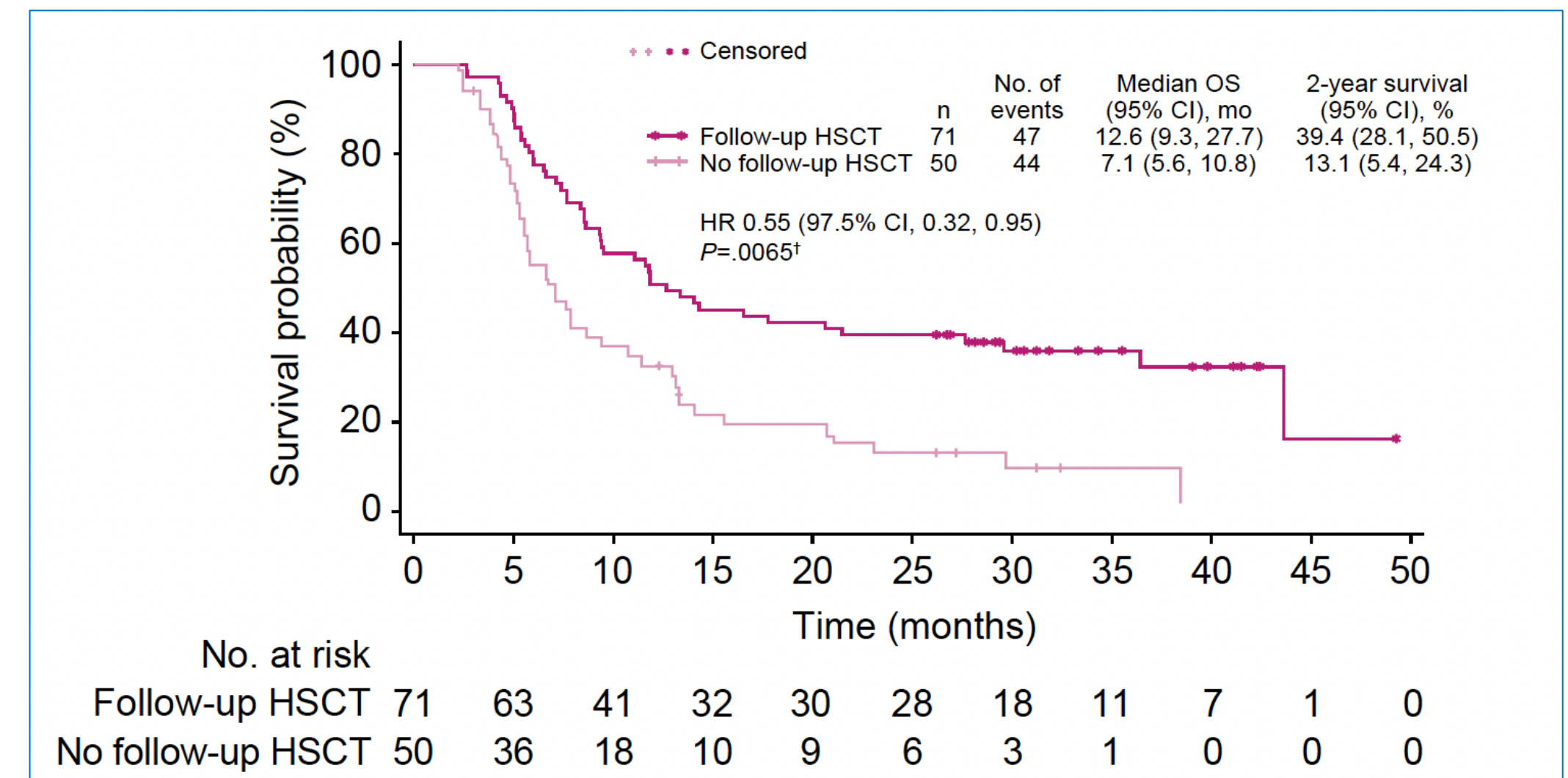
- MRD1 $\geq 10^{-4}$ (or induction failure)
- *IKZF1*del
- *KMT2A*-r

	QUEST N=94	Control N=90	p
Long-term outcome			
5y-CIR (95%CI)	23% (16-33)	49% (40-60)	0.001
5y-DFS (95%CI)	68% (58-76)	42% (31-52)	0.001
5y-OS (95%CI)	79% (69-86)	60% (49-70)	0.03



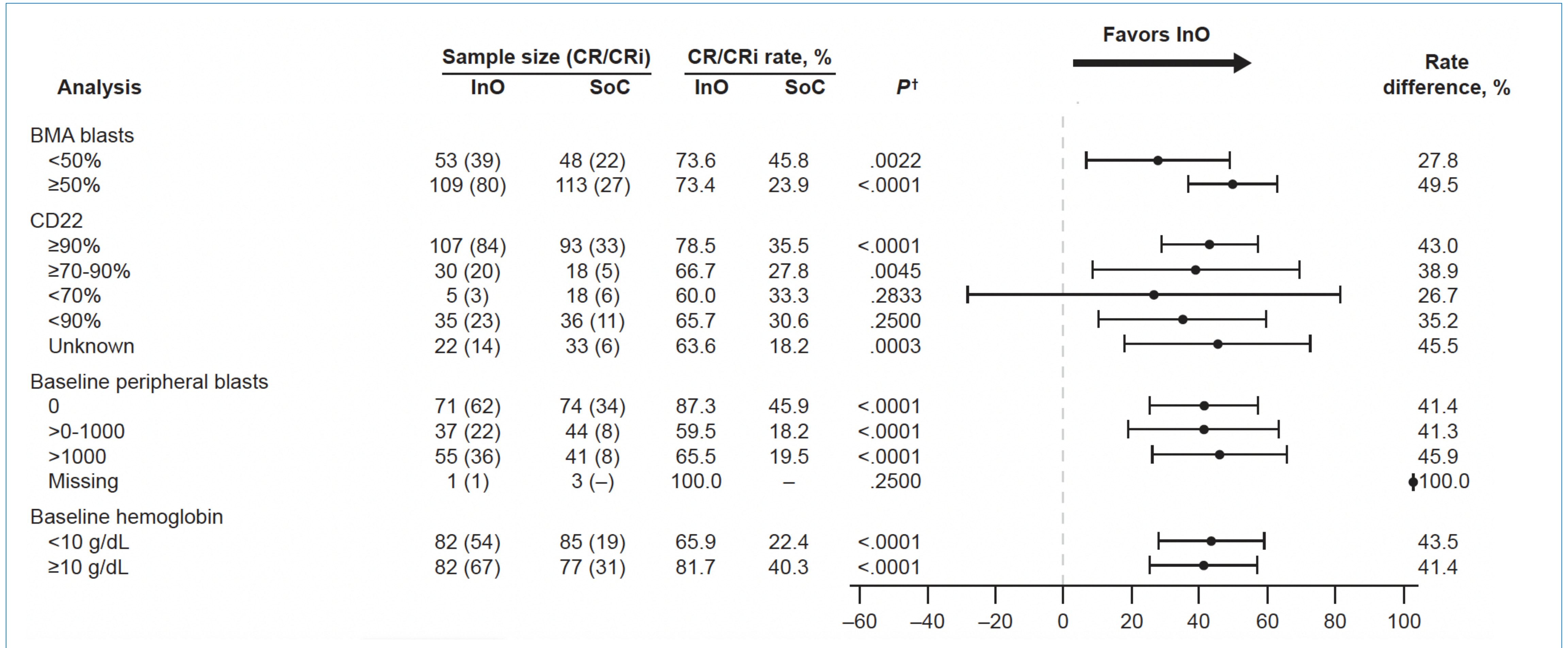
INOTUZUMAB

The “INOVATE” trial



INOTUZUMAB

The INOVATE trial: CR



INOTUZUMAB

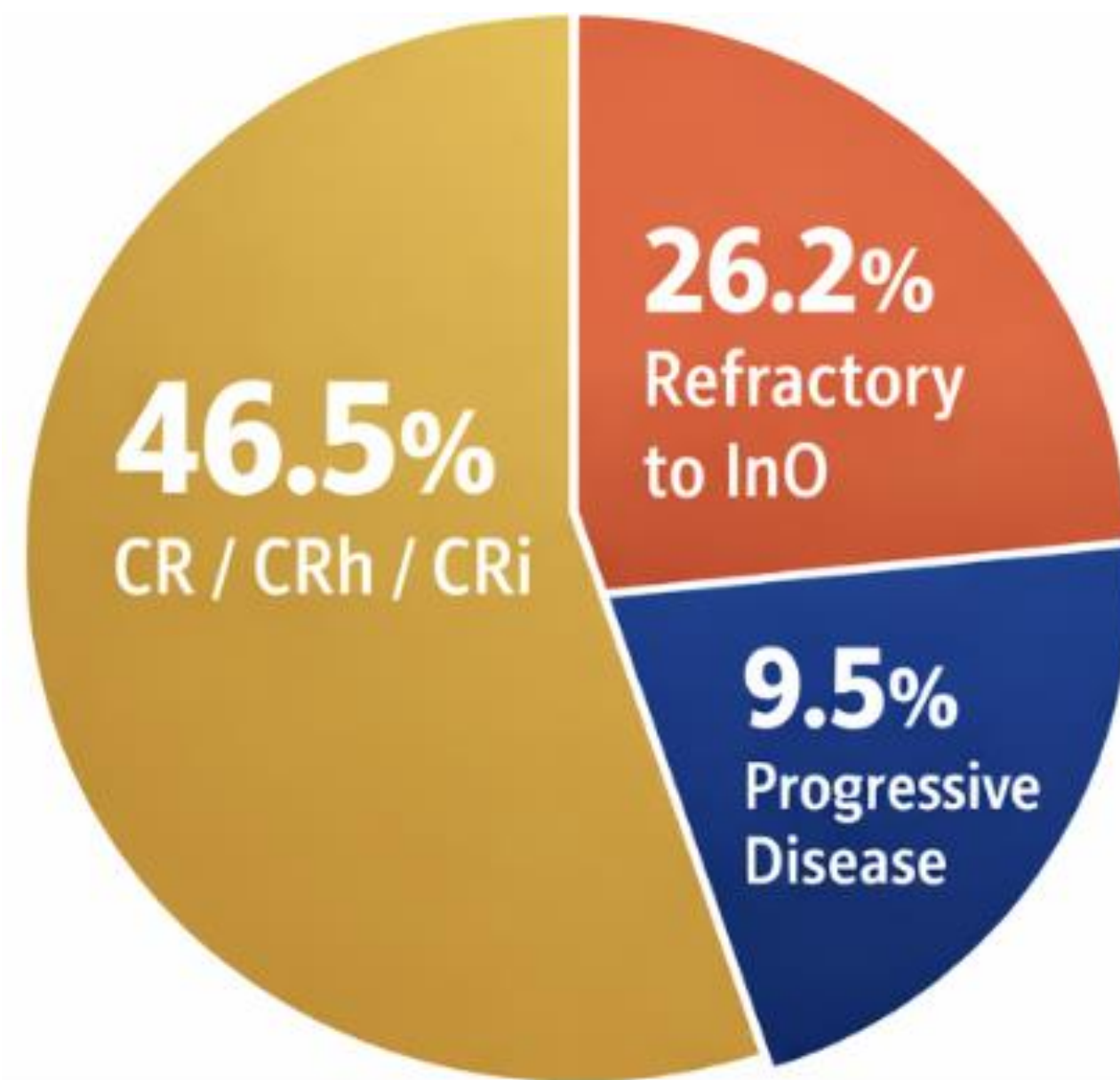
The INOVATE trial: CR

Analysis	Sample size (CR/CRi)		CR/CRi rate, %		<i>P</i> [†]		Rate difference, %
	InO	SoC	InO	SoC			
All patients	164 (121)	162 (50)	73.8	30.9	<.0001		42.9
Duration of first remission							
<12 months	109 (77)	107 (32)	70.6	29.9	<.0001		40.7
≥12 months	55 (44)	55 (18)	80.0	32.7	<.0001		47.3
Salvage status							
Salvage 1	108 (84)	107 (32)	77.8	29.9	<.0001		47.9
Salvage 2	56 (37)	55 (18)	66.1	32.7	.0002		33.3
Age at randomization, years							
<55	104 (78)	103 (29)	75.0	28.2	<.0001		46.8
≥55	60 (43)	59 (21)	71.7	35.6	<.0001		36.1
Cytogenetics							
Ph+	22 (16)	27 (15)	72.7	55.6	.1075		17.2
Ph-	142 (105)	135 (35)	73.9	25.9	<.0001		48.0
Complex	28 (20)	22 (4)	71.4	18.2	<.0001		53.2
Normal with ≥20 metaphases	35 (29)	34 (10)	82.9	29.4	<.0001		53.4
Sex							
Male	91 (68)	102 (26)	74.7	25.5	<.0001		49.2
Female	73 (53)	60 (24)	72.6	40.0	<.0001		32.6
Pre-study transplant							
Yes	29 (20)	32 (10)	69.0	31.3	.0016		37.7
No	135 (101)	130 (40)	74.8	30.8	<.0001		44.0

INOTUZUMAB before CAR-T

A real-world study from Spain, Uk, US

100% 1 cycle, 21% 2 cycles, 4% ≥ 3 cycles
(35% brexu, 35% tisa, 30% other)



CR Maintained: **68.8%** for 6 Months

12-Months after CAR-T infusion



72.5% Survived



62.4%
Had Not Initiated
Salvage Therapy

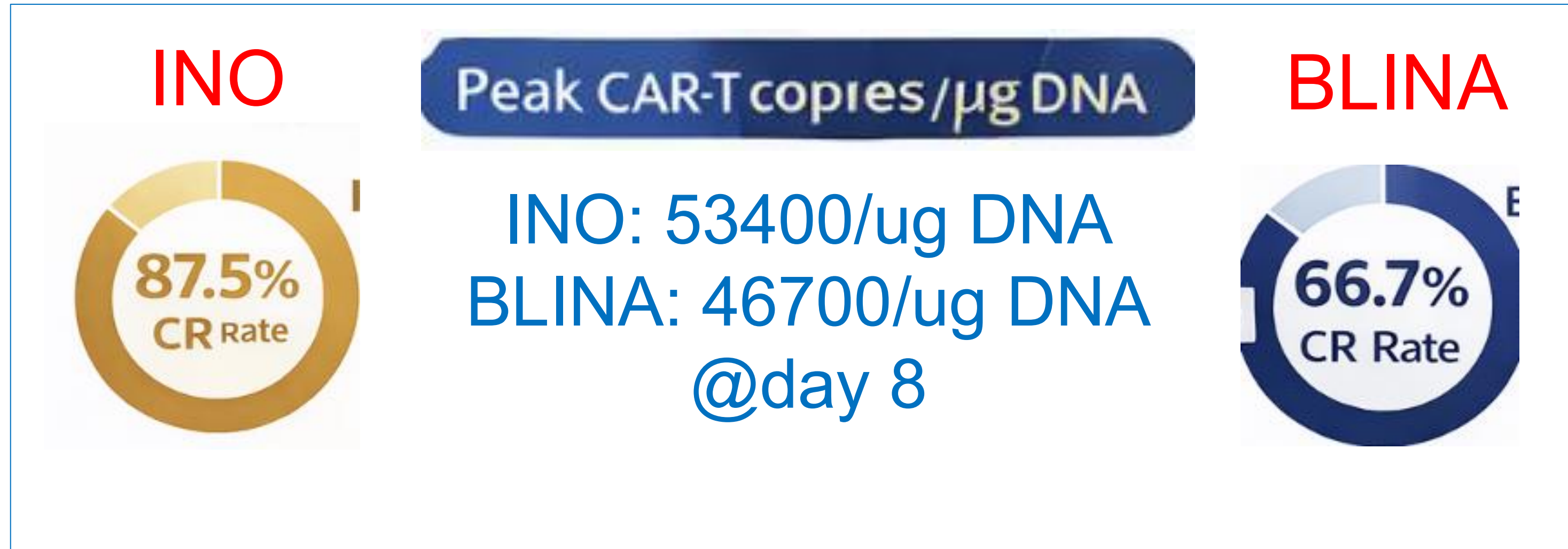
**Median OS
Not Reached**

 **57.3%**
Alive at
Data Collection

INOTUZUMAB vs BLINATUMUMAB before CAR-T

A real-world study from Cina

22 pts



1-Year Overall Survival Comparable INO: **80%** v Blin: **83%** (p=0.91)

CRS gr 1-2 = 77%
ICANS gr 1-2 = 23%
No VOD

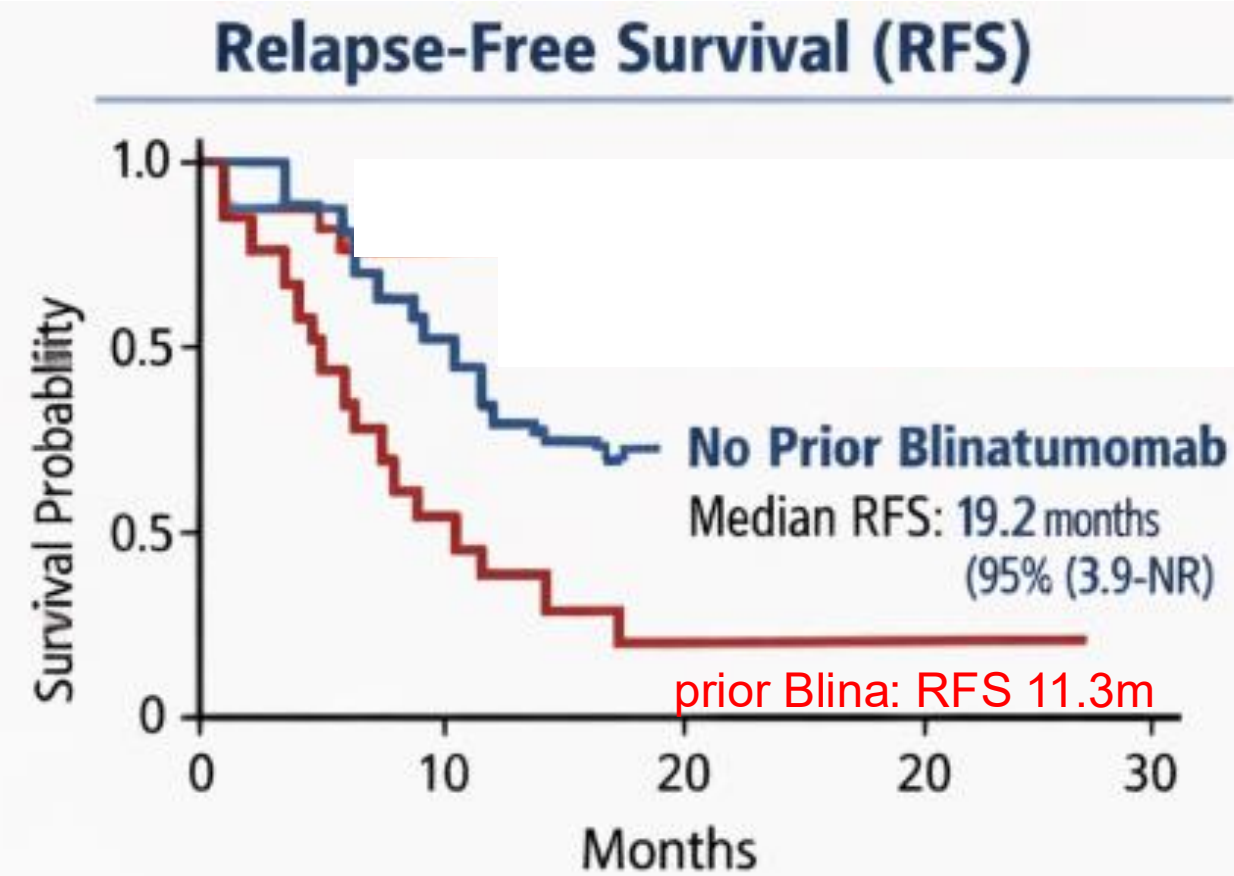
INO vs BLINA before CAR-T

UK experience

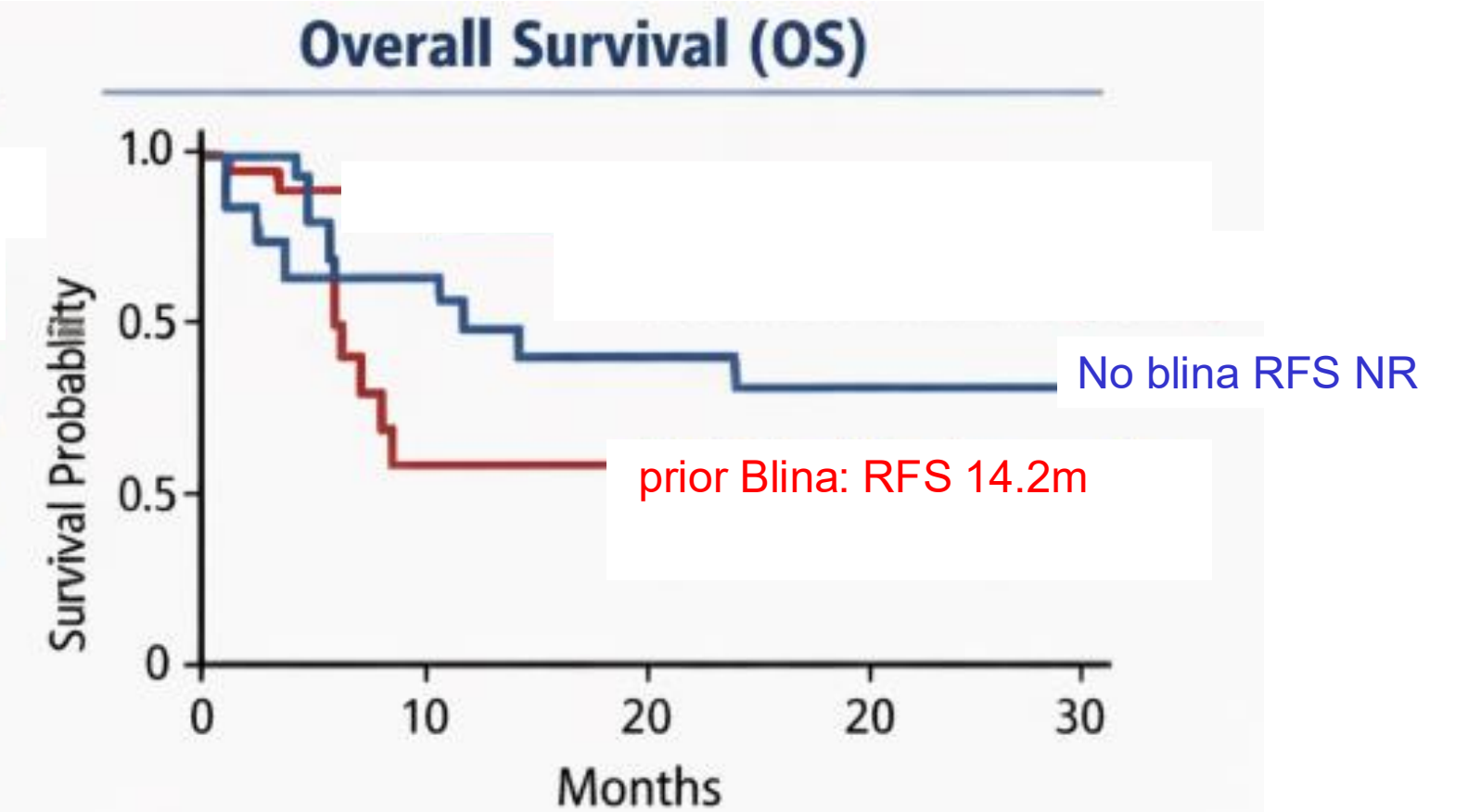
Inotuzumab Exposure

- Any Inotuzumab: $p = 0.375$
- Ino as Bridging: $p = 0.573$

No Impact on OS



$p = 0.046$
Worse RFS with Prior Blinatumomab



$p = 0.042$
Worse OS with Prior Blinatumomab



LAL e LAM : DAY

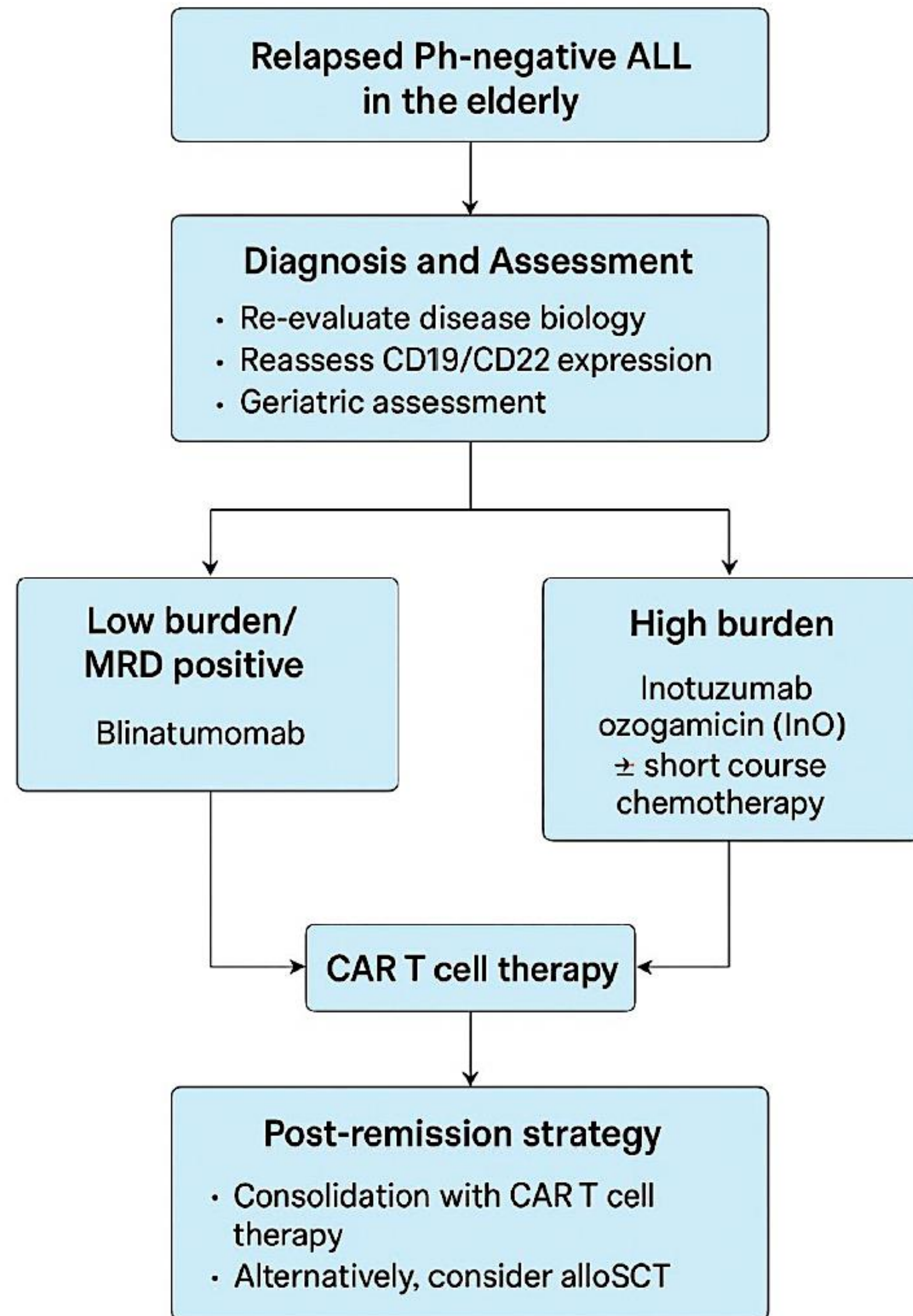
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INO vs BLINA
Which one?

INO vs BLINA in ELDERLY PTS



for extra-medullar disease
INO better than BLINA

ANTIBODIES: the MAIC analysis

INOVATE vs TOWER

Table 2. Summary of Indirect Treatment Comparison Results

	ITT		ADJUSTED		Indirect Treatment Comparisons		
	TOWER, Blina vs SOC, ITT	INO-VATE- ALL, InO vs SOC, ITT	INO-VATE- ALL, InO vs SOC, MAIC	INO-VATE- ALL, InO vs SOC, STC	InO vs Blina, NMA	InO vs Blina, MAIC	InO vs Blina, STC
CR/CRi Remission Rate							
OR (95% CI)	2.40 (1.51, 3.80)	6.30 (3.89, 10.21)	6.75 (3.04, 14.95)	9.38 (4.14, 21.25)	2.63 (1.35-5.12)	2.81 (1.12, 7.05)	3.91 (1.53, 9.99)
HSCT Rate							
OR (95% CI)	1.01 (0.62, 1.63)	3.25 (2.01, 5.26)	4.15 (2.20, 7.85)	3.81 (2.03, 7.18)	3.23 (1.63-6.40)	4.11 (1.85, 9.12)	3.77 (1.71, 8.35)
Event Free Survival							
HR (95% CI)	0.55 (0.43, 0.71)	0.47 (0.36, 0.60)	0.40 (0.28, 0.57)	0.40 (0.28, 0.56)	0.85 (0.60-1.20)	0.73 (0.47-1.13)	0.73 (0.48, 1.11)
RMST Difference (95% CI)	2.10 (0.76,3.43)	4.81 (3.52,6.11)	5.70 (3.90,7.49)	NA	2.71 (0.85, 4.57)	3.60 (1.37, 5.83)	NA
RMST Ratio (95% CI)	1.90 (1.18,3.07)	3.42 (2.34,4.98)	4.31 (2.47,7.54)	NA	1.80 (0.98, 3.31)	2.27 (1.09, 4.74)	NA
Overall Survival							
Overall HR (95% CI)	0.71 (0.55, 0.93)	0.75 (0.57, 0.99)	0.68 (0.47, 0.97)	0.72 (0.50, 1.03)	1.06 (0.72, 1.56)	0.96 (0.61, 1.50)	1.01 (0.65, 1.59)
0-15 month HR (95% CI)	0.73 (0.55, 0.96)	0.83 (0.64, 1.07)	0.74 (0.51, 1.08)	0.79 (0.55, 1.14)	1.14 (0.78, 1.65)	1.01 (0.64, 1.62)	1.08 (0.69, 1.71)
15+ month HR (95% CI)	1.03 (0.10, 10.23)	0.33 (0.17, 0.67)	0.25 (0.08, 0.79)	0.26 (0.11, 0.65)	0.32 (0.03, 3.54)	0.24 (0.02, 3.17)	0.25 (0.02, 2.99)
RMST Difference (95% CI)	2.05 (0.03, 4.07)	1.68 (-0.03, 3.39)	2.35 (-0.08, 4.78)	NA	-0.37 (-3.02, 2.28)	0.30 (-2.86, 3.46)	NA
RMST Ratio (95% CI)	1.25 (0.99, 1.57)	1.19 (1.00, 1.42)	1.27 (0.99, 1.64)	NA	0.95 (0.71, 1.27)	1.02 (0.72, 1.43)	NA

ITT=Intention-to-Treat (RCT trial population); InO= Inotuzumab Ozogamicin; Blina= Blinatumomab; SOC= Standard intensive chemotherapy; NMA=Network Meta-analysis; MAIC=Matching-Adjusted Indirect Comparison; STC=Simulated Treatment Comparison; CR=Complete remission; CRi= Complete remission with Incomplete Hematologic Recovery; OR=Odds Ratio; CI=Confidence Interval; HR=Hazard Ratio; RMST=Restricted Mean Survival Time; HSCT= Hematopoietic Stem-cell Transplant.

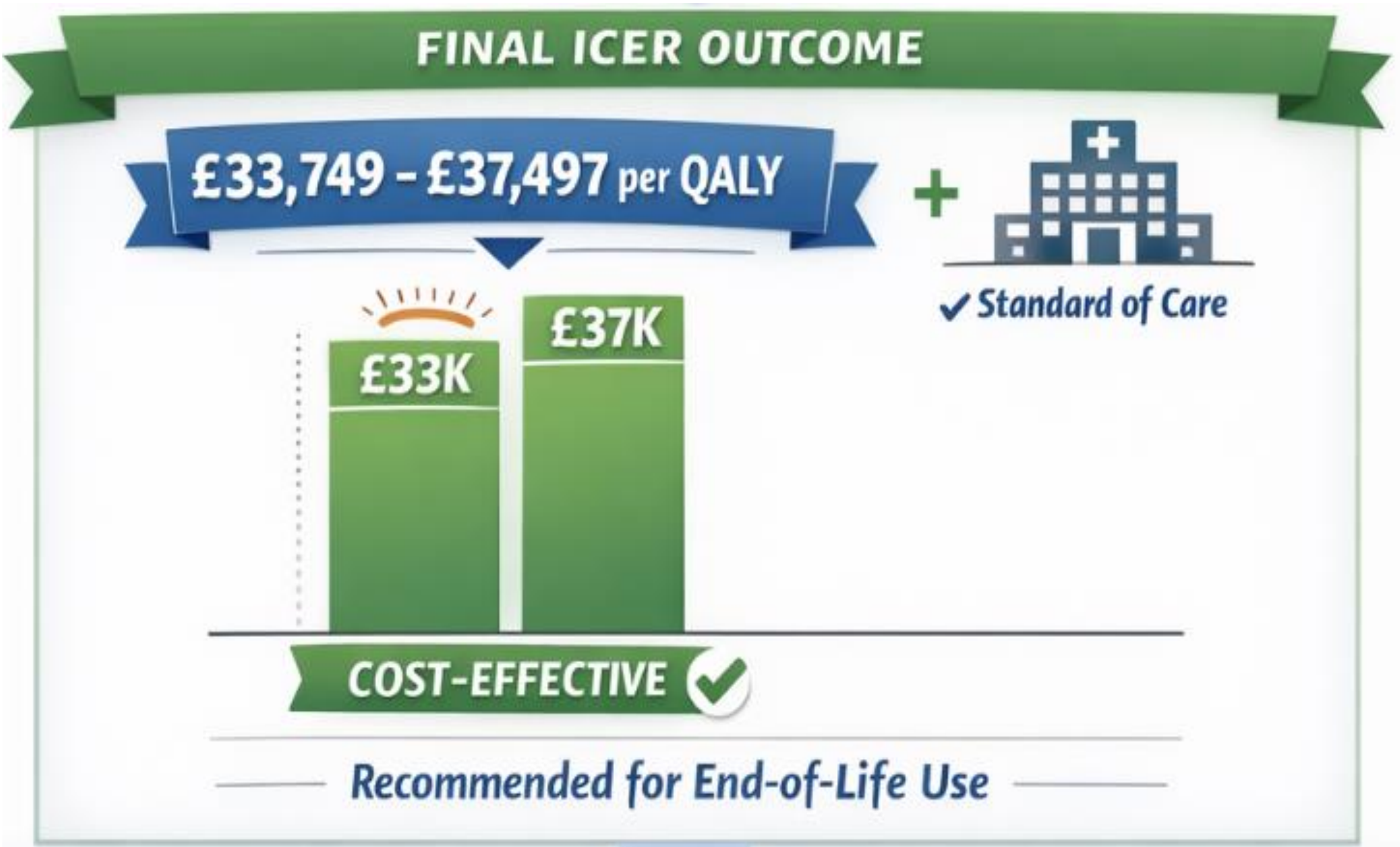
INO better than BLINA
For ORR and CR
Equal for EFS and OS

BLINA, INO & ICER

BLINA



INO





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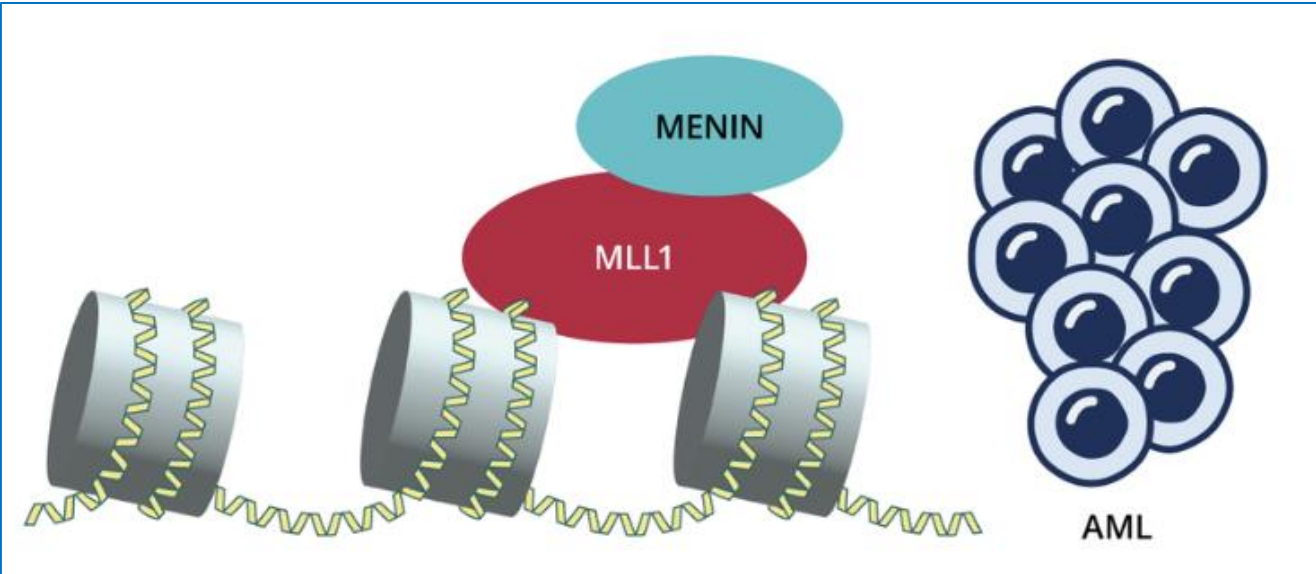
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5. THE FUTURE

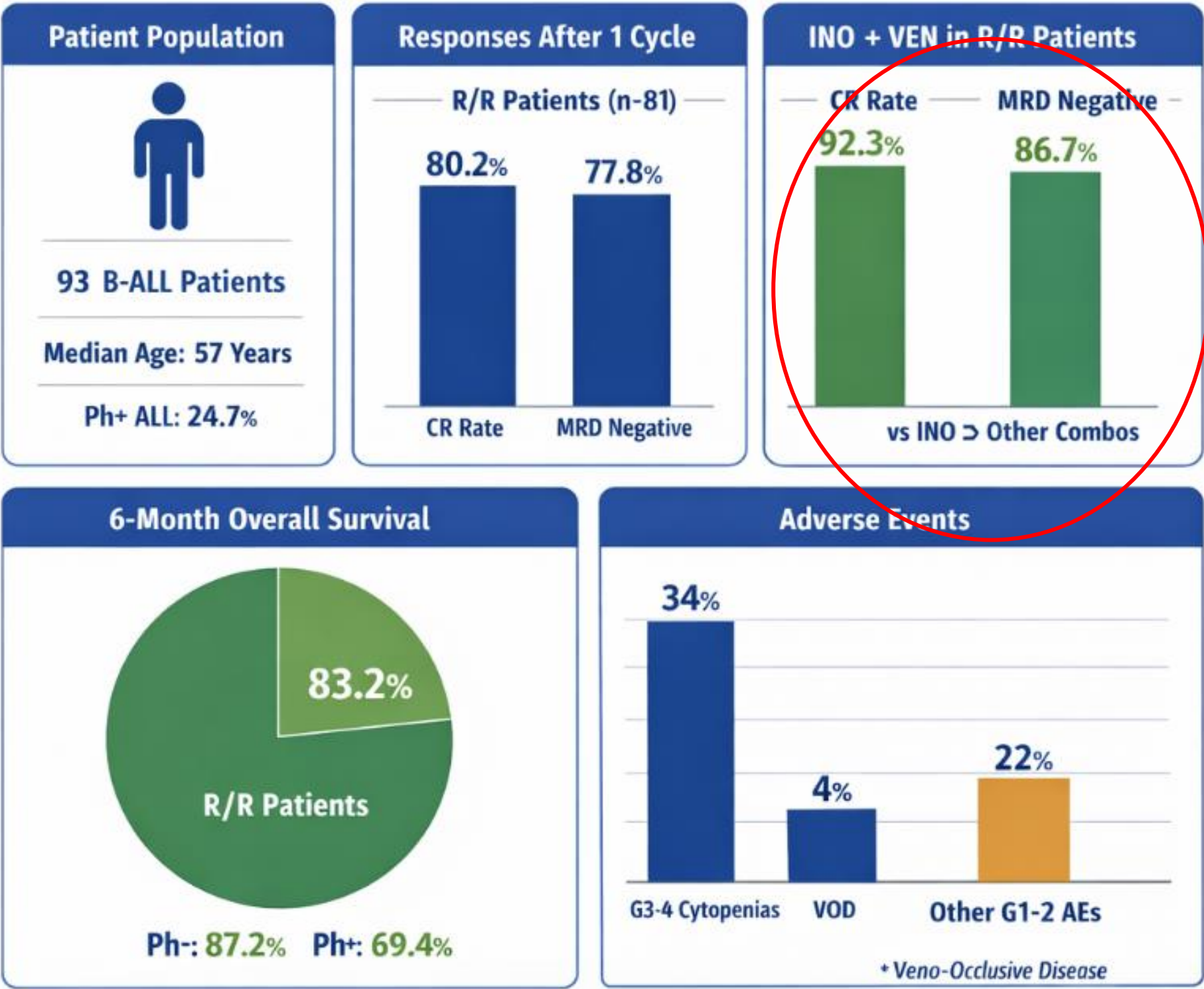
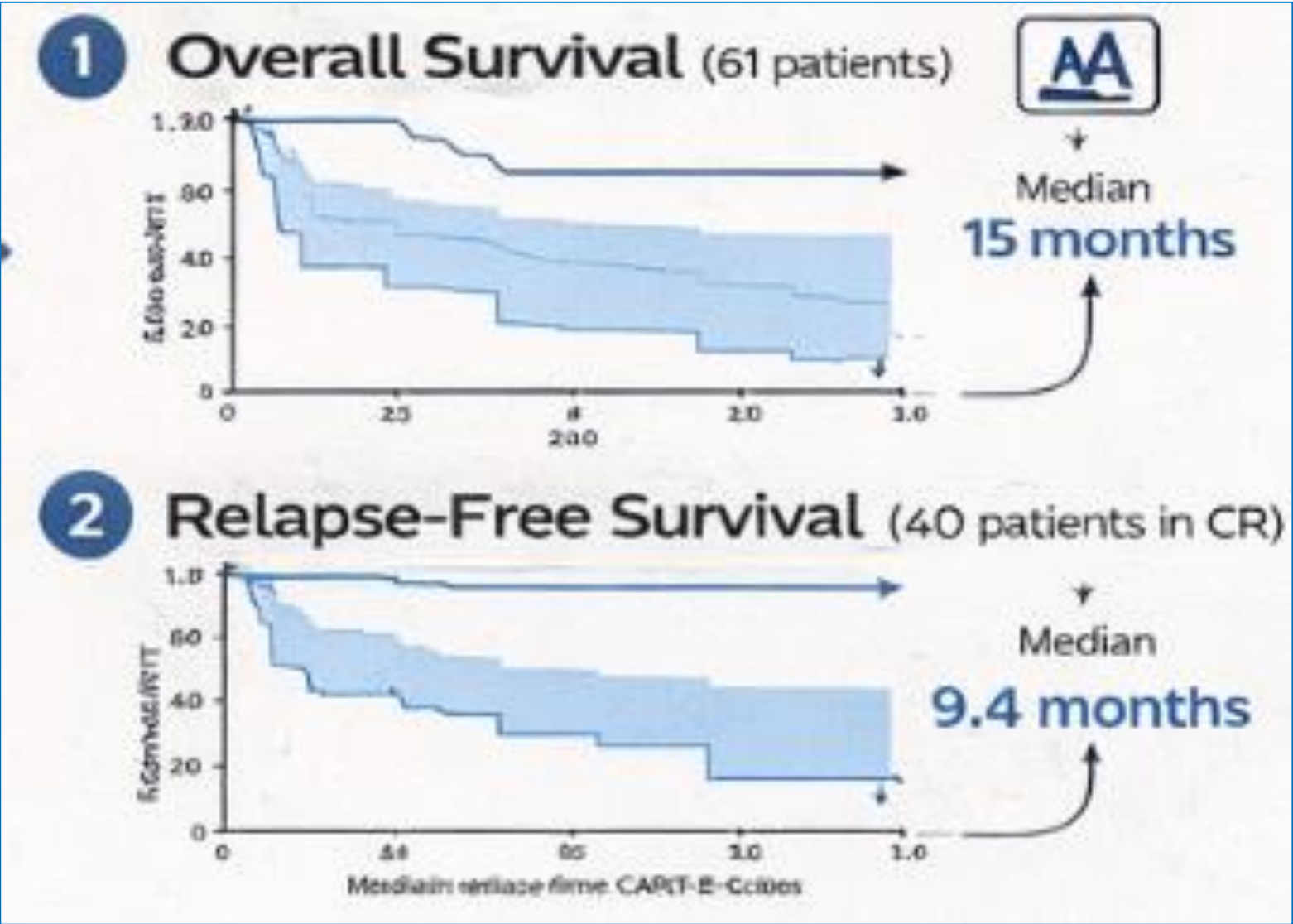
THE FUTURE LANDSCAPE

BETTER 1 LINE!

Menin inhibitors in KMT2Ar



II CAR-T



combinations



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6. TAKE HOME MESSAGES

THEN...

- ✓ The ALL-PH'- continues to be a “hard” disease...
- ✓ The diagnosis is more complex, and the MRD still need a complete harmonization...
- ✓ ALL presents with high costs, prolonged hospitalization and need of many lines of treatments...
- ✓ The role of the antibodies is fundamental, especially as bridge to transplant or CAR-T...
- ✓ Blina and Ino have got also different indications...
- ✓ ICER shows that antibodies are “cost-effective”...
- ✓ Several unmet clinical needs remain: the treatment of elderly pts, the “very high” and TP53 mutated forms...
- ✓ The combination of antibodies in I line or with other drugs (venetoclax) in R/R pts, further target therapies (anti-FLT3) or new CAR-T (anti-CD22) will soon represent the new landscape...



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THANK YOU FOR
ATTENTION!!!

sara.galimberti@unipi.it

