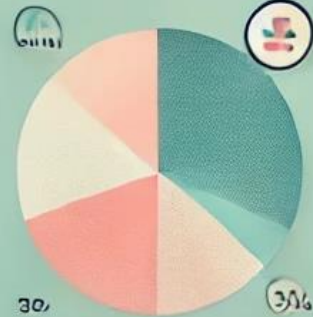
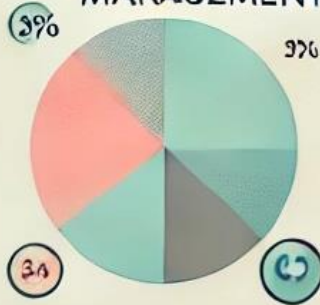
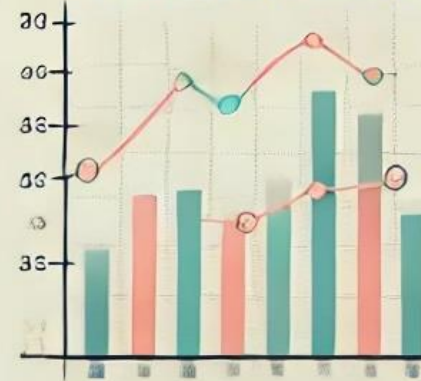


PRE-TRANSPLANT MANAGEMENT ENHANCING ALL PATIENT OUTCOMES

PRE-TRANSPLANT MANAGEMENT



PRE-TRANSPLANT



PRE-TRANSPLANT MANAGEMENT



ENHANCING
ALL PATIENT

PRE-TRANSPLANT

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CMU
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OUTLINE

1

Introduction

Brief overview of ALL

Risk factors

Pathophysiology

2

Diagnosis Risk stratification

Diagnostic tools

Significance of
risk stratification
in treatment planning

3

Therapeutic strategies

ELN2024

Ph negative ALL

Ph positive ALL

Ph-like ALL
T-ALL/LBL

Role of SCT

4

Conclusion

Summarize key point

1

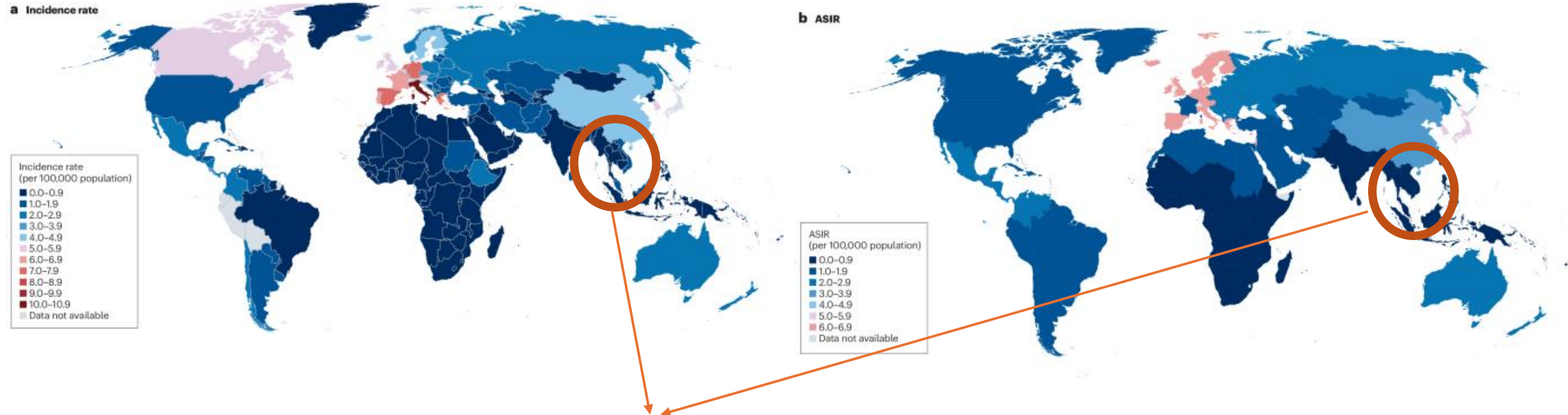
Introduction

- Acute lymphoblastic leukemia (ALL)
uncontrolled proliferation of abnormal, immature lymphoid cells
resulting in clonal accumulation in the BM, blood, and extramedullary sites
- Occurring in both children and adults, more frequent in children
A peak incidence in those aged 1–4 years
The lowest incidence in those aged 25–45 years
- The two main types of ALL
B-cell ALL (B-ALL) and T-cell ALL (T-ALL)

Incidence of acute lymphoblastic leukemia

Incidence rate

Age-standardized incidence rate (ASIR)

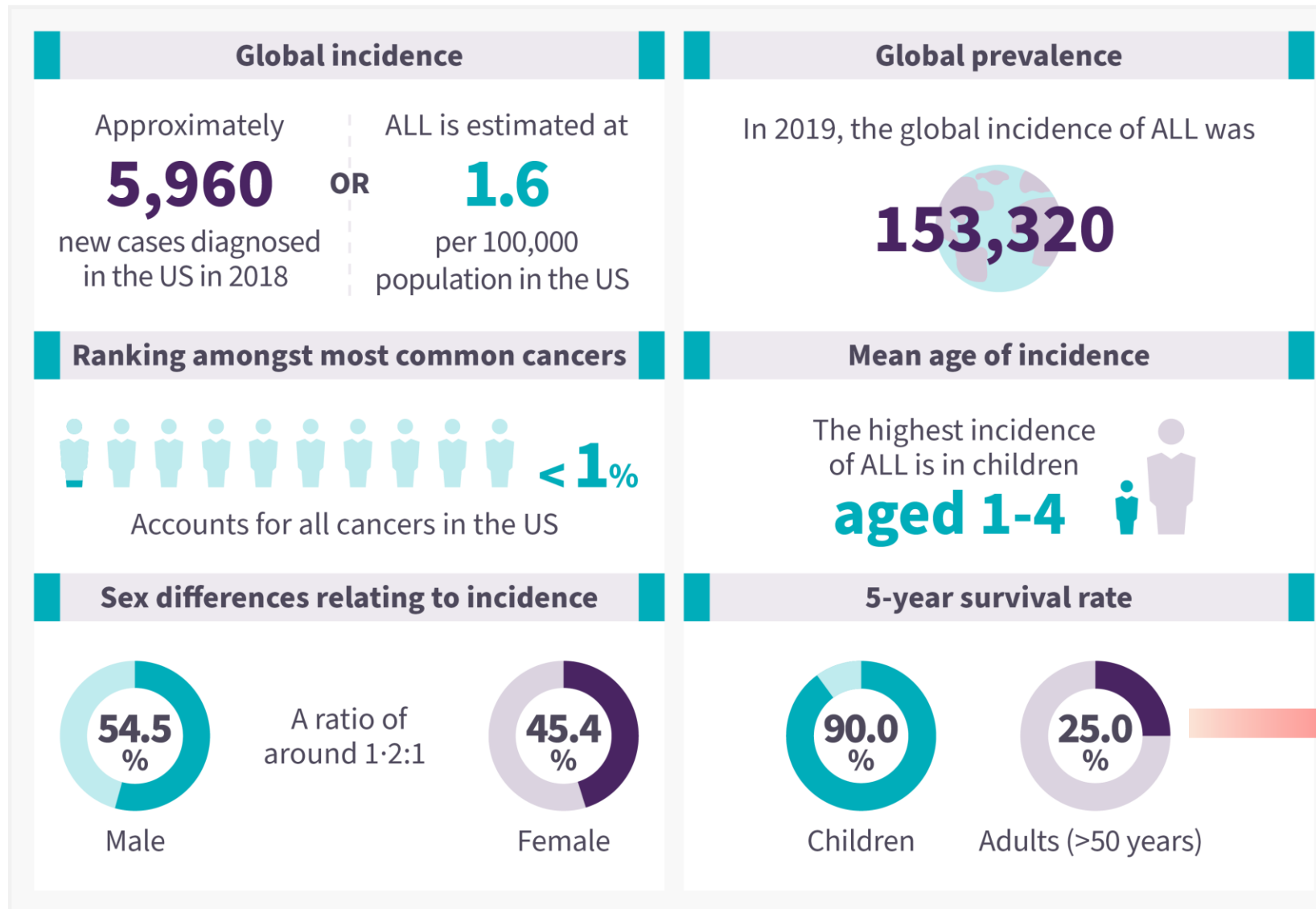


Thailand ~ 1:100,000 population

Population: 71 million

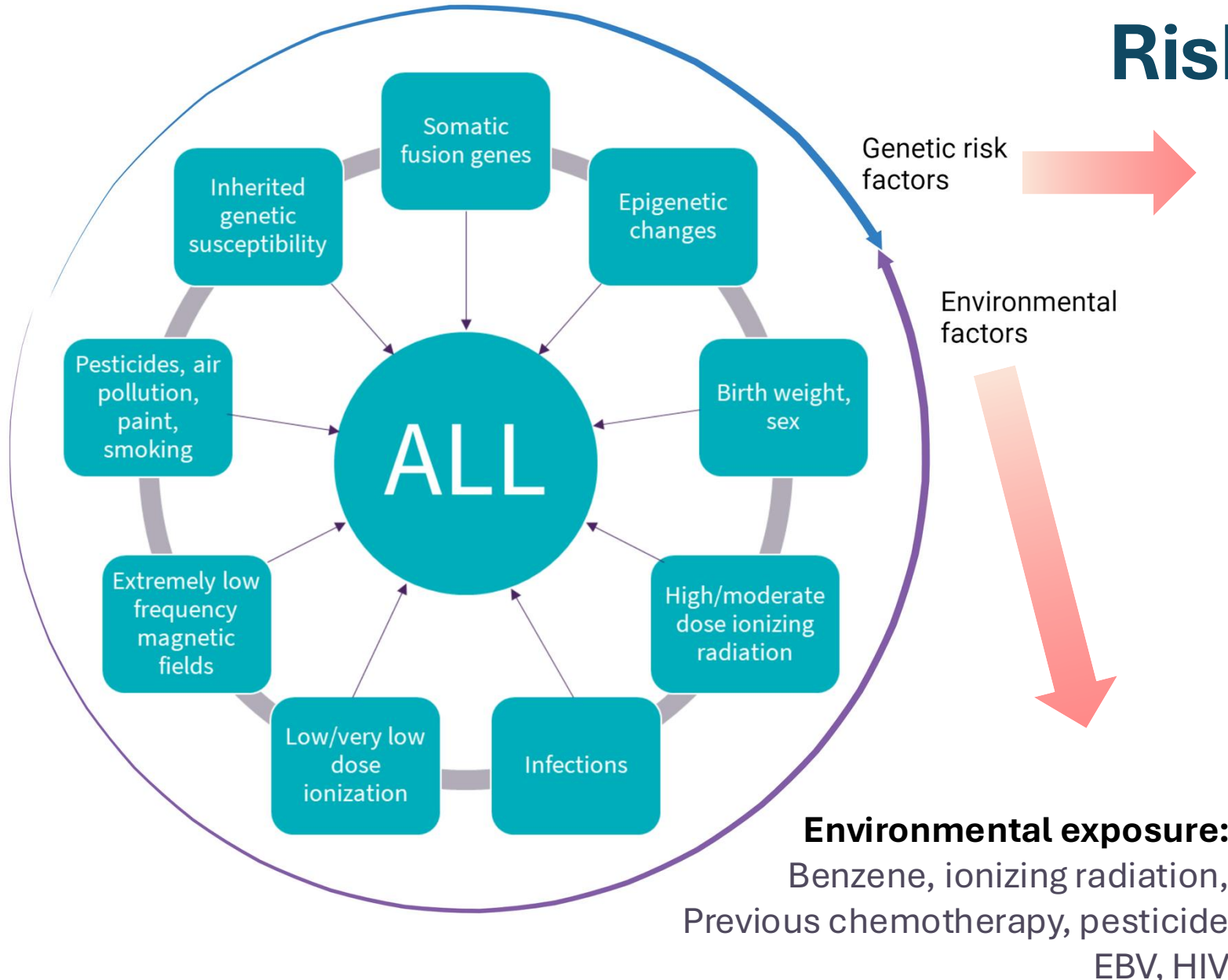


Estimated incidence of ALL = 700⁺⁺ patients/year



**Today,
focusing on adults ALL
(excluded R/R ALL)**

Risk factors of ALL



Congenital syndrome:

Down's syndrome, Fanconi anemia,
ataxia telangiectasia, Bloom syndrome,
Nijmegen breakage syndrome

Inherited variants:

*RID5B, IKZF1, CEBPE, CDKN2A or CDKN2B
PIP4K2A, ETV6*

Constitutional translocation:

rob(15;21)(q10;q10)

Single nucleotide polymorphisms:

rs12402181 in miR-3117
rs62571442 in miR-3689d2

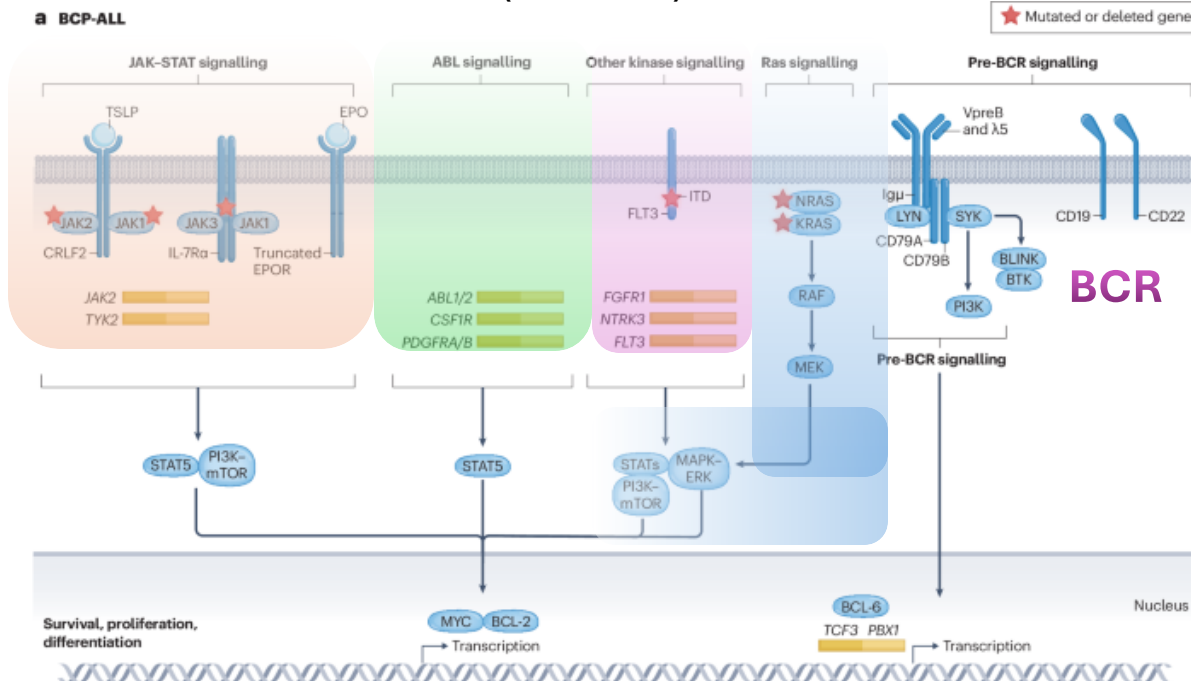
Rare germline mutations:

PAX5, ETV6 and p53

Pathophysiology: signaling pathways involved in ALL

B-cell ALL

(75-80%)

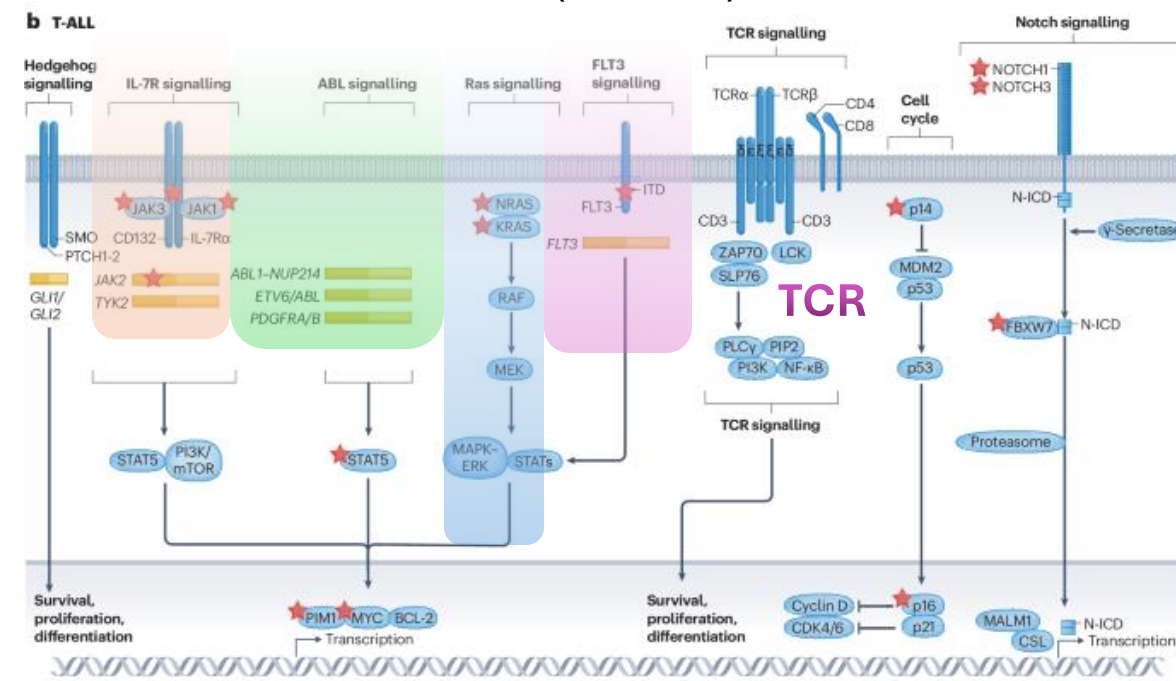


T-cell ALL

(20-25%)

Hedgehog signal

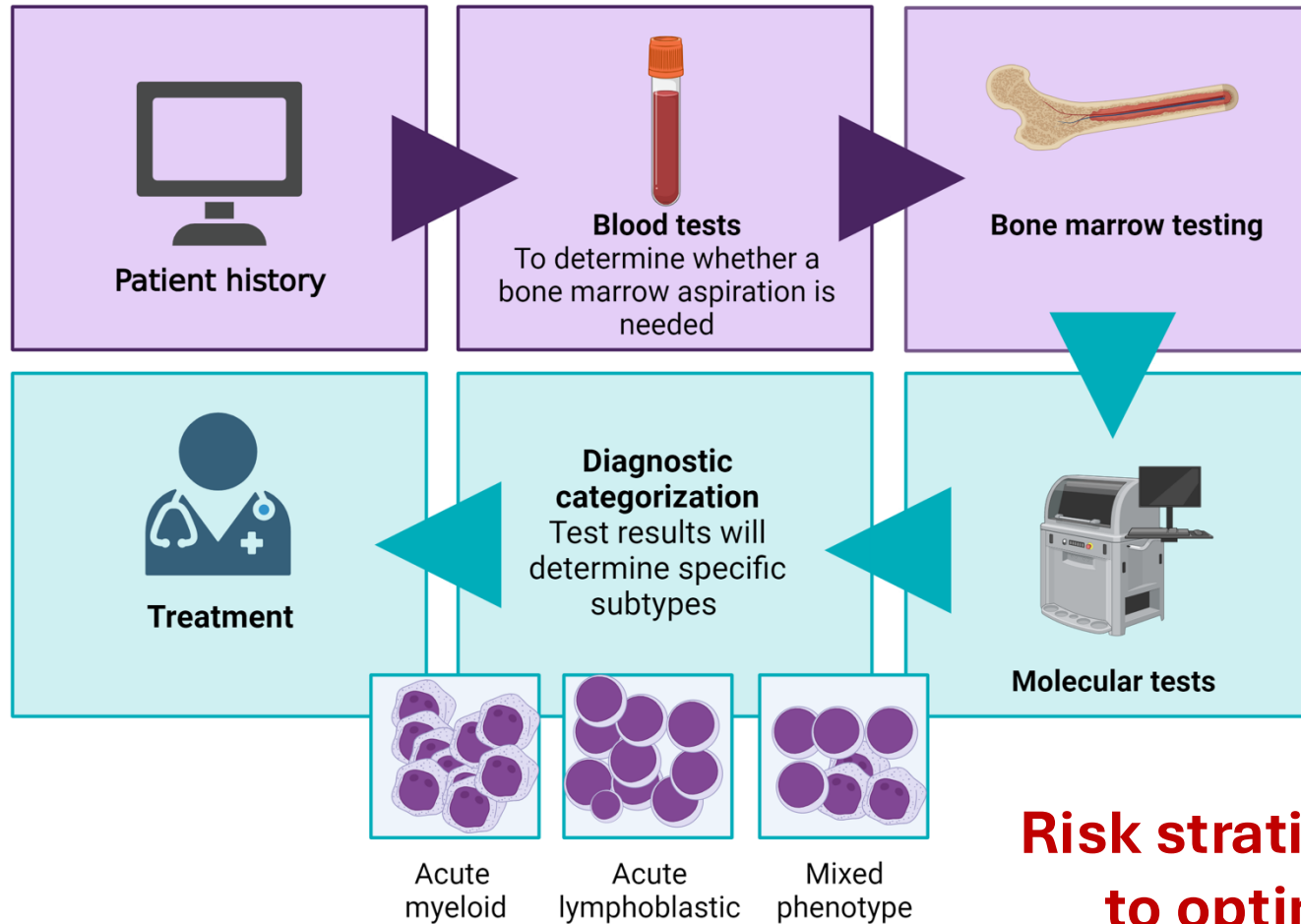
NOTCH



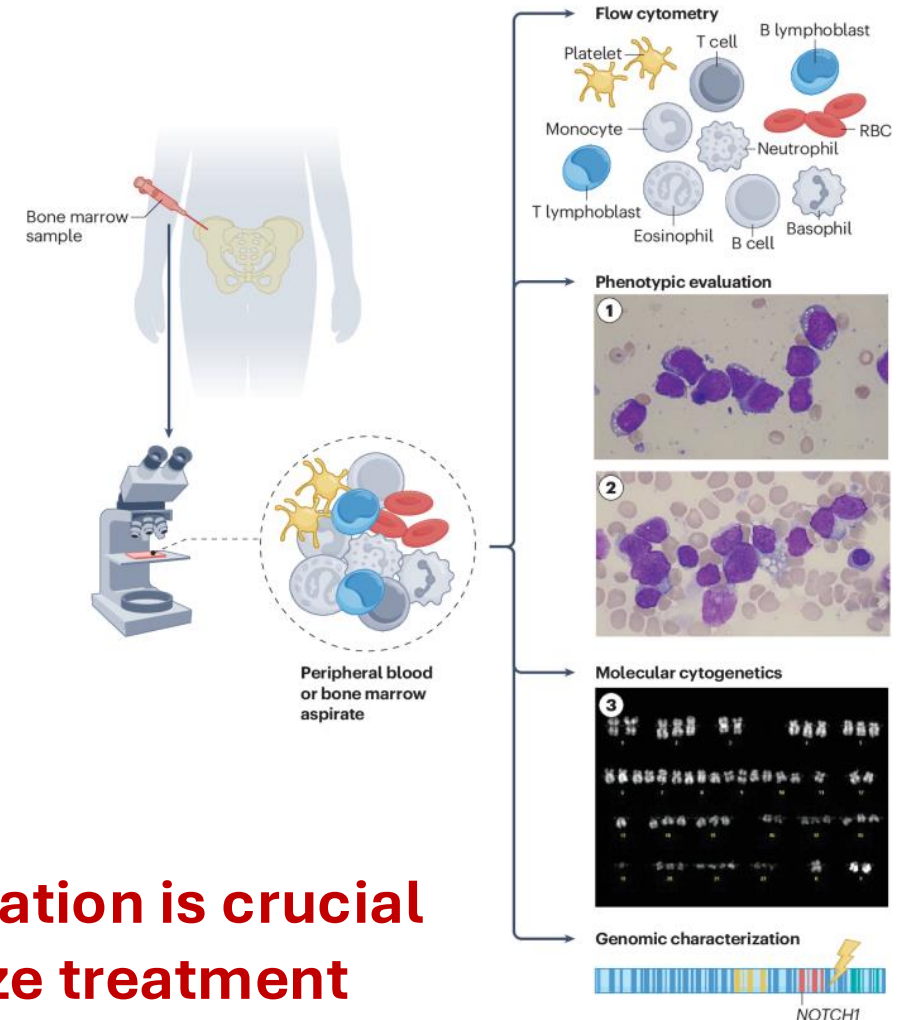
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Diagnosis and Risk stratification

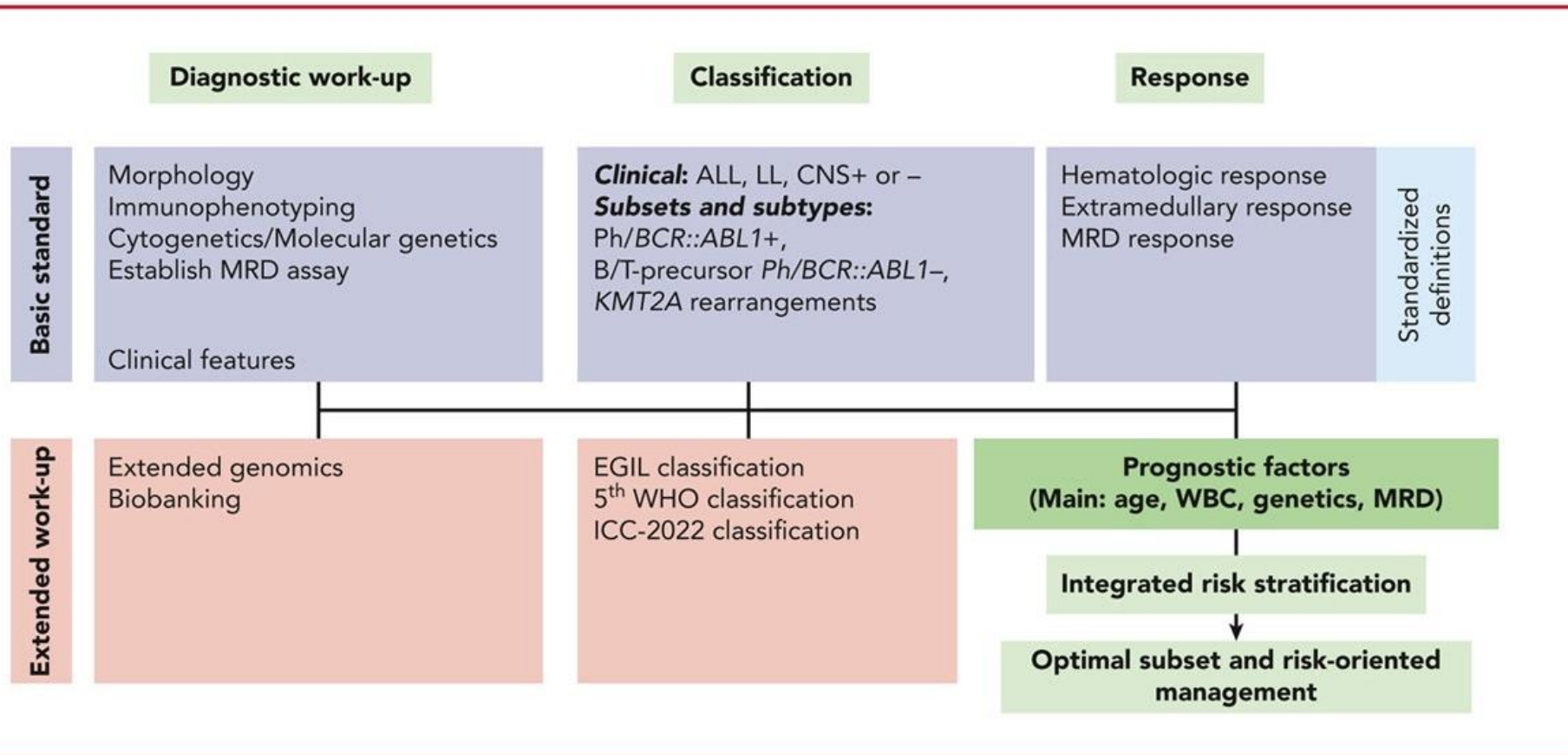
Lymphoblast $\geq 20\%$ in PB or BM



Risk stratification is crucial to optimize treatment



ELN2024 recommendations (Adults ALL)



Basic standard:
All should be performed

MRD:
At diagnosis and followed pt

MRD: Measurable residual disease
LL: Lymphoblastic Lymphoma

Immunophenotyping → MFC

B-lineage ALL

(aberrant coexpression of myeloid markers can be detected ~40%)

CD19, CD22, cCD79a (minimal requirement)
TdT, CD10, CD20, cIgM, sIg kappa or lambda

Pro-B: CD10- → often assoc. t(4;11)/KMT2A

Common-B: CD10+/ cIgM-

Pre-B: cIgM+/ sIg- → often assoc. t(1;19)/TCF3::PBX1

Mature-B: sIg+, CD20+

T-lineage ALL

cCD3, CD7 (minimal requirement)

TdT, CD1a, CD2, CD5, CD4, CD8, TCR α/β or γ/δ

Pro-T: only cCD3+, CD7+ }

Pre-T: CD2+, CD5+ }

ETP-ALL

+ weak CD5
+ ≥ 1 myeloid/stem cell markers

Cortical-T (thymic): CD1a+

Mature-T: sCD3+, CD1a-, CD4+ and/or CD8 +

Cytogenetics and molecular testing

(karyotyping, FISH, reverse transcriptase PCR, NGS)

Prognostic factors of ALL

(High risk or Adverse risk)

	Risk factors
Patient-related	
Age (y)	>30-60 y (continuous variable) >55 y (older adults and elderly)
Performance (ECOG)	>1

	Risk factors
Treatment-response dynamics	
Corticosteroid sensitivity (prephase)	Poor prednisone response (PB count $\geq 1 \times 10^9/L$ at the end of prephase)
Early/incomplete blast cell clearance (BM morphology)	Day 8-15 or end of induction BM blasts $\geq 5\%$
Time to CR (number of courses)	>1 cycle (late CR)
MRD (molecular/flow cytometry)	MRD positivity (from end of induction onwards): $\geq 0.1\%/0.01\%$ after induction $\geq 0.01\%$ /positive after/during consolidation and pre/post-allogeneic SCT

	Risk factors
Disease-related	
WBC ($\times 10^9/L$)	>30 (B), >100 (T)
Immunophenotype	Pro-B, CD20 ⁺ (B), pro/pre-T, ETP, and mature-T (T)
Cytogenetics and fluorescence in situ hybridization	Ph ⁺ , t(4;11), hypodiploidy, and complex*
Genetics	<i>BCR::ABL1</i> ⁺ , <i>KMT2A</i> r Ph-like, mutated <i>CLRF2/TP53/JAK-STAT</i> , adverse CNA profile (B), unmutated <i>NOTCH1/FBWX7</i> , and abnormal <i>RAS/PTEN</i> (T)
Miscellaneous	CNS involvement Poor treatment compliance and undue treatment reductions and delay Pharmacogenomics (affecting antimetabolite disposition) Immune marrow microenvironment Drug response profiling

Main genetics subtype of B-ALL

	Frequency	Mutation	Prognosis
High hyperdiploid (gain of ≥ 5 chromosomes)	<u>25% children</u> ; 3% AYAs and adults	RTK-RAS signalling pathway, histone modifiers	Favourable
Near-haploid (24–31 chromosomes)	2% children; <1% AYAs and adults	RAS-activating, <i>IKZF3</i>	Poor
Low-hypodiploid (32–39 chromosomes)	<1% children; 5% AYAs; <u>>10% adults</u>	<i>TP53</i> , <i>IKZF2</i> , <i>RB1</i>	Very poor
MLL (<i>KMT2A</i>) rearrangements	>80% infants; <1% children; 4% AYAs; 15% adults	MLL (<i>KMT2A</i>) rearrangement, few additional mutations (PI3K-RAS signalling pathway)	Very poor
<i>ETV6</i> – <i>RUNX1</i> translocation, t(12;21)(q13;q22)	<u>30% children</u> ; <5% AYAs and adults	<i>ETV6</i> – <i>RUNX1</i>	Favorable
<i>TCF3</i> – <i>PBX1</i> translocation, t(1;19)(q23;p13)	5% children, AYAs and adults	<i>TCF3</i> – <i>PBX1</i>	Favorable
<i>TCF3</i> – <i>HLF</i> variant of t(1;19)(q23;p13)	<1% acute lymphoblastic leukaemia	<i>TCF3</i> – <i>HLF</i>	Poor

<i>BCR</i> – <i>ABL1</i> Philadelphia chromosome, t(9;22)(q34;q11)	2–5% children, <u>6% AYAs</u> ; <u>>25% adults</u>	<i>BCR</i> – <i>ABL1</i> fusion gene, common deletions of <i>IKZF1</i> , <i>CDKN2A</i> , <i>CDKN2B</i> , and <i>PAX5</i>	Poor (improved with tyrosine kinase inhibitors)
Philadelphia chromosome-like acute lymphoblastic leukemia	10% children; <u>25–30% AYAs</u> ; <u>20% adults</u>	Rearrangements of <i>CRLF2</i> (about 50%), <i>ABL</i> -class tyrosine kinase genes (12%) and <i>JAK2</i> (10%); mutations of <i>EPOR</i> (3–10%); mutations activating <i>JAK</i> – <i>STAT</i> (10%) and <i>RAS</i> (2–8%) signalling pathways	Poor
<i>DUX4</i> and <i>ERG</i> -deregulated acute lymphoblastic leukemia	5–10% acute lymphoblastic leukemia	<i>DUX4</i> rearrangement and overexpression, <i>ERG</i> deletions	Favorable, including if coexistence of <i>IKZF1</i> mutations (about 40% of patients)
<i>MEF2D</i> -rearranged acute lymphoblastic leukemia	4% children; 7% AYAs and adults	<i>MEF2D</i> is fused to <i>BCL9</i> (most frequent fusion event), <i>HNRNPUL1</i> , <i>SS18</i> , <i>FOXJ2</i> , <i>CSF1R</i> , or <i>DAZAP1</i>	Poor
<i>ZNF384</i> -rearranged acute lymphoblastic leukemia	5% children; 10% AYAs and adults	<i>ZNF384</i> rearranged with a transcriptional regulator or chromatin modifier (<i>EP300</i> , <i>CREBBP</i> , <i>TAF15</i> , <i>SYNRG</i> , <i>EWSR1</i> , <i>TCF3</i> , <i>ARID1B</i> , <i>BMP2K</i> , or <i>SMARCA2</i>)	Intermediate

Poorer prognosis mutations appear in **AYA and Adults ALL** compared to childhood ALL

Molecular subgroup of B-ALL

ALL subset	Prevalence and prognosis*	Related aberration(s)
B-lineage ALL		
<i>BCR::ABL1/t(9;22)(q34;q11.2) (Ph⁺)</i>	20%-50%, increasing with age; improved by tyrosine kinase inhibitor therapy	<i>BCR::ABL1</i> rearrangement
Ph-like	25%-27% Unfavorable/controversial for current regimens	Gene expression profile like <i>BCR::ABL1</i> ⁺ ALL but without <i>BCR::ABL1</i> rearrangement
<i>TCF3::PBX1/t(1;19)(q23;p13)</i>	10%-15% Favorable with intensive therapy	<i>TCF3::PBX1</i> rearrangement
<i>KMT2A(MLL)::AFF1/t(4;11)(q21;q23.3), KMT2A-rearranged/t(v;11q23.3)</i>	~5% Unfavorable	<i>KMT2A::AFF1</i> or <i>KMT2A</i> -other partner gene rearrangement
<i>IGH::MYC/t(8,14)(q24;q32)</i>	1%-5% Unfavorable in B-precursor ALL	<i>IGH::MYC</i> rearrangement
<i>TCF3::HLF/t(17;19)(q22;p13.3)</i>	<1% Unfavorable	<i>TCF3::HLF</i> rearrangement
<i>iAMP21</i>	~2% Intermediate/unfavorable	—
14q32 translocations	<5%, higher in adolescents Intermediate/unfavorable	<i>IGH</i> fusion with partner genes <i>CRLF2</i> , <i>ID4</i> , <i>CEBP</i> , <i>BCL2</i> , <i>EPOR</i> , <i>LHX4</i> , and <i>IL-3</i>
9p13 deletions/translocations	~25% No impact on outcome	<i>PAX5</i> fusion with partner genes <i>ETV6</i> , <i>ELN</i> , <i>POM121</i> , <i>PML</i> , <i>FOXP1</i> , <i>MLLT3</i> , <i>JAK2</i> , <i>C20orf112</i> , <i>AUTS2</i> , <i>CHFR</i> , <i>SOX5</i> , and <i>POM121C</i>
7p12.2 focal deletions/mutations	50%; 80% in Ph ⁺ and Ph-like Controversial prognosis	Deletions of <i>IKZF1</i>
<i>DUX4</i> -rearranged and <i>ERG</i> -deregulated	3%-7% Favorable	<i>ERG</i> and <i>IKZF1</i> deletions
<i>MEF2D</i> -rearranged ALL	3%-4% Poor	
<i>ZNF384</i> -rearranged ALL	6%-7% Intermediate	Partner gene <i>EP300</i> , <i>CREBBP</i> , <i>TAF15</i> , <i>SYNRG</i> , <i>EWSR1</i> , <i>TCF3</i> , and <i>ARID1B</i>
<i>CDX2::UBTF</i>	2.7%-4% Poor	High expression of <i>CDX2</i> and gain (1q); <i>UBTF::ATXN7L3</i> ; <i>CDX2</i> -cis-deregulation

Molecular subgroup of T-ALL

ALL subset	Prevalence and prognosis*	Related aberration(s)
T-lineage ALL		
TAL and LMO rearrangements/del(1)(p32), t(1;14)(p32;q11), t(1;7)(p32;q34), t(7;9)(q34;q32), t(11;14)(p15;q1), t(11;14)(p13;q1), t(7;11)(q35;p13)	30%-40% Favorable and partly depending on additional lesions	SIL-TAL1 rearrangement, TCR rearrangements with TAL1, TAL2, LMO1, and LMO2
HOXA aberrations/inv(7)(p15q34), t(7;7)(p15;q34), t(10;11)(p13;q14), t(v;11q23), del(9)(q34)	20%-25% Outcome depending on additional lesions	TCR-HOXA rearrangement, MLLT10 and MLL rearrangements with various partners, SET-NUP214 rearrangement
TLX1-10q24 rearrangements/t(7;10)(q34;q24), t(10;14)(q24;q11)	20%-30% No impact on prognosis	TCR-TLX11 rearrangement
ETP ALL	10%-15% Unfavorable/controversial	Deregulation of myeloid transcription factors, of members of RAS pathway and of epigenetic regulators
TLX3-5q35 rearrangement/t(5;14)(q35;q32)	10% No impact on prognosis	TLX3-BCL11B rearrangement
t(8;14)(q24;q11)	1% Unfavorable	MYC involvement
ABL1 rearrangements	~3% Potentially targetable by tyrosine kinase inhibitors	NUP214, EML1; ETV6
LYL/MEF2C rearrangement and immature cluster/t(7;19)(q34;p13), del(5)(q14)	3%-17% Unfavorable; improved by intensive treatment	TCR with LYL1 MEF2C rearrangements

3

Therapeutic strategies

Induction

- Glucocorticoid
- Vincristine
- L-asparaginase
- Anthracycline
- Intrathecal chemotherapy

Consolidation

- Glucocorticoid
- High-dose methotrexate
- Low-dose cytarabine
- Asparaginase
- Intrathecal chemotherapy

Intensification

- Glucocorticoid
- Vincristine
- Asparaginase
- Anthracycline
- Intrathecal chemotherapy

Maintenance

- Glucocorticoid
- Methotrexate
- Mercaptopurine
- Vincristine
- Intrathecal chemotherapy

Allogeneic hematopoietic stem cell transplantation is a consolidation treatment primarily undertaken by **high-risk patients** or those with **persistent MRD**.

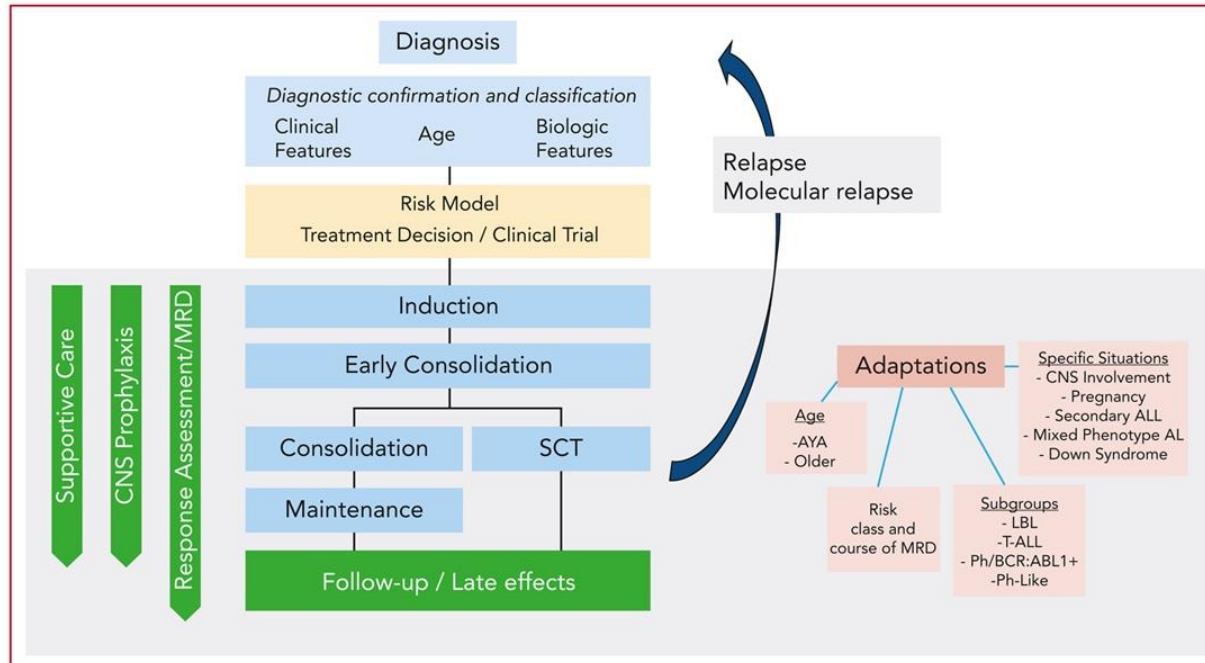
Importance of pre-transplant management

*‘Treatment is usually risk-adapted **using prognostic factors and course of MRD** for treatment decision’*

(regarding intensity of chemotherapy, use of immunotherapies, indication for stem cell transplantation)

**Management of ALL in Adults: 2024 ELN
Recommendations from a European Expert Panel**

ELN2024 treatment recommendations (Adults ALL)



Recommended for adult ALL

Pediatric-based
Age (AYA, Older)
Subset (Ph, Ph-like)
MRD

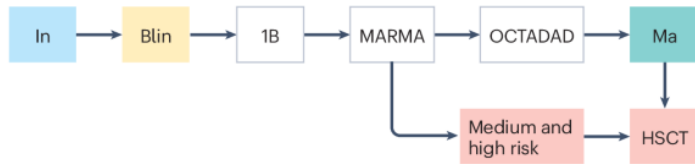
Conclusions: Pediatric-based, age, subset, and MRD risk-adapted therapy is recommended for adult ALL. Treatment modifications in case of persistent or recurrent MRD are of utmost importance. Inclusion in multicenter study group trials at diagnosis and in early-phase trials at relapse should be fostered.

Gökbuget et al. DOI: 10.1182/*blood*.2023023568

Ph negative ALL

Infant regimen

Modified infant-06



Pediatric regimen

COG UKALL



St Jude total XV/XVI

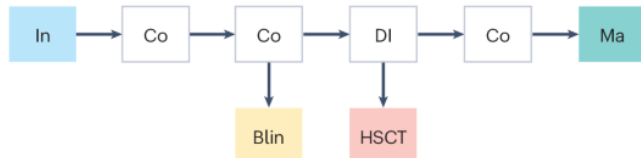


AYA regimen

SWOG



GRAALL



Adults regimen

Hyper-CVAD



Older Adults regimen

Mini-HCVD



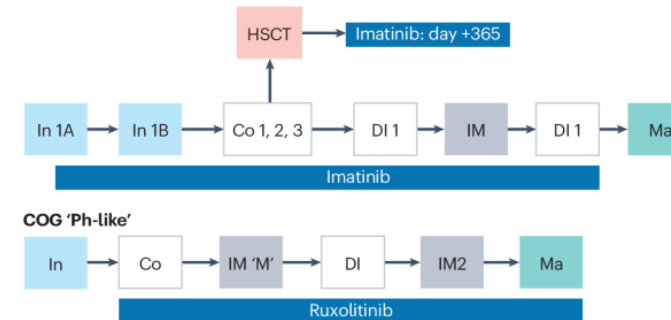
EWALL



Ph positive ALL

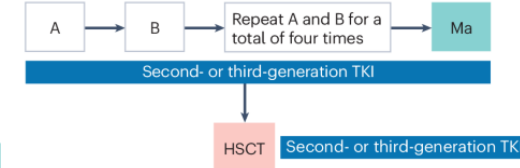
Pediatric regimen

EsPhALL Ph-positive

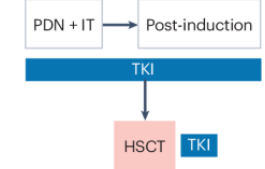


Adults regimen

Hyper-CVAD



GIMEMA



GIMEMA D-ALBA



Ph negative ALL

Pediatric-based chemotherapy in adults ALL

- Meta-analysis 25 out of 27 reports
➔ favored pediatric-based approach as standard of care (SoC)
- Up to 45 to 55 years, overall survival (OS) improved ~ 60%

The typical compounds are

corticosteroids (especially dexamethasone [Dexa])

vincristine

antimetabolites (6-thiopurines, cytarabine, and methotrexate)

asparaginase (ASP; pegylated or not)

plus

intensive supportive care

avoidance of inappropriate dose reductions/delays

a risk-adapted SCT

CR ~90%

Refractory ~5%

Induction death ~5%

Consolidation

- Outcome is best with rotational multidrug cycles consisting of HD-MTX and HD-AC (CNS-penetrating agent) PEG-ASP and other drugs

HD-AC 4-8 doses at 1-3 g/m²

HD-MTX 1-1.5 g/m²
(higher up to 3-5 g/m²)

→ prefer for high-risk and T-ALL

- Average duration ≥6 months (6 to 8 total courses)
- HD-AC, HD-MTX, etoposide, and cyclophosphamide
→ improve outcome of high-risk subsets & T-ALL

***No single regimen can be recommended as SoC
(Heterogenous protocols with comparable results)***

HD-MTX: high-dose methotrexate

HD-AC: high-dose ara-C (cytarabine)

Gökbuget N. Blood 2024;143(19):1903-1930.

Frontline targeted therapy in Ph-negative B-ALL

- Anti-**CD20** antibodies (Rituximab/Ofatumumab)
- Anti-**CD22** conjugated calicheamicin (Inotuzumab)
- Bispecific **CD19**/CD3 antibody (Blinatumomab)



CD20



CD22



CD19

Anti-CD20 antibodies (Rituximab/Ofatumumab)

CD20: Surface of all B-cell → 30-50% of adult B-lineage (B-LIN) ALL → express > 20% poor OS, higher relapse

Study (reference)	ALL subset	Combination treatment	Age (y)	No.	CR (%)	CRD/ RFS (%)	OS (%)	EFS (%)	FUP	Annotations
Rituximab/ofatumumab (anti-CD20 antibody)										
MDACC ²⁷	CD20 ⁺ B-ALL	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	CD20 ⁺ B-ALL	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	CD20 ⁺ B-ALL	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	CD20 ^{+/−} B-ALL (29% Ph ⁺)	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	CD20 ^{+/−} B-ALL	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)

Rituximab should include ≥ 8 doses

Decrease relapse risk, leading to increase rate of SCT

Anti-CD22 antibody (Inotuzumab)

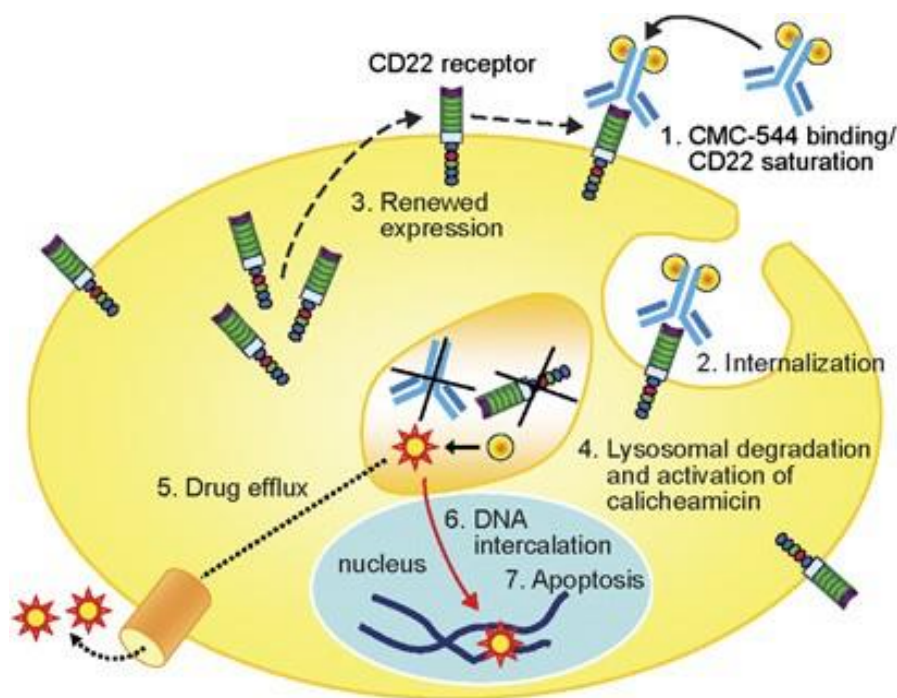
CD22: Surface glycoprotein inhibit B-cell signaling → nearly all of adult B-ALL → express approx. 70% blasts

INO-VATE: approved for R/R B-ALL 0.8 mg/m² d1 then 0.5 mg/m² d8,d15 (21-day cycle)

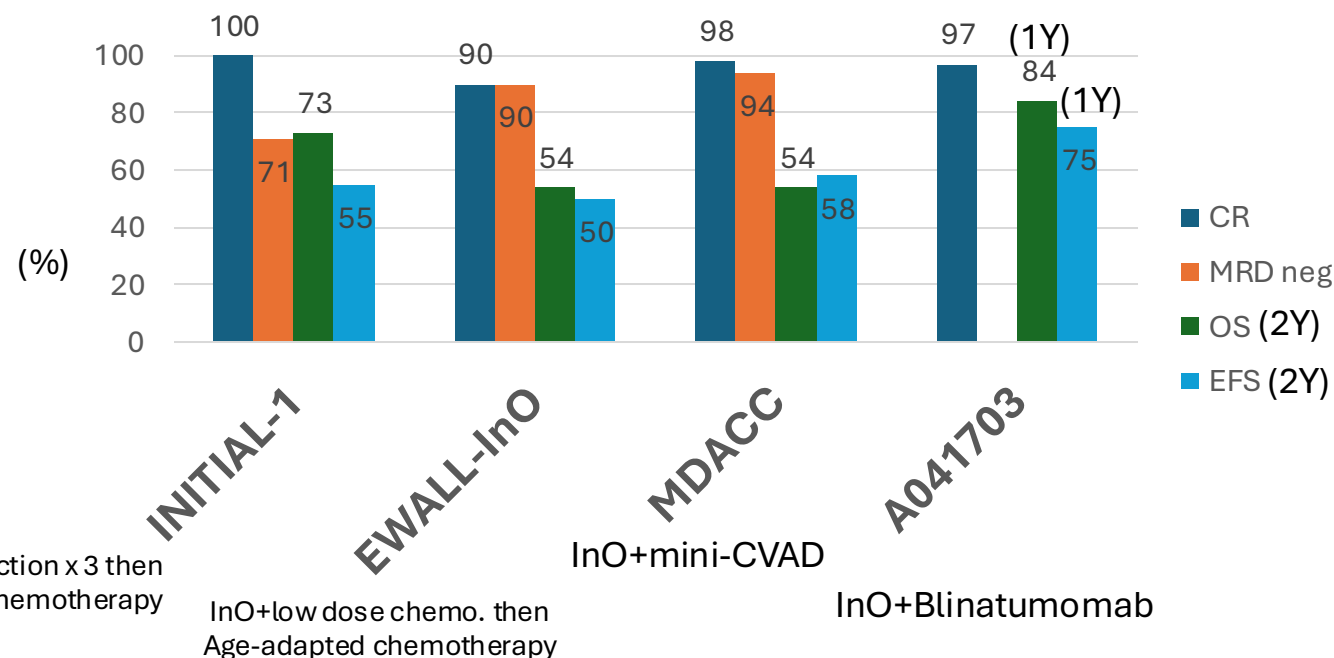
InO vs. standard chemo if CR/CRi: 0.5 mg/m² d1,d8,d15 (28-day cycle)

CR/CRi **80.7%** vs. 29.4%

MRD negative **78.4%** vs. 28.1%



Frontline InO-based in B-ALL



AE of special interest: **Veno-occlusive disease**

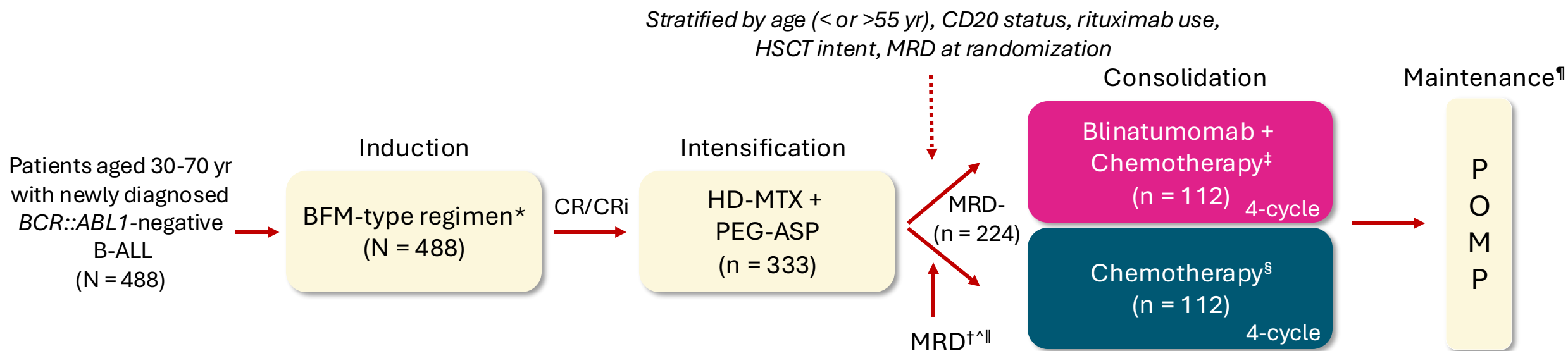
Blinatumomab

Study (reference)	ALL subset	Combination treatment	Age (y)	No.	CR (%)	CRD/ RFS (%)	OS (%)	EFS (%)	FUP	Annotations
Blinatumomab										
GIMEMA LAL 2317 ³²	CD19 ⁺ B-ALL	SOC + blinatumomab x2 in consolidation	18-65	146	90	56-87	65-91	48-85	1.5 y	95% MRD negative after blinatumomab I (P = .001); OS by age (P = .0009) and DFS/EFS by Ph-like (P = .006) and MRD (P = .0002)
GRAALL-2014-QUEST ³³	CD19 ⁺ B-ALL (high risk)	SOC + blinatumomab x5 in consolidation/ maintenance	35 (18-60)	95	NR	69-90	92	—	1.5 y	74% MRD negative after blinatumomab; DFS by high or very high risk class (P = .018)
MDACC ³⁴	B-ALL	Hyper-CVAD + blinatumomab x2 after induction and/or x2-4 after consolidation ± R/ ofatumumab (CD20 ⁺) ± InO x4 after consolidation	34 (17-59)	58 (20 with InO)	100	84	85	—	3 y	76% and 95% MRD negative after cycle 1 and overall, resp.; no relapse/death in InO-treated group (OS 100%)
MDACC ³⁵	B-ALL	Hyper-CVAD 4 cycles (50% dose reduction) + blinatumomab x4 after induction and x3 after consolidation + R/ ofatumumab (CD20 ⁺) in induction/consolidation	37 (29-45)	38	100	73	81	—	3 y	Amended to Hyper-CVAD 2 cycles (75% dose reduction) in HR patients; overall MRD negativity 97%; OS 88% no HR feature vs 76% any HR feature
HOVON ³⁶	CD19 ⁺ B-ALL (37% Ph ⁺)	SOC + blinatumomab x2 (prephase and after consolidation I)	53 (18-70)	71	77	—	53 (Ph ⁻)	68 (Ph ⁻)	2 y	53% and 91% MRD negative after blinatumomab I and II, resp.; EFS and OS 71% and 73% in patients ≤60 years
GMALL08 ³⁷	CD19 ⁺ B-ALL (MRD positive)	Blinatumomab 1 cycle in MRD positive patients after consolidation I	18-35	63	all CR/ MRD+	—	—	71	3 y	55% molecular CR after blinatumomab I; subsequent SCT indicated in all patients
ECOG-ACRIN (phase 3) ³⁸	CD19 ⁺ B-ALL (MRD negative)	A: SOC consolidation B: SOC consolidation + blinatumomab x4	51 (30-70)	112 112	81	—	NR 71.4	—	5 y	CR rate on all study patients (n = 488); median OS arm B not reached (NR, >70% at 5 years) vs 71.4 months (P = .003)

Increase MRD response

E1910-ACRIN Phase III

Consolidation chemotherapy ± Blinatumomab in MRD negative Ph-neg B-ALL



*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

Secondary endpoints: MRD status, RFS

Litzow MR, et al. NEJM 2024;391(4):320-333.

4-cycle of Blinatumomab
+
4-cycle of chemotherapy

2x Blinatumomab

3x Chemotherapy

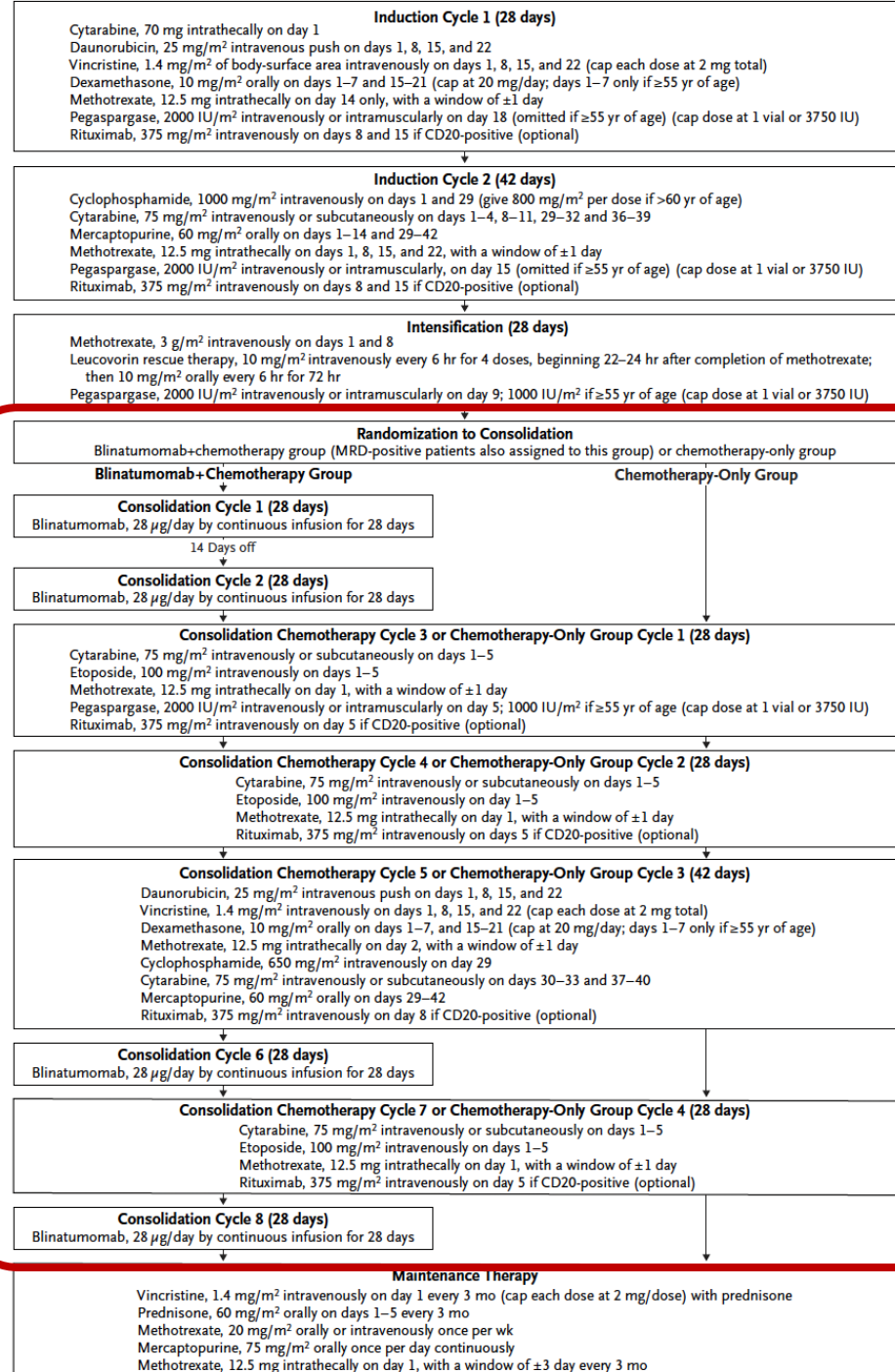
1x Blinatumomab

1x Chemotherapy

1x Blinatumomab

4-cycle of chemotherapy

4x Chemotherapy

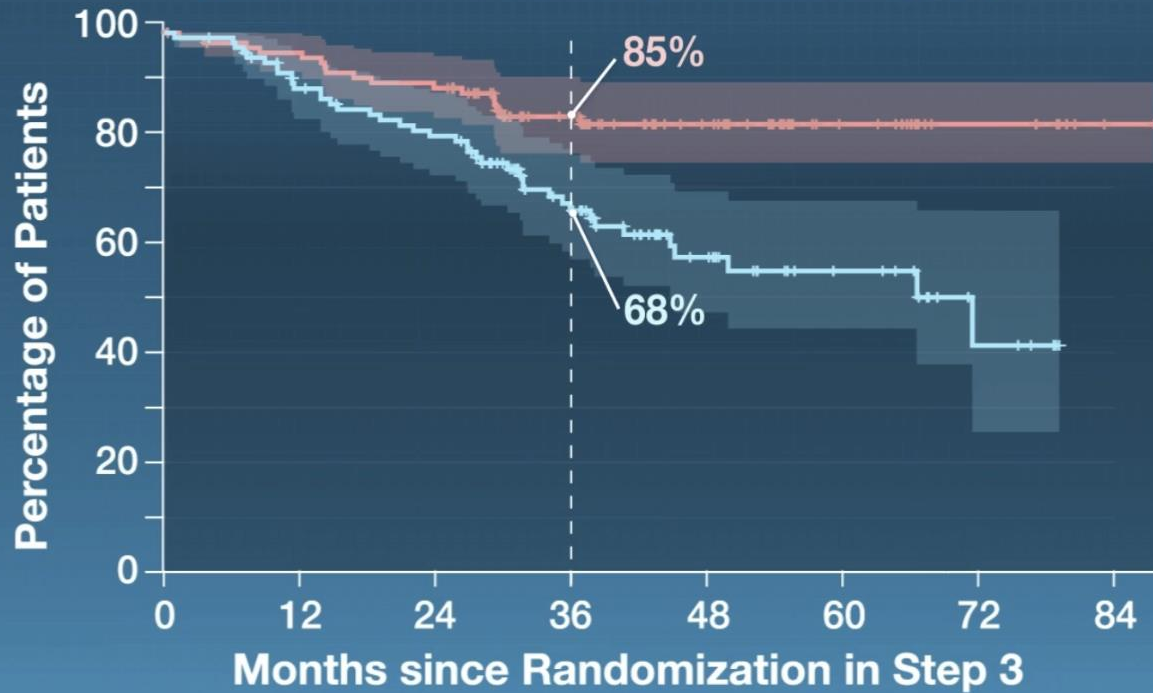


PRIMARY END POINT

3-Year Overall Survival

Hazard ratio for death, 0.41 (95% CI, 0.23–0.73)

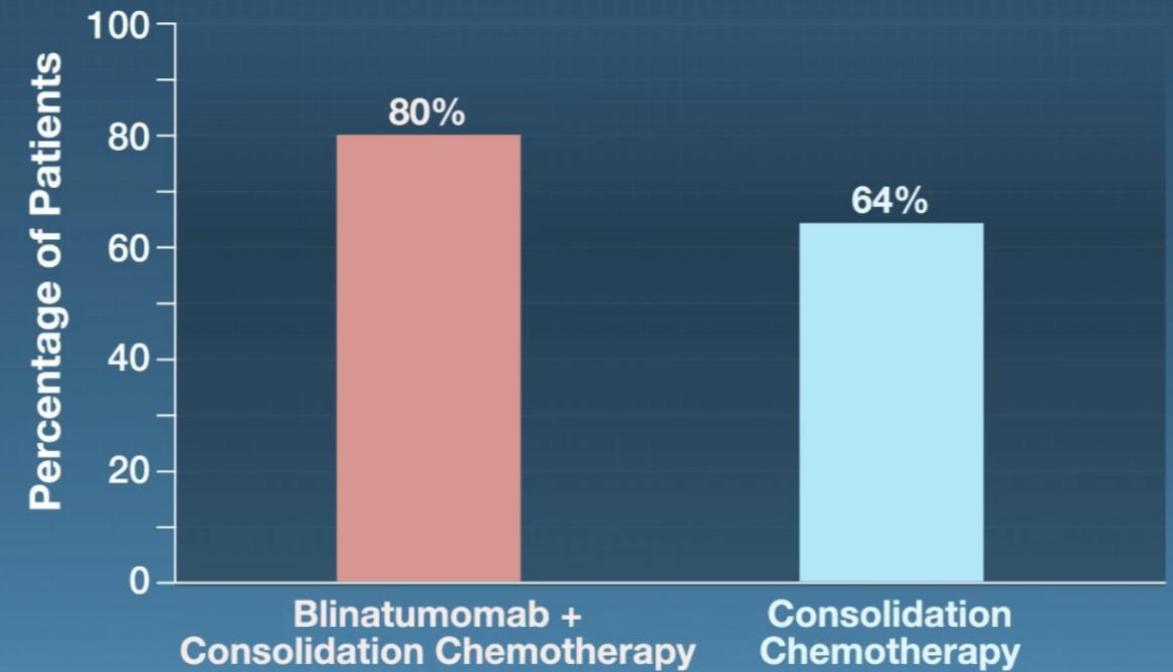
■ Blinatumomab + Chemotherapy ■ Chemotherapy only



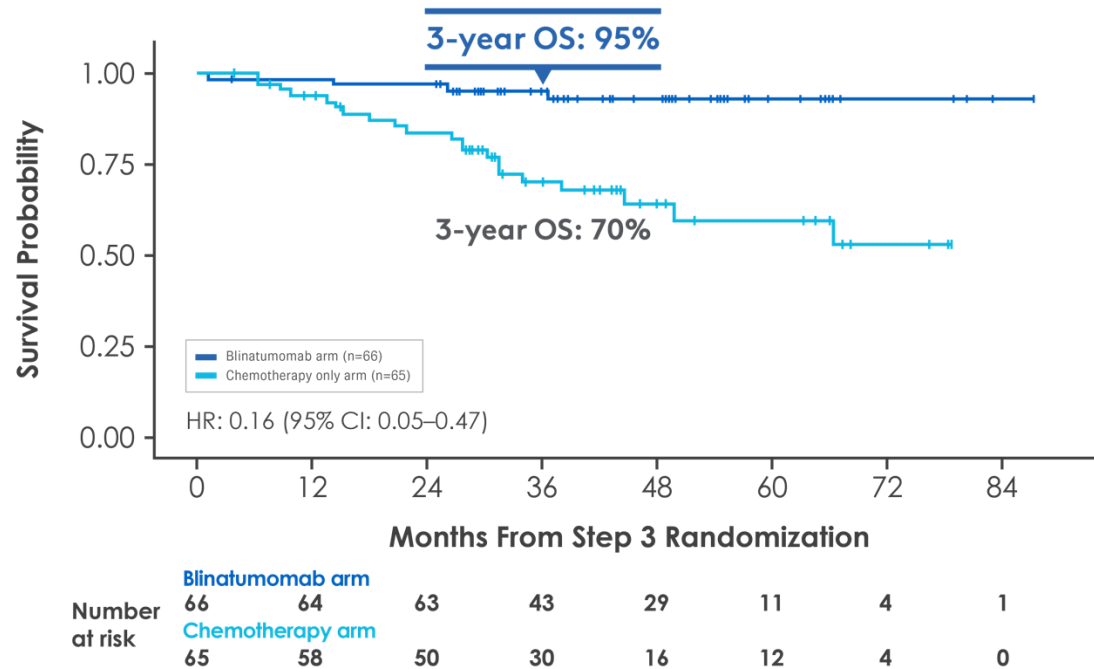
RELAPSE-FREE SURVIVAL

3-Year Relapse-free Survival

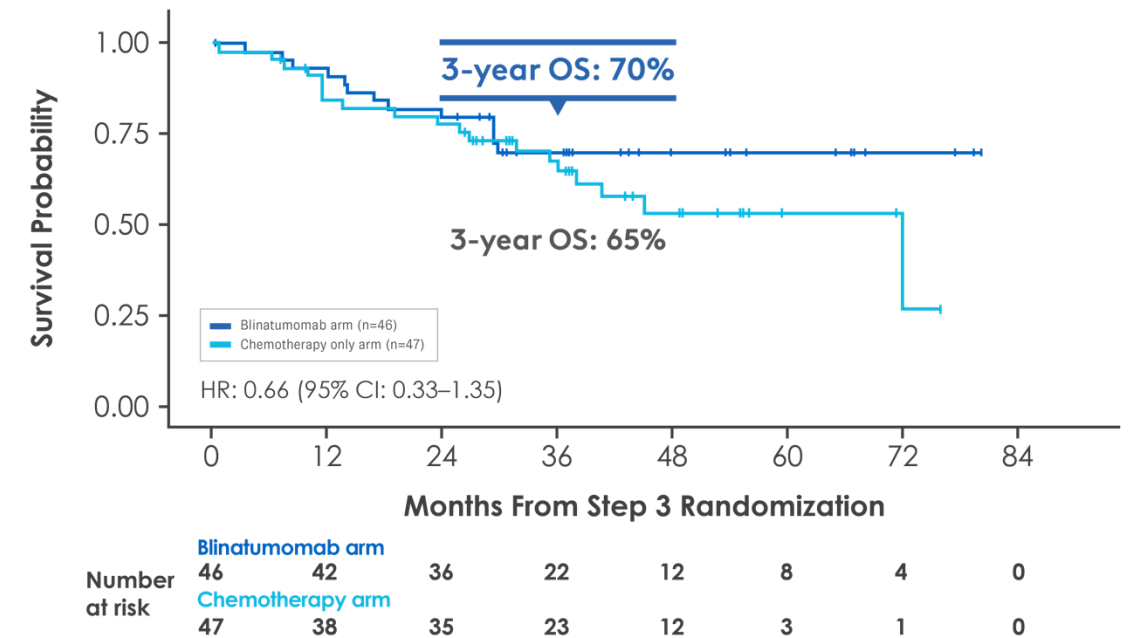
Hazard ratio for relapse or death, 0.53 (95% CI, 0.32–0.87)



OS in Patients Who Were MRD(-): < 55 Years of Age



OS in Patients Who Were MRD(-): ≥ 55 Years of Age



- RFS benefit was also observed in patients with MRD negativity, regardless of if they were < 55 years or ≥ 55 years
 - < 55 years of age: 3-year RFS was 87% in the blinatumomab arm vs 70% in the chemotherapy only arm (HR: 0.31 [95% CI: 0.14–0.69])
 - ≥ 55 years of age: 3-year RFS was 69% in the blinatumomab arm vs 57% in the chemotherapy only arm (HR: 0.74 [95% CI: 0.39–1.43])

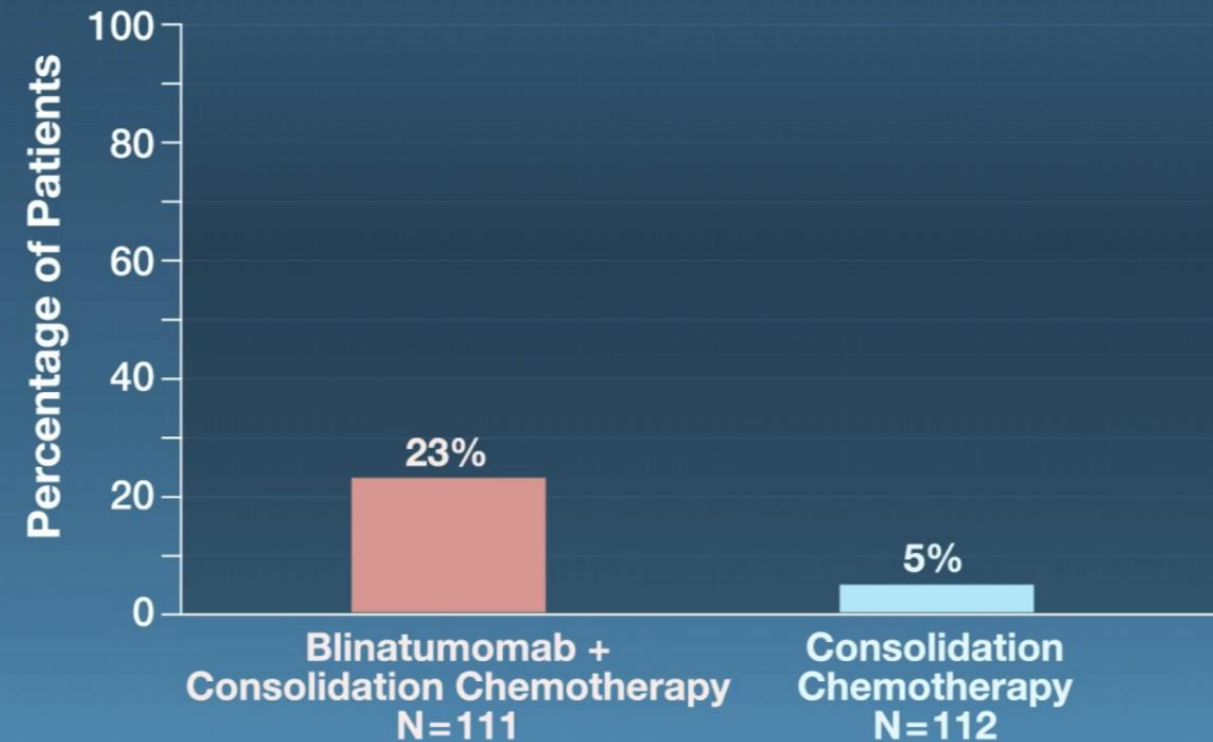
OS and RFS benefit in only subset of < 55 years of age

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
	<i>percentage of patients</i>					
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

NEUROPSYCHIATRIC EVENTS

Patients with Grade 3–5 Treatment-Related Neurologic or Psychiatric Adverse Events ($P<0.001$)



E1910-ACRIN: Conclusion

○ - ○ - ○ - ○ - ○



Blinatumomab-based consolidation

MRD negative Ph neg B-ALL

improved survival

Frontline targeted therapy in Ph-negative B-ALL

- Anti-**CD20** antibodies (Rituximab/Ofatumumab)
 - **Rituximab**: at least 8 doses, most studies combined to Adults regimen
 - **Ofatumumab**: failed to demonstrate survival benefit (historically compared to **Rituximab**)
- Anti-**CD22** conjugated calicheamicin (Inotuzumab)
- Bispecific **CD19**/CD3 antibody blinatumomab (Blinatumomab)
 - encouraging results

Maintenance therapy (MT)

- MT is strongly recommended in all patients !
- Long-term drug exposure to eradicate MRD !
- MT was not tested in randomized trials but
any attempts to omit maintenance = inferior outcomes
insufficient MT = worsen OS

MP, MTX – main drug

POMP (MP, MTX, Prednisolone, Vincristine)

2-2.5 years is recommended

3-month interval of MRD is suggested

Landsburg DJ. AJH 2013;88(8):657-660.
Schmiegelow K. J Ped Hemato Oncol 2014;36(7):503-517.
Hayakawa F. Blood Cancer J 2014;4(10):e252.

Ph negative ALL

- Preferred pediatric regimen
- Add on frontline targeted therapy (CD20,CD22,CD19 targeting)
- Maintenance therapy

Ph positive ALL

Frontline treatment Ph+ ALL

- Intensive chemotherapy strategy
 - Intensive chemotherapy + TKI
- De-intensified regimen
 - Low intensity chemotherapy + TKI
 - Steroids + TKI induction followed by chemotherapy
 - Chemotherapy-free strategy
 - Steroids + TKI
 - Blinatumomab + TKI

Frontline treatment Ph+ ALL

- Intensive chemotherapy strategy
 - Intensive chemotherapy + **TKI**

HyperCVAD, GMALL
Pediatric-adapted
etc.

- De-intensified regimen
 - Low intensity chemotherapy + **TKI**
 - Steroids + **TKI** induction followed by chemotherapy
 - Chemotherapy-free strategy
 - Steroids + **TKI**
 - Blinatumomab + **TKI**

TKIs

Duration
Dosing
Choice

Key phase 3 randomized studies in Ph+ ALL

Group/study/years	TKI	Randomization question	N	Age in years, median (range)	CR (%)	Early mortality (%)	Molecular response (%)	alloHCT, CR1 (%)	RFS/EFS (%)	OS (%)
GRAALL (SAKK) GRAAPH-2005 NCT00327678 2006–2011	IMATINIB	Induction intensity: low (vincristine, dex) vs high (hyper-CVAD)	266 135 low (A) 133 high (B)	47 (18–59) 45 (18–59) 45 (21–59)	94.8 98.5 91.0 p=0.006	5.6 (day 60) 2.2 9.0 p=0.017	25.8 (MR4, C2) 28.6 22.6 p=0.35	63.3 61.6 65.3 p=0.53	37.1 (5-yr EFS) 42.2 (5-yr EFS) 32.1 (5-yr EFS) p=0.13	45.6 (5 yr) 48.3 (5 yr) 43.0 (5 yr) p=0.37
GRAALL (SAKK) GRAAPH-2014 NCT02611492 2016–2019	NILOTINIB	Consolidation intensity: low (HD-MTX) vs high (HiDAC, HD-MTX)	156 79 low (B) 77 high (A)	47 (IQR 39–54) 47 (IQR 39–54) 49 (IQR 39–54)	94.2 94.9 93.4 p=0.74	3.2 (day 60) 2.5 3.9 p=0.68	26.4 (MR4, C4) 24.1 28.9 p=0.59	60.0 59.5 60.5 p=0.97	- 58.5 (4-yr RFS) 76.2 (4-yr RFS) p=0.029	- 73.4 (4 yr) 79.4 (4 yr) p=0.27
China CCCG-ALL2015 ChiCTR-IPR-14005706 2015–2018	DASATINIB	IM vs DAS with chemo	189 97 IM 92 DAS	7.8 (IQR 5–11) - Pediatrics - Ph+ALL	96.8 94.8 98.9 p=0.21	1 death (IM arm)	-	None	- 48.9 (4-yr EFS) 71.0 (4-yr EFS) p=0.005	- 69.2 (4-yr) 88.4 (4-yr) p=0.04
Global PhALLCON NCT03589326 2018–2022	PONATINIB	IM vs PON with low-intensity chemo	245 81 IM 163 PON	54 (19–82) 52 (19–75) 54 (19–82)	-	0	(MR4, C9) 44.9 62.1	32.7 37.0 30.5	- Med EFS 29mos Med EFS NR (HR 0.65, 95% CI 0.39–1.1)	- Med OS NR Med OS NR (HR 0.76, 95% CI 0.38–1.5)

Chemo intensity:

Induction **Lower** intensity = **higher** CR, **lower** early death, similar survival

Consolidation **Higher** intensity = similar CR & early death, but **higher** EFS (not OS)

TKIs: (compared to IM)

DAS: **Higher** EFS & OS

PON: **Higher** MR4, similar survival (short f/u time)

2G (DAS,NIL) and 3G (PON) TKI based – Ph+ALL

TKI	Reference	N	Age	Treatment	CR rate (%)	Molecular response (%)	Allogeneic SCT rate (%)	RFS/EFS (%)	Survival (%)
Dasatinib									
70 mg BID	Foa et al, 2011 ¹³⁰	53	54 (24-77)	Prednisone		15 (d 85)	42	22 (20 mo)	31 (20 mo)
50 mg BID/100 mg QD 100 mg QD-70 mg QD	Ravandi et al, 2015 ¹³⁴	72	55 (21-80)	Hyper-CVAD	96	65	17	44 (5 y)	46 (5 y)
50 mg BID/100 mg QD 70 mg QD	Ravandi et al, 2016 ¹²⁹	97	44 (20-60)	Hyper-CVAD	88	—	42	62 (3 y)	69 (3 y)
140 mg QD; >70 y: 100 mg QD	Rousselot et al, 2016 ¹³⁵	71	69 (55-83)	EWALL backbone		24	10	28 (5 y)	36 (5 y)
140 mg QD	Foà et al, 2020 ¹⁴²	63	54 (24-82)	Corticosteroids	98	60 (2 cycles of blinatumomab)	38	88 (18 mo med. FU)	95 (18 mo med. FU)
Nilotinib									
400 mg BID	Kim et al, 2015 ¹⁴³	90	47 (17-71)	Intensive chemotherapy	91	77 (3 mo)	63	72 (2 y)	72 (2 y)
400 mg BID	Ottmann et al, 2018 ¹⁴⁴	72	66 (55-85)	EWALL backbone	94	58 <0.01	33	42 (4 y)	47 (4 y)
Ponatinib									
45-30-15 mg QD	Jabbour et al, 2018 ¹²⁷	76	47 (39-61)	Hyper-CVAD	98	83	20	67 (5 y)	71 (5 y)
30-15 mg QD	Ribera et al 2022 ¹⁴¹	30	49 (19-59)	Intensive chemotherapy alone	100	71 at week 16	87	70 (3 y)	96 (3 y)
45-30-15 QD	Martinelli et al, 2022 ¹⁴⁵	44	66.5		90.9 at week 6, 86.4 at month 6	47.7 at week 6 40.9 at month 6	11 (transplant unplanned)	48 (3 y)	58 (3 y)

2G (DAS,NIL) and 3G (PON) TKI based – Ph+ALL

TKI	Reference	N	Age	Treatment	CR rate (%)	Molecular response (%)	Allogeneic SCT rate (%)	RFS/EFS (%)	Survival (%)
Dasatinib									
70 mg BID	Foa et al, 2011 ¹³⁰	53	54 (24-77)	Prednisone		15 (d 85)	42	22 (20 mo)	31 (20 mo)
50 mg BID/100 mg QD 100 mg QD-70 mg QD	Ravandi et al, 2015 ¹³⁴	72	55 (21-80)	Hyper-CVAD	96	65	17	44 (5 y)	46 (5 y)
50 mg BID/100 mg QD 70 mg QD	Ravandi et al, 2016 ¹²⁹	97	44 (20-60)	Hyper-CVAD	88	—	42	62 (3 y)	69 (3 y)
140 mg QD; >70 y: 100 mg QD	Rousselot et al, 2016 ¹³⁵	71	69 (55-83)	EWALL backbone		24	10	28 (5 y)	36 (5 y)
140 mg QD	Foà et al, 2020 ¹⁴²	63	54 (24-82)	Corticosteroids	98	60 (2 cycles of blinatumomab)	38	88 (18 mo med. FU)	95 (18 mo med. FU)

2G (DAS,NIL) and 3G (PON) TKI based – Ph+ALL

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Nilotinib									
400 mg BID	Kim et al, 2015 ¹⁴³	90	47 (17-71)	Intensive chemotherapy	91	77 (3 mo)	63	72 (2 y)	72 (2 y)
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2G (DAS,NIL) and 3G (PON) TKI based – Ph+ALL

DAS-based

Group (study)	Low-intensity induction?	Phase	Regimen	N	Age in years, median (range)	CMR (%)	alloHCT, CR1 (%)	DFS/RFS/ EFS (%)	OS (%)
GIMEMA (Italy) LAL1205 NCT00391989 2006–2008	Yes	2	Ind: DAS, pred Cons: per investigator	53	54 (24–77)	23 (best)	34	51 (1.7-yr DFS)	69 (1.7 yr)
MDACC (US) NCT00390793 2006–2012	No	2	Ind/cons: DAS + hyper-CVAD	72 (63*)	55 (21–80)	65 (best)	17	42 (5-yr EFS) 44 (5-yr DFS)	46 (5 yr)
EWALL (Europe) Ph01 NCT02888977 2007–2010	Yes	2	Ind: DAS, vinc, dex Cons: DAS, low-int chemo	71	69 (59–83)	24 (MRD2)	10	27 (5-yr EFS) 28 (5-yr RFS)	36 (5 yr)
SWOG (US) SWOG 0805 NCT00792948 2009–2013	No	2	DAS + hyper-CVAD	94 (60*)	44 (20–60)	-	52	55 (3-yr EFS) 62 (3-yr RFS)	69 (3 yr)
CALGB (US) C10701 NCT01256398 2010–2014	Yes	2	Ind: DAS, dex Cons: alloHSCT or autoHSCT; or chemo (>70 yrs)	65	60 (22–87)	40 (end course IV)	48	37 (5-yr DFS)	48 (5 yr)
GIMEMA (Italy) TOTAL Therapy LAL1509 NCT03318770 2011–2013	Yes	2	Ind: DAS, pred Cons: if CMR → DAS; no CMR → DAS plus HSCT or chemo	60	42 (19–59)	18 (end ind)	37	47 (5-yr DFS)	56 (5 yr)
DFCI DF/HCC 18-170 2018–2022	Yes	1	Ind: DAS, ASC, pred Cons: DAS, ASC	22	64 (33–85)	-	33	63 (2-yr EFS)	75 (2 yr)

NIL-based

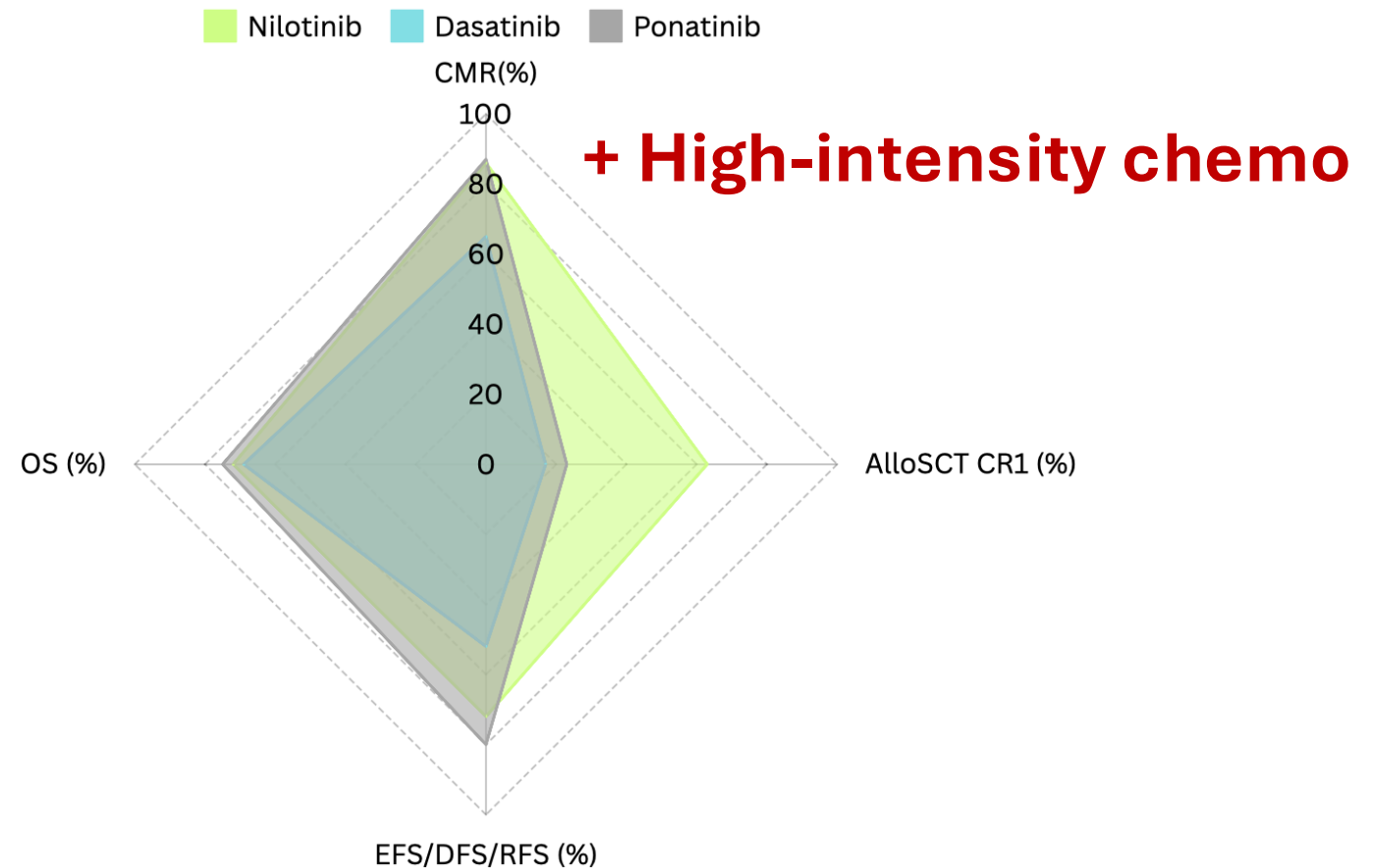
Group (study)	Low-intensity induction?	Phase	Regimen	N	Age in years, median (range)	CMR (%)	alloHCT, CR1 (%)	DFS/RFS/ EFS (%)	OS (%)
KAALLWP (Korea) NCT00844298 2009–2012	No	2	Ind/cons: NIL + chemo	90	46 (17–71)	86 (best)	63	72 (2-yr RFS)	72 (2 yr)
EWALL (Europe) Ph02 NCT01528085 2012–2020	Yes	2	Ind: NIL, vinc, pred Cons: NIL, low-int chemo	72	65 (55–85)	14 (end ind) 58 (end cons)	33	42 (4-yr EFS)	47 (4 yr)
GRAALL (SAKK) GRAAPH-2014 NCT02611492 2015–2019	Yes	3	Ind: NIL, vinc, pred Cons: NIL + high- (A) vs. low- (B) int chemo (1:1)	156	47 (39–54 IQR)	26 (TP4)	60	A: 76 (4-yr RFS) B: 58 (4-yr RFS) p=0.028	A: 79 (4 yr) B: 72 (4 yr) p=0.88

PON-based

Group (study)	Low-intensity	Phase	Regimen	N	Age in years, median	CMR (%)	alloHCT, CR1 (%)	DFS/RFS/ EFS (%)	OS (%)
MDACC (US) NCT01424982 2011–2019	No	2	PON + hyper-CVAD	86 (66*)	46 (21–80)	87 (best)	23	65 (6-yr EFS) 80 (6-yr DFS)	75 (6 yr)
GIMEMA (Italy) INCB4344-20/ LAL1811 NCT01641107 2014–2017	Yes	2	PON + pred	44	67 (26–85); 80% ≥ 60 yrs	41 (week 24) 82% (overall)	14	14.3 mo (med, EFS)	NR (median)
PETHEMA (Spain) PONAIFIL NCT02776605 2017–2020	No	2	PON + high-int chemo	30	49 (19–59)	47 (ind) 71% (cons)	87	70 (3-yr EFS)	96 (3 yr)
PhALLCON (Global) NCT03589326 2018–2022	Yes	3	PON vs IM + low-int chemo (2:1)	245	54	MR4.5 after C9 46 (PON) 26 (IM)	31 (PON) 37 (IM)	Med EFS 29.0 Med EFS NR (HR 0.65, 95% CI 0.39–1.1)	Med OS NR Med OS NR (HR 0.76, 95% CI 0.38–1.52)

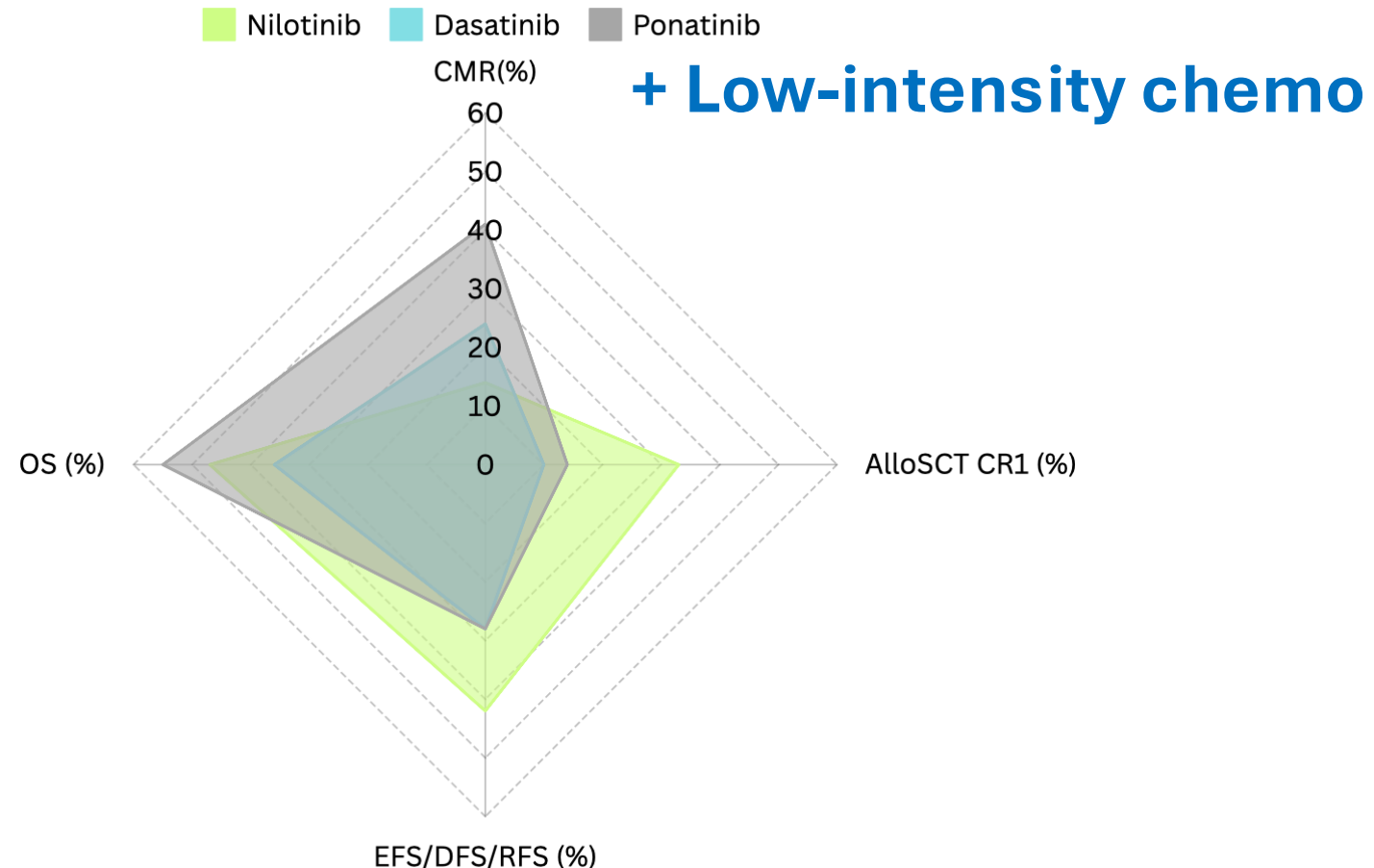
2G (DAS,NIL) and 3G (PON) TKI based – Ph+ALL

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CALGB (US) C10701 NCT01256398 2010–2014	Yes	2	Ind: DAS, dex Cons: alloHCT or autoHCT; or chemo (>70 yrs)	65	60 (22–87)	40 (end course IV)	48	37 (5-yr DFS)	48 (5 yr)
GIMEMA (Italy) TOTAL Therapy LAL1509 NCT03318770 2011–2013	Yes	2	Ind: DAS, pred Cons: if CMR → DAS; no CMR → DAS plus HSCT or chemo	60	42 (19–59)	18 (end ind)	37	47 (5-yr DFS)	56 (5 yr)
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2G (DAS,NIL) and 3G (PON) TKI based – Ph+ALL

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CALGB (US) C10701 NCT01256398 2010–2014	Yes	2	Ind: DAS, dex Cons: alloHSCT or autoHSCT; or chemo (>70 yrs)	65	60 (22–87)	40 (end course IV)	48	37 (5-yr DFS)	48 (5 yr)
GIMEMA (Italy) TOTAL Therapy LAL1509 NCT03318770 2011–2013	Yes	2	Ind: DAS, pred Cons: if CMR → DAS; no CMR → DAS plus HSCT or chemo	60	42 (19–59)	18 (end ind)	37	47 (5-yr DFS)	56 (5 yr)
DFCI DF/HCC 18–170 2018–2022	Yes	1	Ind: DAS, ASC, pred Cons: DAS, ASC	22	64 (33–85)	-	33	63 (2-yr EFS)	75 (2 yr)
KAALLWP (Korea) NCT00844298 2009–2012	No	2	Ind/cons: NIL + chemo	90	46 (17–71)	86 (best)	63	72 (2-yr RFS)	72 (2 yr)
EWALL (Europe) Ph02 NCT01528085 2012–2020	Yes	2	Ind: NIL, vinc, pred Cons: NIL, low-int chemo	72	65 (55–85)	14 (end ind) 58 (end cons)	33	42 (4-yr EFS)	47 (4 yr)
GRAALL (SAKK) GRAAPH-2014 NCT02611492 2015–2019	Yes	3	Ind: NIL, vinc, pred Cons: NIL + high- (A) vs. low- (B) int chemo (1:1)	156	47 (39–54 IQR)	26 (TP4)	60	A: 76 (4-yr RFS) B: 58 (4-yr RFS) p=0.028	A: 79 (4 yr) B: 72 (4 yr) p=0.88
MDACC (US) NCT01424982 2011–2019	No	2	PON + hyper-CVAD	86 (66*)	46 (21–80)	87 (best)	23	65 (6-yr EFS) 80 (6-yr DFS)	75 (6 yr)
GIMEMA (Italy) INCB4344–20/ LAL1811 NCT01641107 2014–2017	Yes	2	PON + pred	44	67 (26–85); 80%±60 yrs	41 (week 24) 82% (overall)	14	14.3 mo (med, EFS)	NR (median)
PETHEMA (Spain) PONAFIL NCT02776605 2017–2020	No	2	PON + high-int chemo	30	49 (19–59)	47 (ind) 71% (cons)	87	70 (3-yr EFS)	96 (3 yr)
PhALLCON (Global) NCT03589326 2018–2022	Yes	3	PON vs IM + low-int chemo (2:1)	245	54	MR4.5 after C9 46 (PON) 26 (IM)	31 (PON) 37 (IM)	Med EFS 22.0 Med EFS NR (HR 0.65, 95% CI 0.39–1.1)	Med OS NR Med OS NR (HR 0.76, 95% CI 0.38–1.52)



Choice of TKIs (in chemo + TKI)

1G TKI

Imatinib

HyperCVAD

IM

CR 90-93%, AlloSCT 30-46%

5Y-OS 38-43%

2G TKIs

Dasatinib
Nilotinib

HyperCVAD, JALSG,
etc.

DAS

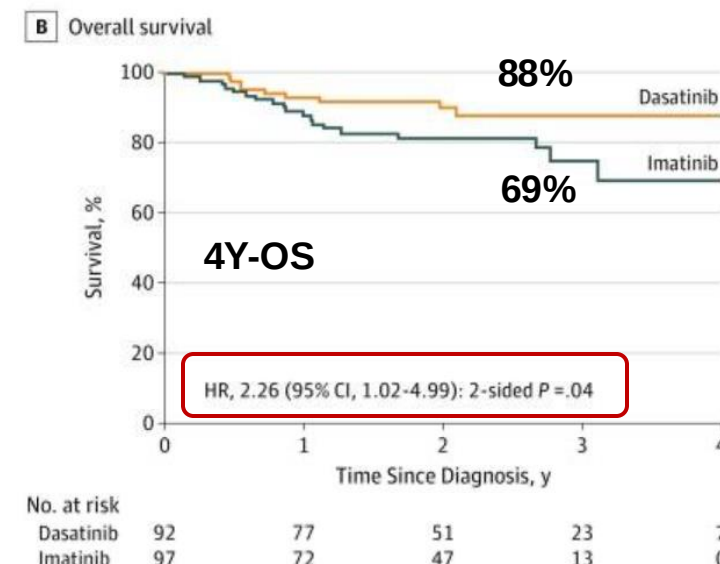
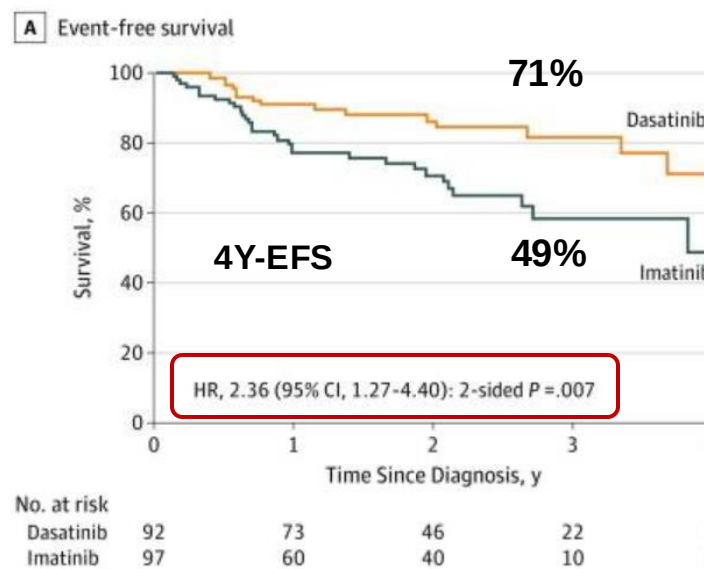
CR 88-100%, AlloSCT 17-74

5Y-OS 46-81%

NIL

CR 83%, AlloSCT 53%

5Y-OS 45%



	DAS	IM
Any relapse	19.8%	34.4%
Isolated CNS	2.7%	8.4%

CIR: Cumulative incidence of relapse

2G TKIs
Higher remission
Allow more AlloSCT
Superior survival

Daver N, et al. Haematologica 2015;100:653-661.

Fielding AK, et al. Blood 2014;123:843-850.

Ravandi F, et al. Cancer 2015;121:4158-4164.

Ravandi F, et al. Blood Adv 2016;1:250-259.

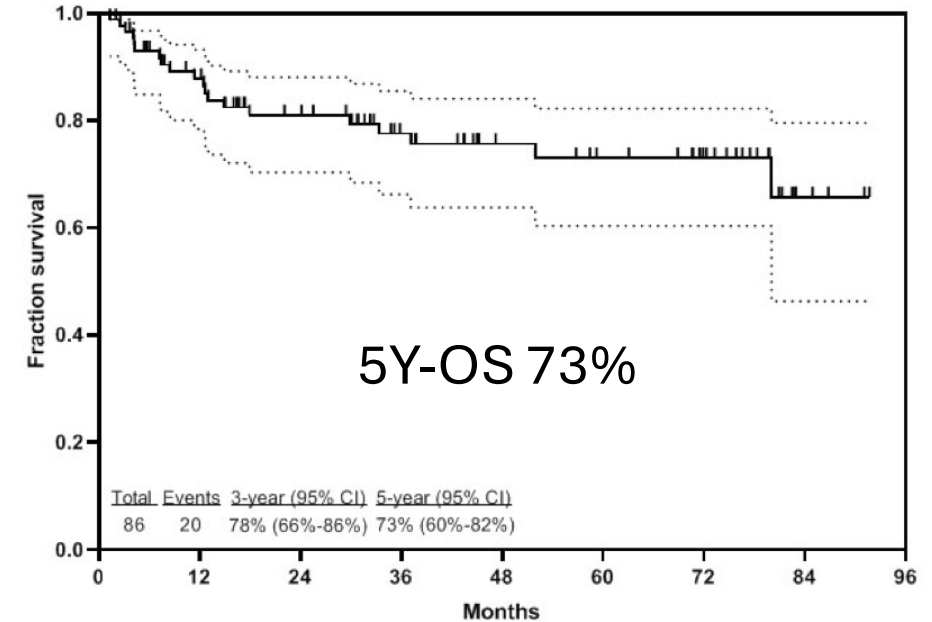
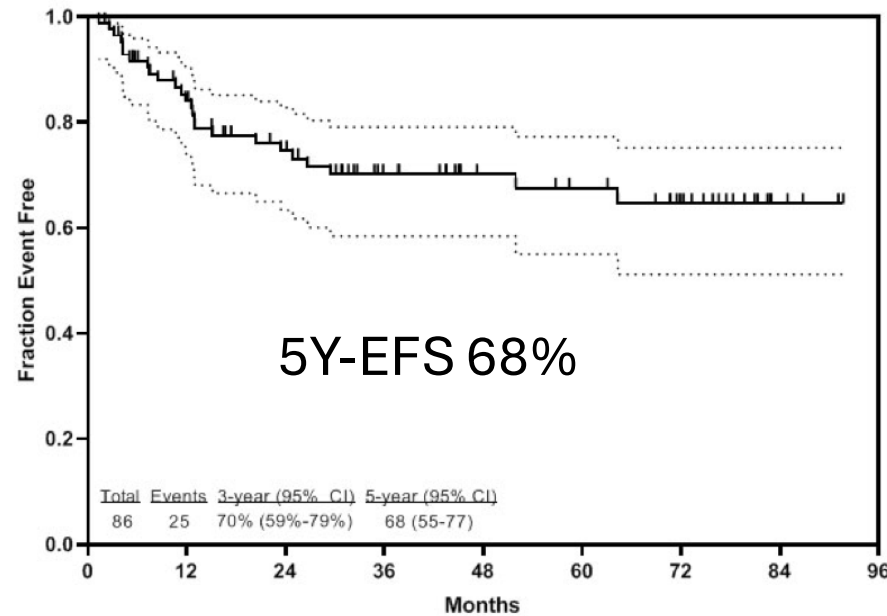
Sugira I, et al. Blood Adv 2022;6:624-636.

Liu B, et al. Ann Hematol 2019;98:633-645.

Shen S, et al. JAMA Oncol 2020;6:358-366.

Choice of TKIs (in chemo + TKI)

3G TKI
Ponatinib
+
HyperCVAD
 CR 100%, CMR 84%
 AlloSCT 22%



Trend better survival in non-AlloSCT (6mo-analysis)

	Non-AlloSCT	AlloSCT
5Y-OS	86%	69%
	(p=0.08)	

Ponatinib vs. Imatinib as Frontline Ph+ ALL

Matching adjusted indirect comparison (MAIC) study

3G TKI

Ponatinib

2 Ponatinib studies

Phase 2:

MDACC

(n = 87)

Pona + HyperCVAD

Phase 2:

GIMEMA LAL1811

(n = 44)

Pona + Steroid

1G TKI

Imatinib

3 Imatinib studies

Phase 3:

GRAAPH-2005

(n = 133)

IM + HyperCVAD

IM + RIC (n = 135)

Phase 2:

NCT00038610

(n = 54)

IM + HyperCVAD

Phase 2:

CSI57ADE10

(n = 55)

IM monotx then

Age-adapted chemo+IM

Propensity score-like regression

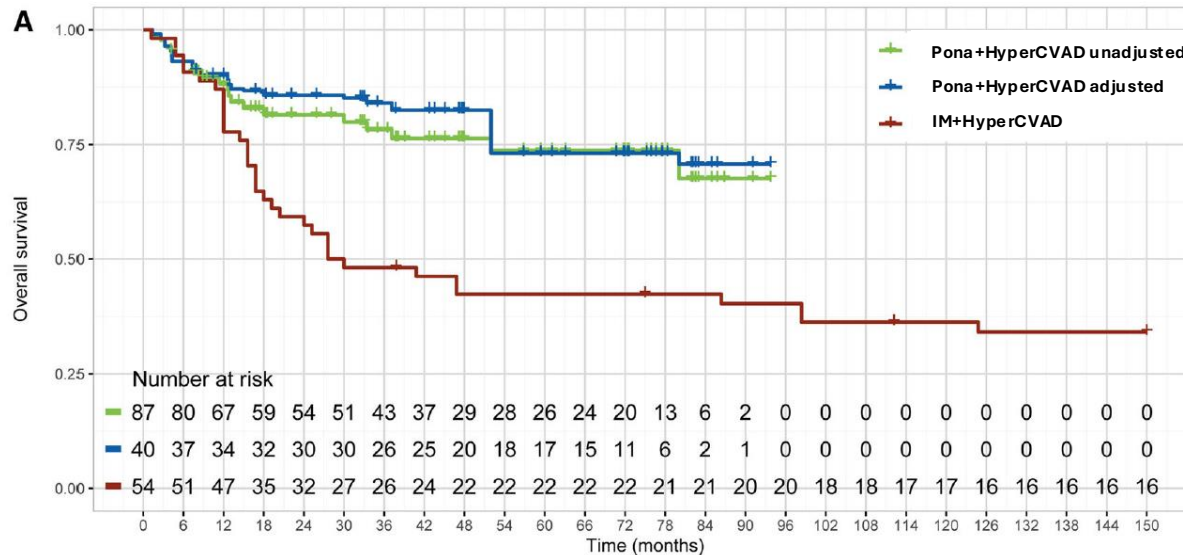
Baseline characteristics

Clinically validated prognostic factors

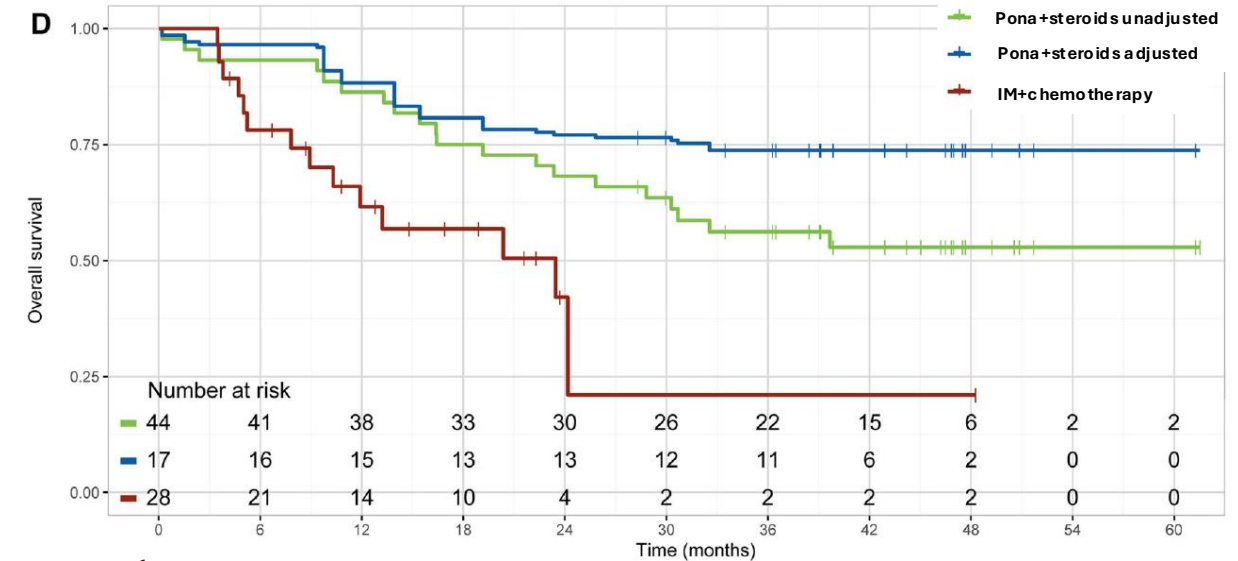
Ponatinib vs. Imatinib as Frontline Ph+ ALL

Overall survival analysis

+ HyperCVAD



+ Steroid/Age-adapted chemo



3G TKI + Chemo
Better survival than 1G TKI

Ph+ALL key points

Chemo intensity

TKIs (compared to IM)

Induction

Lower intensity = higher CR, lower early death, similar survival

Preferred 2G or 3G TKIs

Consolidation

Higher intensity = similar CR & early death, but higher EFS (not OS)

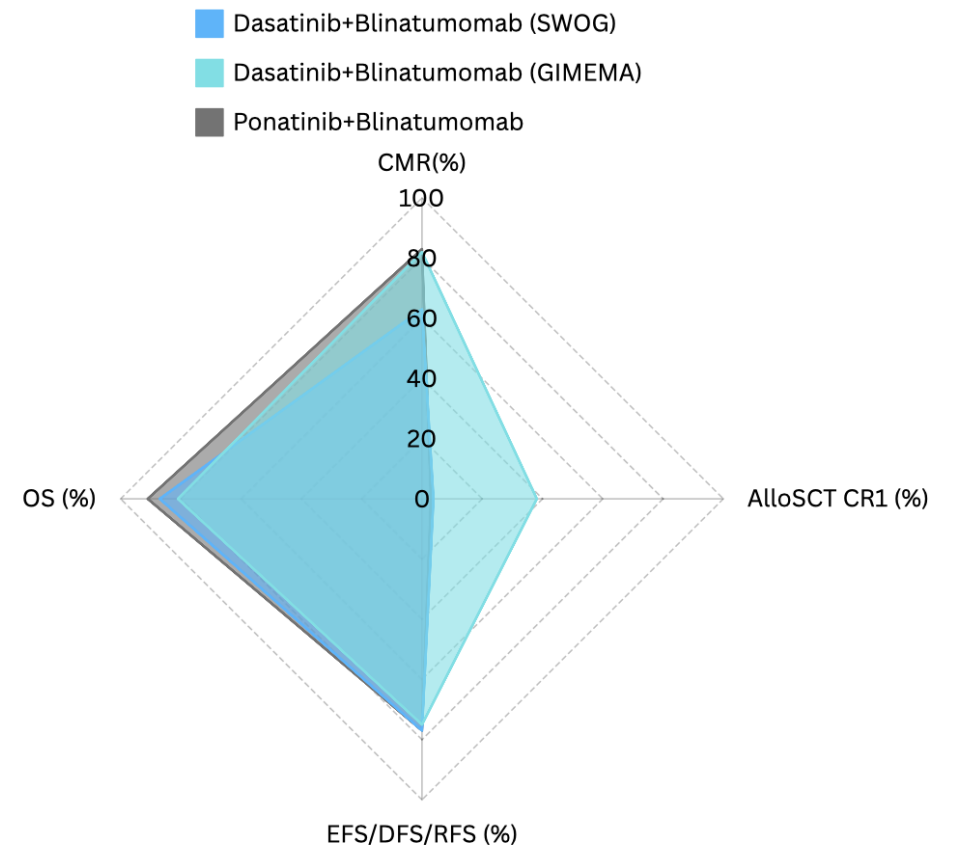
Ph+ ALL

Diagnostics/evaluation	Patient: Age, fitness/frailty, cardiovascular risk factors, support Disease: <i>Genetic risk:</i> cytogenetic, molecular (<i>IKZF1</i> ; <i>IKZF1</i> plus) <i>MRD monitoring:</i> RT-PCR p190 vs p210; NGS or PCR for clonal tracking
When possible, (a) enroll on clinical trial, (b) follow published regimen	
Phase: Induction Goal: Complete remission (CR)	TKI: DAS or PON or clinical trial PLUS: Low intensity (steroids, steroids + vincristine, steroids + blinatumomab)
Phase: Consolidation Goal: Prolong CR (indefinitely)	TKI: DAS or PON or clinical trial -If DAS, consider change to PON if inadequate response -If PON, dose reduce to 15 mg after achievement of CMR PLUS: 1. TKI alone (<i>if alloHCT planned or palliative goal</i>) 2. Chemotherapy (<i>age adjusted</i>) 3. Blinatumomab (<i>within 3 months</i>) 4. AlloHCT
CNS prophylaxis	IT chemotherapy (12–15) High-dose methotrexate and/or cytarabine
Monitoring	<i>BCR::ABL1</i> RT-PCR NGS, to establish presence of CML-like biology, and if present to supplement <i>BCR::ABL1</i> transcript monitoring

Chemotherapy-free & Blinatumomab in Ph+ ALL

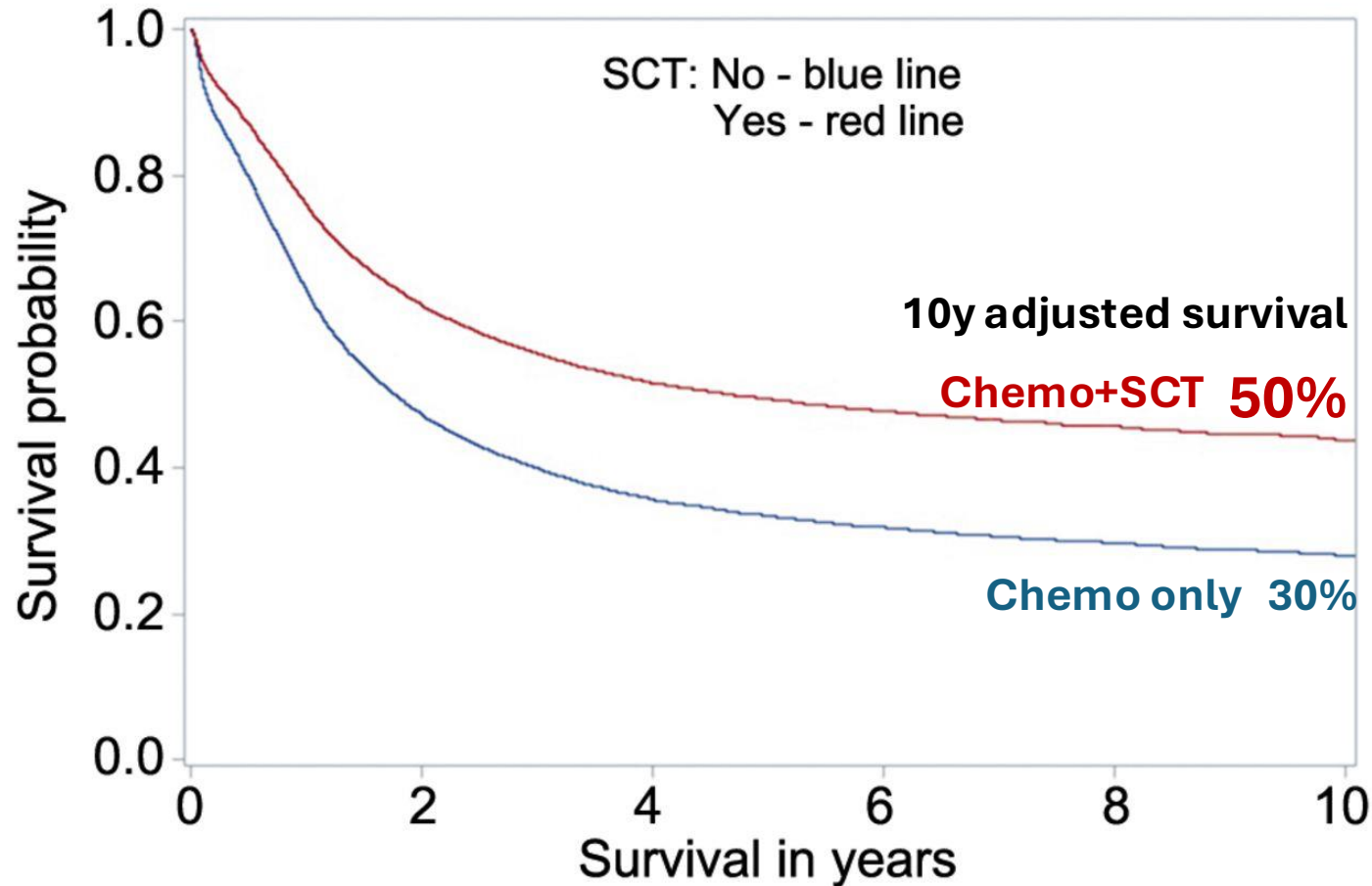
Group (study)	Phase	Regimen	Years	N	Age in years, median (range)	CMR (%)	alloHCT, CR1 (%)	RFS/EFS (%)	OS (%)
SWOG (US) SWOG 1318 NCT02143414	2	<u>Ind:</u> DAS, pred x 84 days <u>Cons:</u> DAS, blina x 3C <u>CNS:</u> 8 IT chemo	2015–2021	24	73 (65–87)	63 (12/19, anytime)	3.8	77 (3-yr DFS)	87 (3-yr)
GIMEMA (Italy) LAL2116 D-ALBA NCT02744768	2	<u>Ind:</u> DAS, pred x 85 days <u>Cons:</u> DAS, blina x 5C <u>CNS:</u> 12 IT chemo	2017–2019	63	54 (24–82)	60 (blina C2) 82 (blina C4)	38.1	75 (4-yr EFS)	81 (4-yr)
MDACC (US) NCT03263572	2 ^a	<u>Ind/cons:</u> PON + blina (C1-C5) <u>CNS:</u> 12 IT chemo	2018–	60 (39 ^b) to date	55 (20–83)	83 (98 by NGS)	3.3	77 (3-yr EFS)	91 (3-yr)
DFCI (US) DF/HCC 18–170 NCT03595917	1 ^a	<u>Ind:</u> DAS, ASC, pred x 1C <u>Cons:</u> DAS, ASC, blina x 5C <u>CNS:</u> 12 IT chemo	2022– (blina cohort)	15 ^a	Eligibility: ≥18	-	Per treating physician	-	-
ECOG-ACRIN (US) EA9181 NCT04530565	3 ^a	<u>Ind:</u> DAS or PON + pred <u>Cons:</u> DAS or PON + hyper-CVAD vs blina (1:1) <u>CNS:</u> IT chemo + HD-MTX intensification x 1C	2020–	348 ^a	Eligibility: 18–75	-	Per treating physician	-	-
GIMEMA (Italy) ALL2820 NCT04722848	3 ^a	<u>Ind/cons:</u> PON + blina vs IM + chemo (2:1) <u>CNS:</u> 15 IT chemo	2021–	236 ^a	Eligibility: ≥18	-	Based on IKZF1 plus and MRD	-	-
GRAALL (SAKK) GRAAPH-2024	3 ^a	<u>Ind:</u> PON, blina, chemo <u>Cons:</u> alloHCT vs chemo/blina <u>CNS:</u> IT and systemic chemo	-	-	-	-	Randomize if in CMR (NGS)	-	-

^a ongoing studies



Role of SCT in ALL

Role of SCT in ALL (overall)



Effect of stem cell transplantation in Adults ALL (NCDB: national cancer database)

N = 17,504

Relative to patients who were treated with chemotherapy only, **the patients who got chemotherapy and stem cell transplant had a decreased risk of mortality by 39%.**

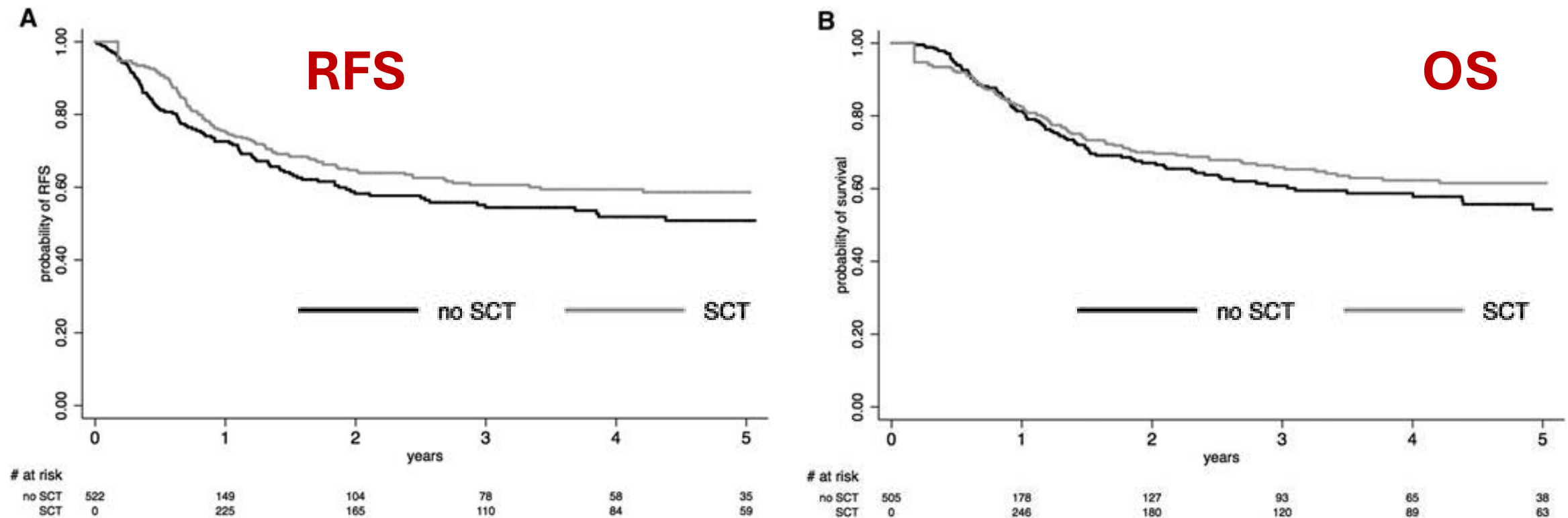
HR 0.61 (95%CI: 0.55-0.67)

Of the 5,409 patients aged of 18 and 39 years i.e. **adolescent and young adults (AYA)**, **no statistically significant survival** difference was found between patients treated with stem cell transplant and those not.

AlloSCT in CR1: Ph neg ALL

- Most of the trials demonstrated a **beneficial effect** of MSD-SCT (vs. AutoSCT or Chemotherapy)
- However, these studies were performed **before the era** of routine **assessment of MRD** and with **non-pediatric-based** comparator arms

AlloSCT in CR1: Ph neg ALL (pediatric-inspired Rx)

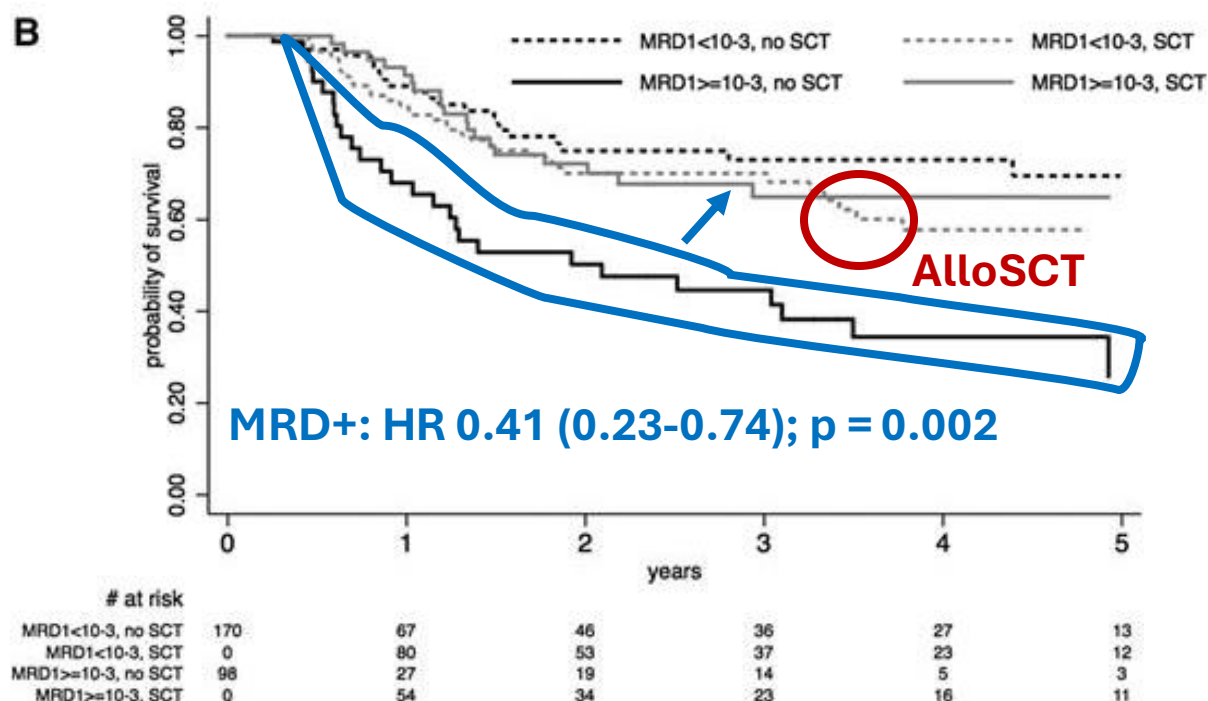
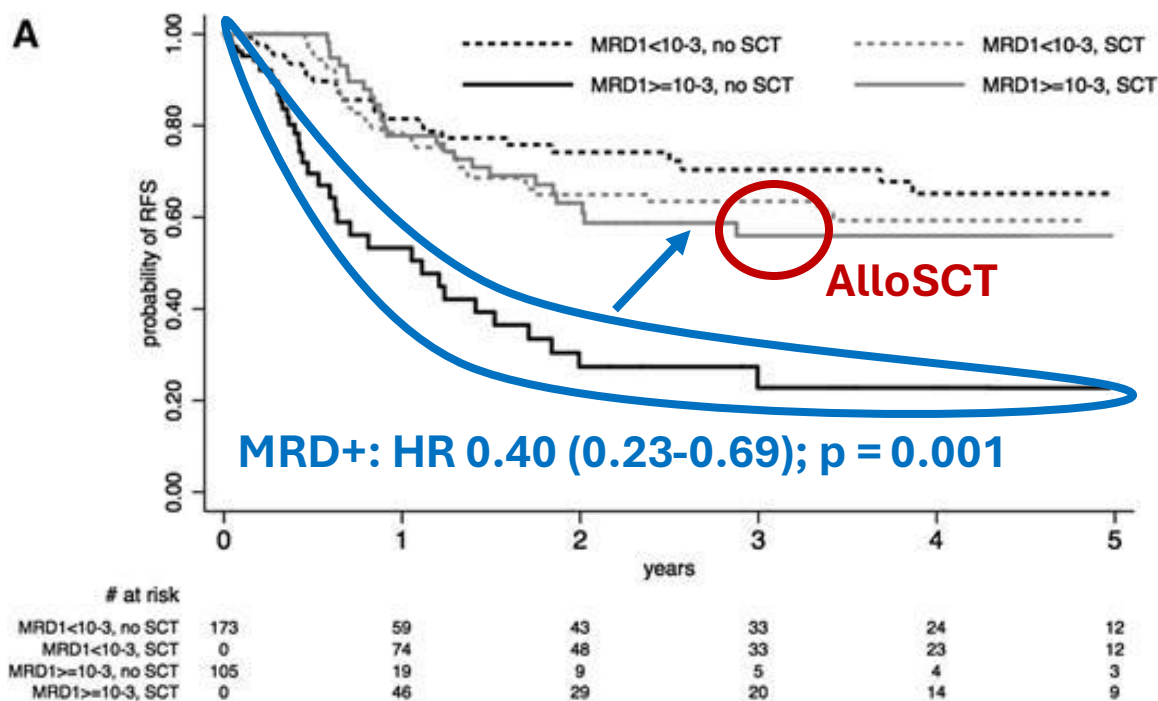


AlloSCT in CR1: Ph neg ALL (pediatric-inspired Rx)

RFS

Subgroup of MRD response

OS



AlloSCT in CR1: **Survival benefit in MRD-positive** after pediatric-inspired Rx

AlloSCT in CR1 or CR2 (Ph+)

Long-Term Follow-up of Allogeneic Hematopoietic Stem Cell Transplantation for Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Impact of Tyrosine Kinase Inhibitors on Treatment Outcomes

Partow Kebriaei,¹ Rima Saliba,¹ Gabriela Rondon,¹ Alexandre Chiattonne,¹ Rajyalakshmi Luthra,² Paolo Anderlini,¹ Borje Andersson,¹ Elizabeth Shpall,¹ Uday Popat,¹ Roy Jones,¹ Laura Worth,³ Farhad Ravandi,⁴ Deborah Thomas,⁴ Susan O'Brien,⁴ Hagop Kantarjian,⁴ Marcos de Lima,¹ Sergio Giralt,⁵ Richard Champlin¹

AlloSCT in CR1 = **better OS** benefit

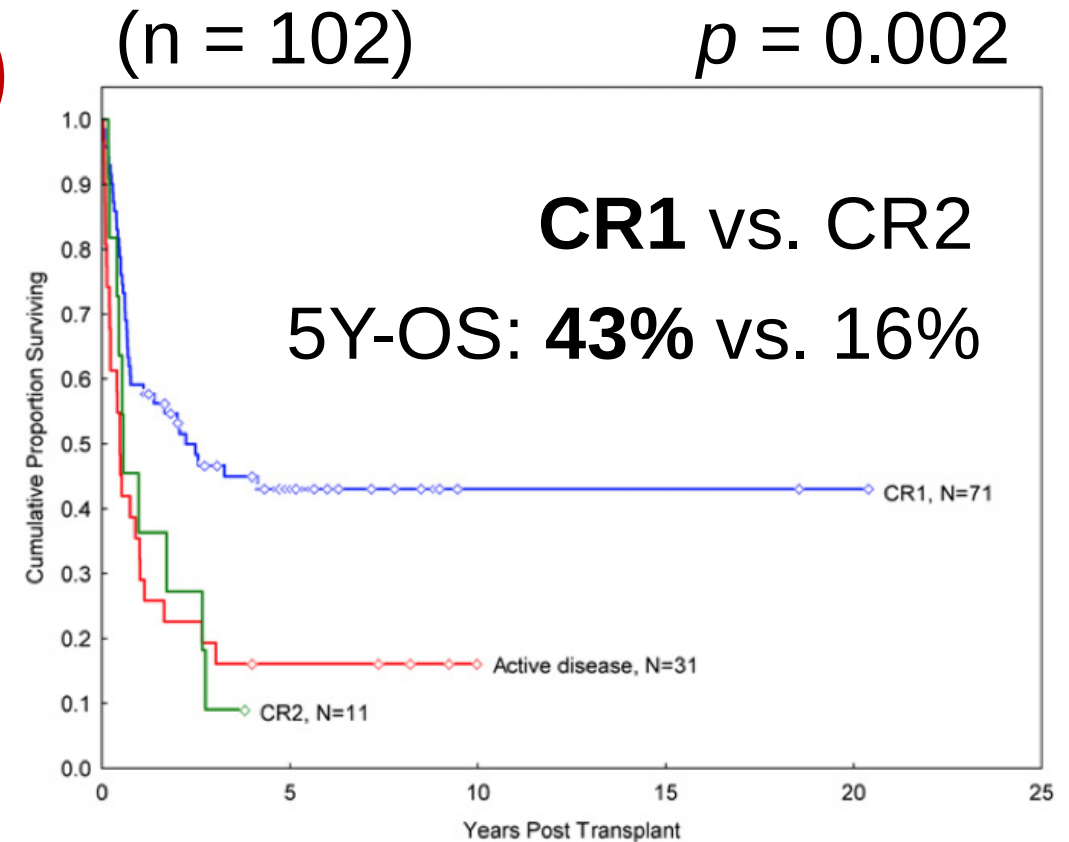


Figure 1. OS by disease status at time of HSCT. OS rates at 5 years for patients in CR1, CR2, and active disease were 43%, 9%, and 16%, respectively.

AlloSCT in CR1 better OS

Reference	TKI	Phase	N	Median Age, yr (Range)	Allo-HSCT, %	OS	DFS
Chalandon, 2015	I	3	268	47 (18–59)	63	$p = 0.02$ (5 yr) *	$p = 0.036$ (5 yr) *
Fielding, 2014	I	3	175	42 (16–64)	60	52% vs. 19% (4 yr) *	69% vs. 18% (4 yr) *
Bassan, 2010	I	2	59	47 (19.5–66)	63	42% (5 yr) vs. 29% (3 yr) *	46% (5 yr) vs. 8% (3 yr) *
Tanguy, 2013	I	2	45	45 (16–59)	51	76% vs. 33%; $p = 0.17$ (4 yr) *	71% vs. 33%; $p = 0.26$ (4 yr) *
Daver, 2015	I	2	45	51 (17–84)	30	NA	63% vs. 43%; NS (5 yr)
Chiaretti, 2016	I	2	51	45.9 (15–60)	42	$p = 0.03$ *	$p = 0.06$ *
Lou, 2017	I	2	153	40 (18–68)	39	73% vs. 22%; $p < 0.0001$ (3 yr) *	66% vs. 16%; $p < 0.0001$ * (3 yr) #
Hatta, 2018	I	2	99	45 (15–64)	61	NA	54% vs. 36%; NS (5 yr)
Ravandi, 2015	D	2	72	55 (21–80)	17	33% vs. 49% (5 yr, NS)	NA
Kim, 2015	N	2	90	47.0 (17–71)	63	80% vs. 72%; NS (2 yr)	78% vs. 49%, $p = 0.045$ (2 yr) *
Jabbour 2018	P	2	65	47 (39–61)	20	70% vs. 87%; NS (5 yr)	NA

I: Imatinib, D: Dasatinib, N: Nilotinib, P: Ponatinib

* Support the role of AlloSCT at CR1 in Ph+ ALL
EFS

This benefit were less clear in 2G & 3G TKIs combination

Impact of **CMR** in Ph+ ALL

Non-AlloSCT analysis

HyperCVAD + **TKIs**

n = 85, ND-Ph+ ALL

MRD assessed at CR & 3-month
(RQ-PCR for *BCR/ABL1*)

Molecular response

MMR: 3-log reduction *BCR/ABL1* (<0.1%)

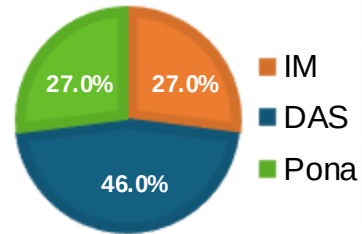
CMR: MRD negative (<0.01%)

CMR at 3-month: Better RFS, OS

4Y-RFS: 63%

4Y-OS: 66%

(even not receive AlloSCT !!)



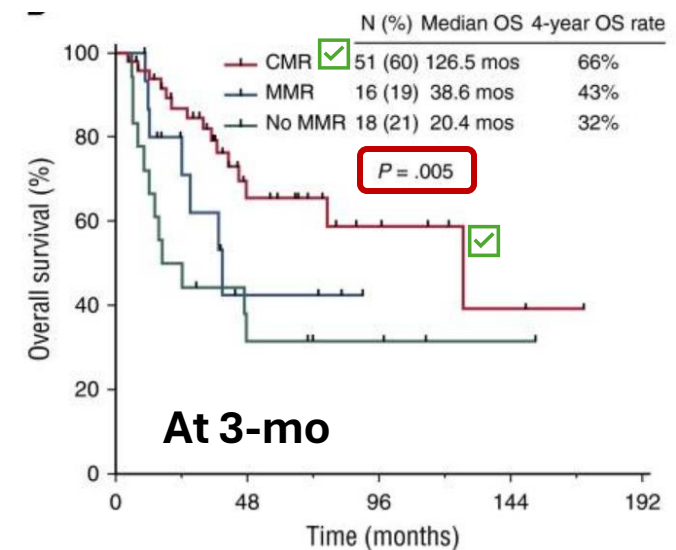
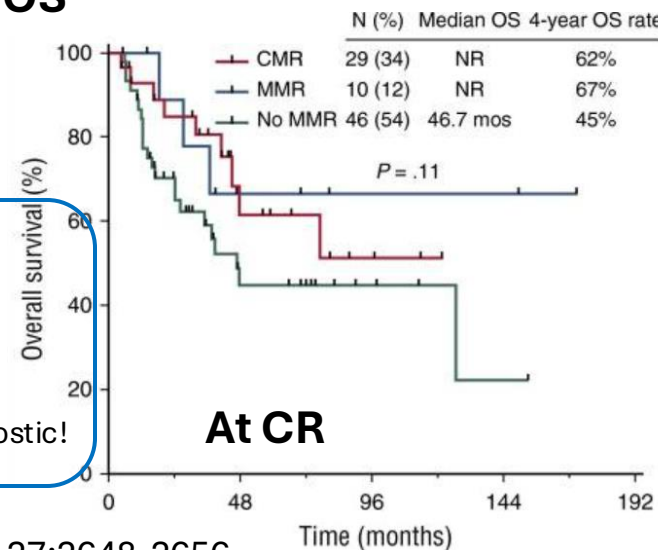
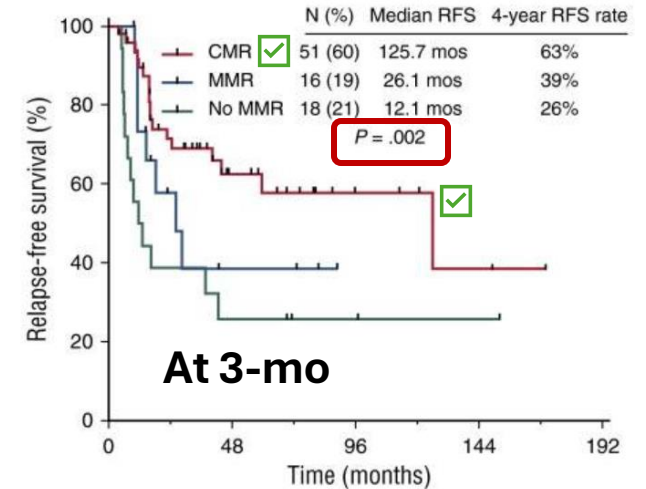
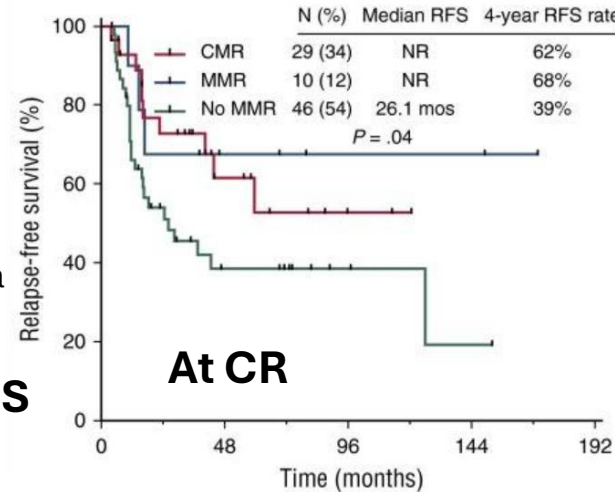
RFS

OS

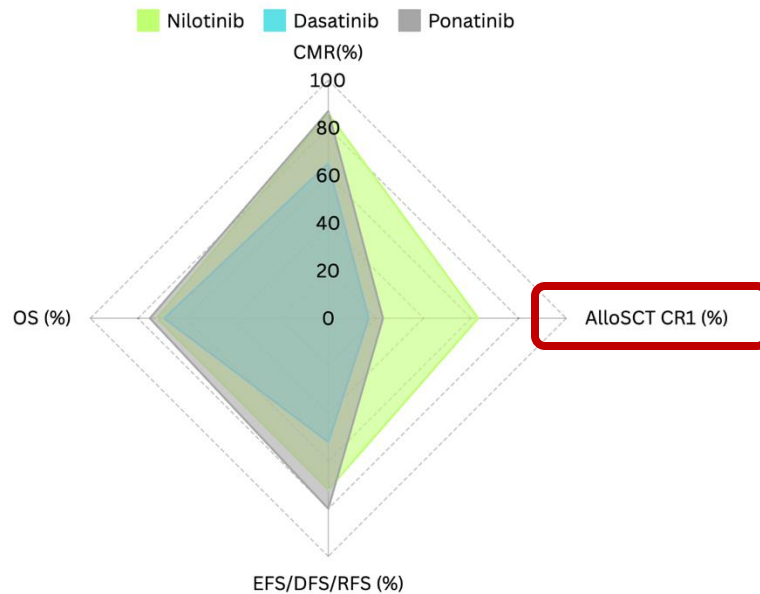
FU study

Ponatinib
Less relapse
Better OS

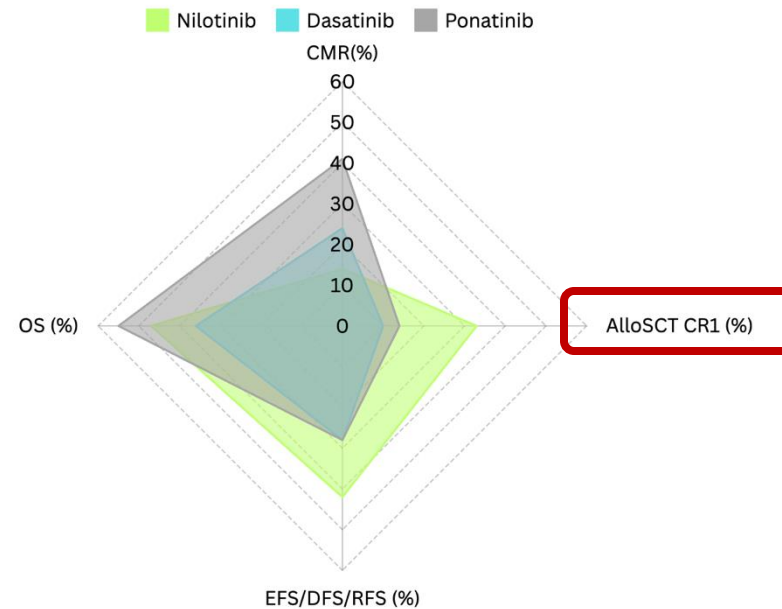
AlloSCT- not prognostic!



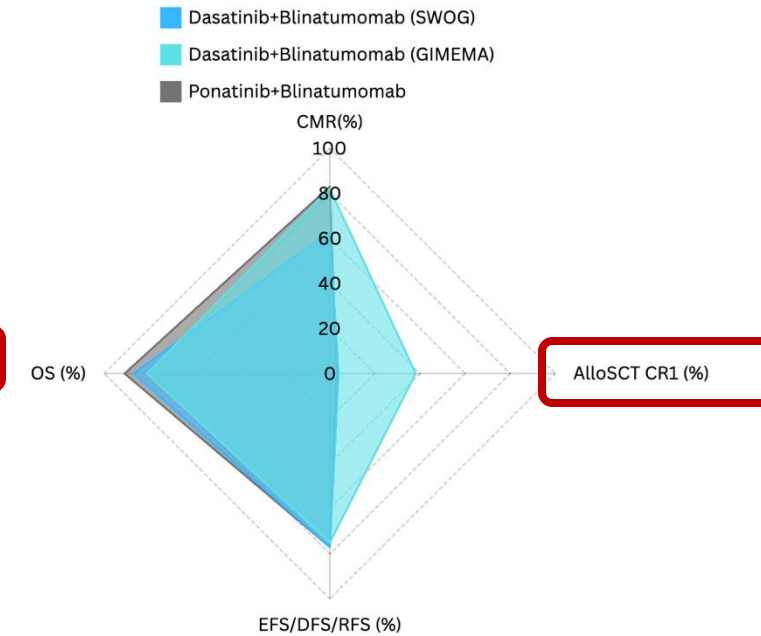
Ph+ ALL in the new era



+ High-intensity chemo



+ Low-intensity chemo



Chemo-free Rx

Ph+ ALL

Diagnostics/evaluation	Patient: Age, fitness/frailty, cardiovascular risk factors, support Disease: <i>Genetic risk:</i> cytogenetic, molecular (<i>IKZF1</i> ; <i>IKZF1</i> plus) <i>MRD monitoring:</i> RT-PCR p190 vs p210; NGS or PCR for clonal tracking
When possible, (a) enroll on clinical trial, (b) follow published regimen	
Phase: Induction Goal: Complete remission (CR)	TKI: DAS or PON or clinical trial PLUS: Low intensity (steroids, steroids + vincristine, steroids + blinatumomab)
Phase: Consolidation Goal: Prolong CR (indefinitely)	TKI: DAS or PON or clinical trial -If DAS, consider change to PON if inadequate response -If PON, dose reduce to 15 mg after achievement of CMR PLUS: 1. TKI alone (<i>if alloHCT planned or palliative goal</i>) 2. Chemotherapy (<i>age adjusted</i>) 3. Blinatumomab (<i>within 3 months</i>) 4. AlloHCT
CNS prophylaxis	IT chemotherapy (12–15) High-dose methotrexate and/or cytarabine
Monitoring	<i>BCR::ABL1</i> RT-PCR NGS, to establish presence of CML-like biology, and if present to supplement <i>BCR::ABL1</i> transcript monitoring

Diagnostics/evaluation	Patient: Age, fitness/frailty, cardiovascular risk factors, support Disease: <i>Genetic risk:</i> cytogenetic, molecular (<i>IKZF1</i> ; <i>IKZF1</i> plus) <i>MRD monitoring:</i> RT-PCR p190 vs p210; NGS or PCR for clonal tracking
When possible, (a) enroll on clinical trial, (b) follow published regimen	
Phase: Induction Goal: Complete remission (CR)	TKI: DAS or PON or clinical trial PLUS: Low intensity (steroids, steroids + vincristine, steroids + blinatumomab)
Phase: Consolidation Goal: Prolong CR (indefinitely)	TKI: DAS or PON or clinical trial -If DAS, consider change to PON if inadequate response -If PON, dose reduce to 15 mg after achievement of CMR PLUS: 1. TKI alone (<i>if alloHCT planned or palliative goal</i>) 2. Chemotherapy (<i>age adjusted</i>) 3. Blinatumomab (<i>within 3 months</i>) 4. AlloHCT
AlloHCT, in CR1	Favoring yes 1. High-risk genetic features (chromosomes: complex, "double" Ph; <i>IKZF1</i> plus) 2. No achievement of CMR by 3 months (with TKI+/- chemotherapy) 3. Fit, appropriate donor 4. No blinatumomab available or not tolerated Favoring no 1. No high-risk genetic features 2. Achievement of CMR by 3 months (with TKI+/- chemotherapy) 3. Blinatumomab Unknown 1. Poor response to TKI+/- chemo but CMR with blinatumomab 2. High-risk genetics but optimal MRD response
CNS prophylaxis	IT chemotherapy (12-15) High-dose methotrexate and/or cytarabine
Monitoring	<i>BCR::ABL1</i> RT-PCR NGS, to establish presence of CML-like biology, and if present to supplement <i>BCR::ABL1</i> transcript monitoring

Ph-like ALL
(*BCR::ABL1*-like ALL)

Ph-like ALL (*BCR::ABL1*-like ALL)

10-30% of B-ALL

(B-other: Ph neg without defining molecular abnormalities e.g., KMT2A, hypodiploid, hyperdiploid)

Gene expression profile: similar to Ph+ ALL

Diagnosis

110 gene probe sets
257 gene probe sets

Prediction analysis of microarrays (PAM) classifier

(only 9 probe sets overlapped between 2 lists)

Identify **poor outcome patients** and tyrosine kinase fusion genes

15-gene LFS (Low-density array: LDA) gene expression card

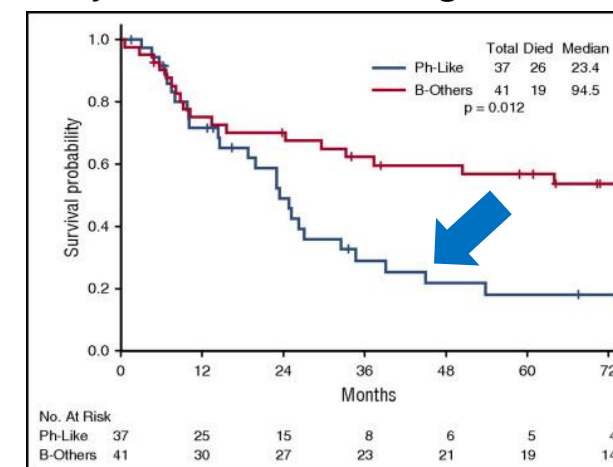
(87% concordance to PAM)

***BCR::ABL1*-like predictor using RT-qPCR**

(using 9 overexpressed genes)

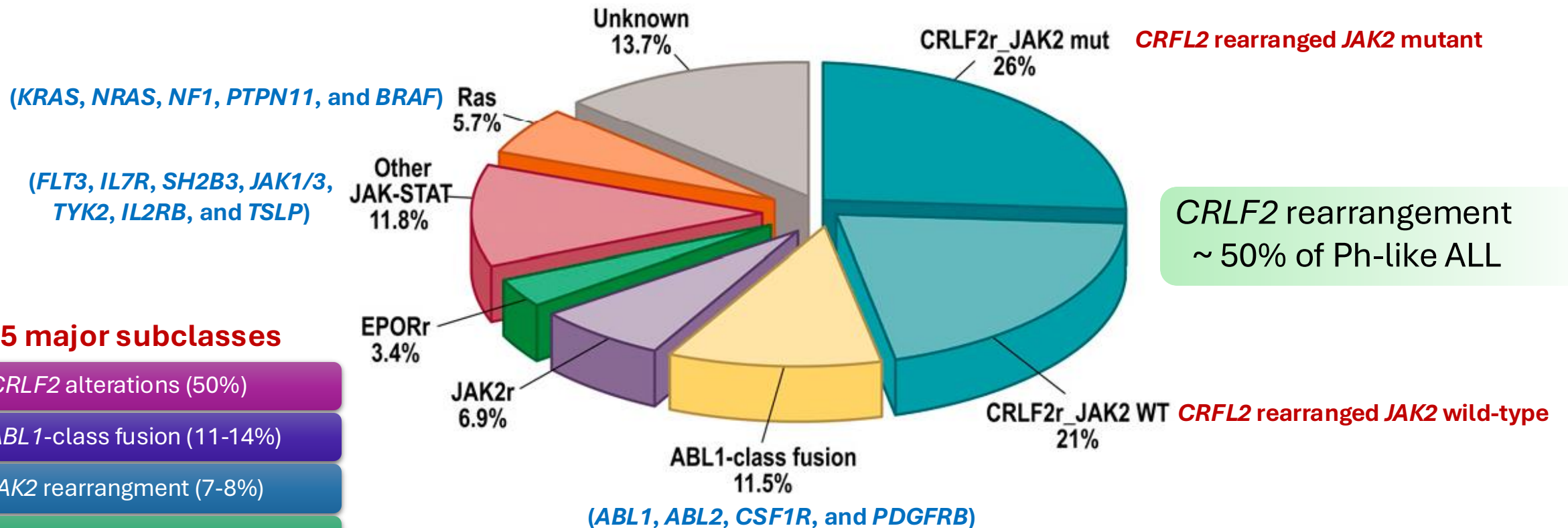
JAK/STAT | RAS | CRLF2

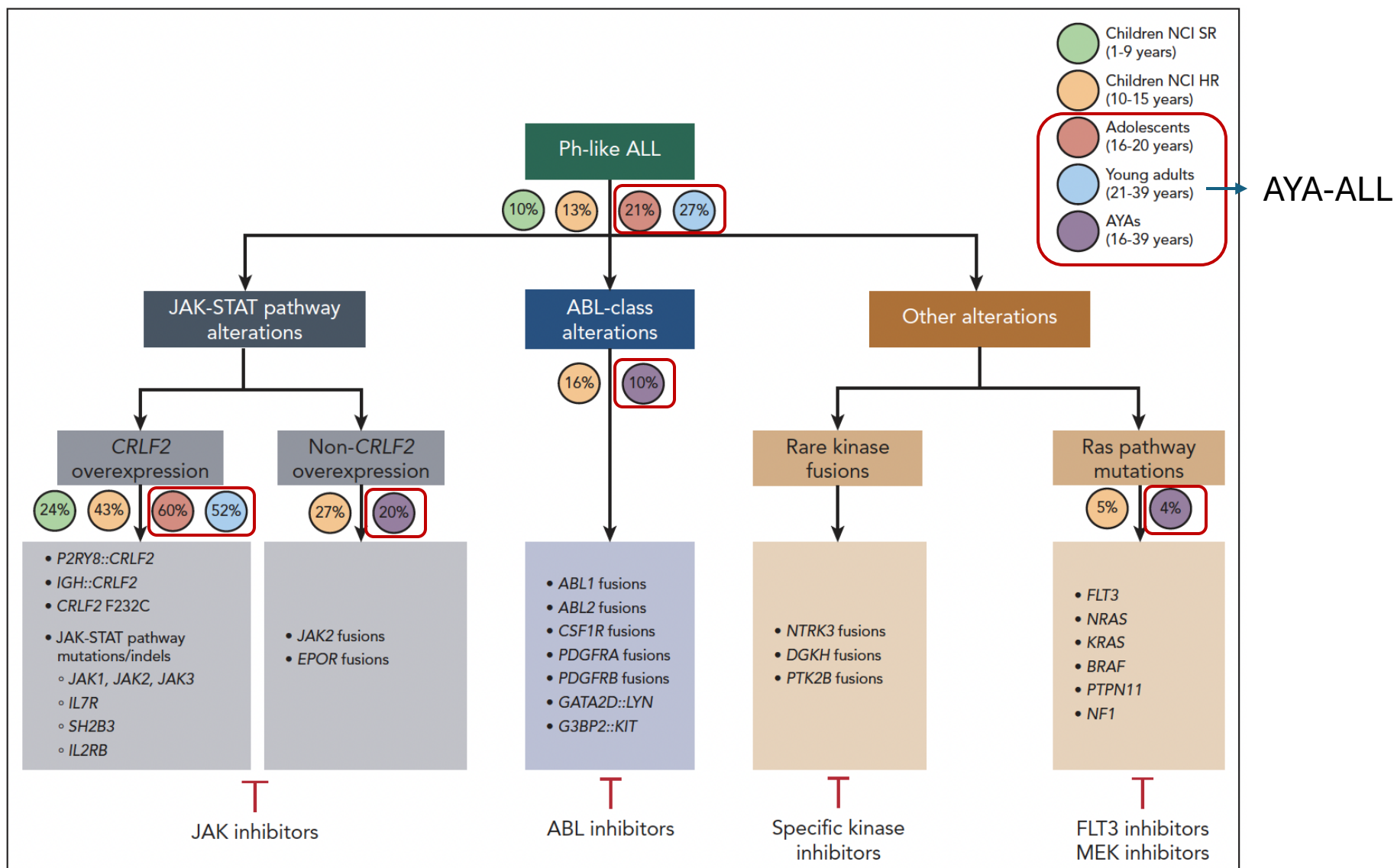
	<i>BCR/ABL1</i> -like	non- <i>BCR/ABL1</i> -like	p-value
JAK/STAT pathway members mutated cases	11/25 (44%) [^]	0/23	p<0.001
<i>JAK1/2</i> mutations	7/25 (28%)	0/23	p=0.007
<i>CRLF2</i> mutations	4/25 (16%)	0/23	p=0.065
<i>IL7R</i> mutations	2/25 (8%)	0/23	ns
RAS pathway members mutated cases	3/25 (12%)	6/23 (26.1%)*	ns
<i>FLT3</i> mutations	0/25	1/23 (4.3%)	ns
<i>KRAS/NRAS</i> mutations	3/25 (12%)	6/23 (26.1%)	ns
<i>IKZF1</i> deletions	15/17 (88.2%)	6/14 (42.8%)	p=0.01
<i>EBF1</i> deletions	8/17 (47%)	1/14 (7.1%)	p=0.018
<i>BTG1</i> deletions	6/17 (35.3%)	1/14 (7.1%)	p=0.029
<i>CRLF2</i> overexpressing cases	17/26 (57.7%)	4/26 (7.7%)	p<0.001



Remain challenging and there is not standard of testing!!

Frequency of Ph-like ALL subtype



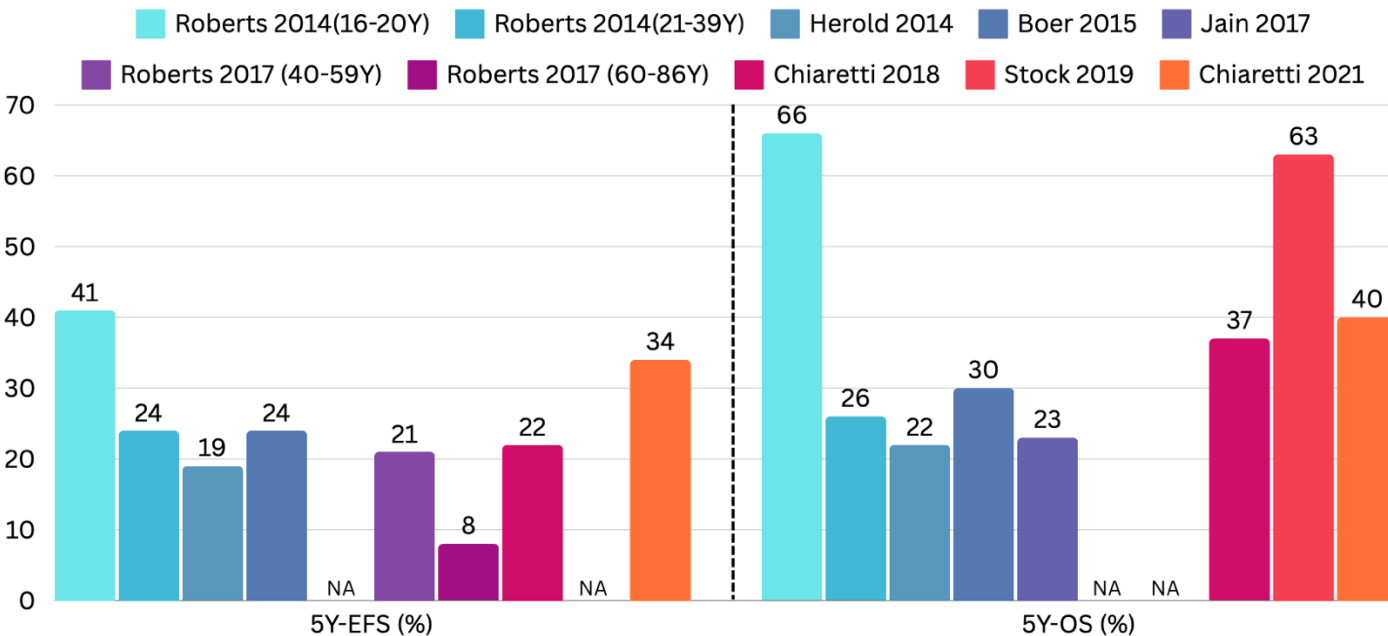


Study	Age group (y)	Total patients and frequency of Ph-like ALL in B-other*
Roberts et al, 2014 ¹⁶²	16-20	77 (21%)
	21-39	46 (27%)
Herold et al, 2014 ¹⁶³	16-20	5 (19%)
	21-39	12 (18%)
	40-55	4 (9%)
	55-84	5 (7%)
Boer et al, 2015 ¹⁵⁹	16-20	6 (25%)
	21-39	9 (19%)
	40-71	6 (11%)
Jain et al, 2017 ¹⁶⁴	15-39	33 (42%)
	40-84	16 (24%)
Roberts et al, 2017 ¹⁶⁵	21-39	96 (28%)
	40-59	62 (20%)
	60-86	36 (24%)
Chiaretti et al, 2018 ¹⁶¹	0-15	2 (9%)
	15-35	29 (29%)
	35	23 (31%)
Stock et al, 2019 ⁶	17-39	41 (31%)
Chiaretti et al, 2021 ¹⁶⁶	18-65	28 (32%)

Ph-like ALL incidence (PAM-classifier) in US cohort

Younger adults (AYA) 21-39Y : 28%

Older adults > 39Y : 20-24%



MRD response and prognosis (Ph-like ALL)

- 70% of Ph-like ALL → remained MRD positive
- Inferior EFS and OS
- Impact of MRD response are conflicting
- Aiming MRD negativity retains prognostic importance

Ph-like ALL: treatment

Several of preclinical data and anecdotal reports

Imatinib

Dasatinib

Ponatinib

ABL1-class fusion

Ruxolitinib

(preclinical)

JAK2 fusion

EPOR rearrangement

JAK/STAT

Blinatumomab

Inotuzumab

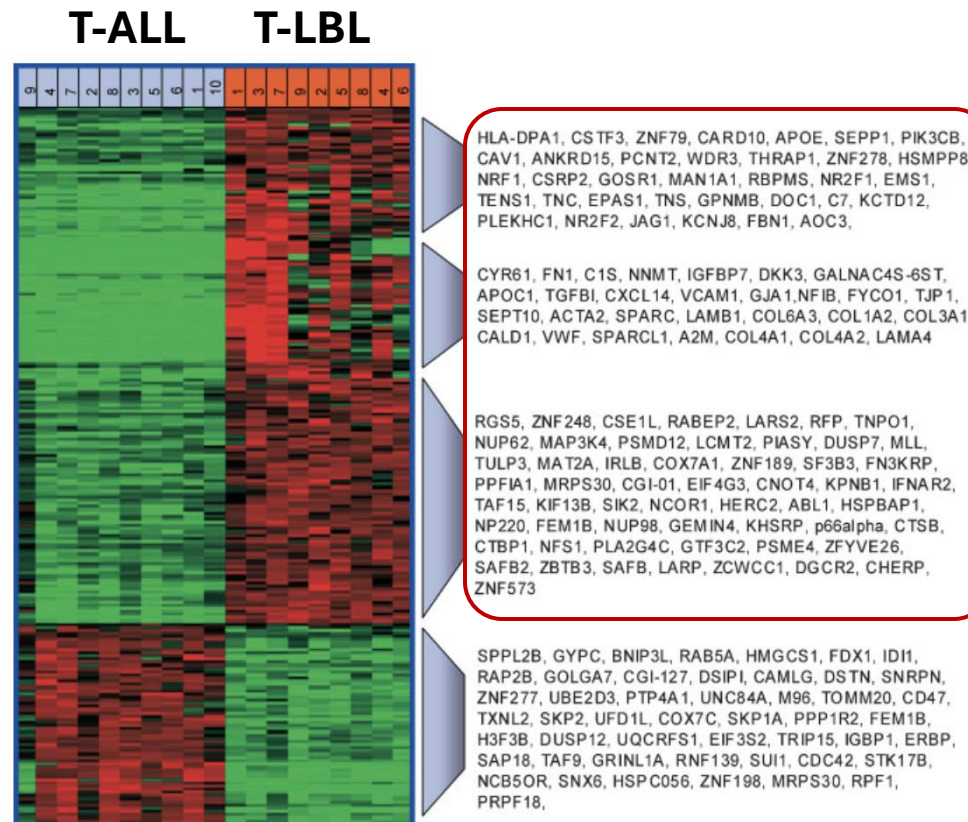
For clinical practice → identify ABL1-fusion (FISH) + MRD-based Rx modification
Offering AlloSCT and/or targeted tx
(because of poor MRD response in most of patients)

No studies confirming SCT benefits

T-ALL and T-LBL

T-ALL and T-LBL

- T-ALL: 25% of adults ALL → LBL 80-90% are T-cells (T-LBL)
- Treatment: similar to B-ALL including pediatric inspired regimen



Male predominance
90% mediastinal bulky mass

T-LBL

70% thymic subtype (favorable)
 18% early T subtype (worse)
 9% mature T subtype (worse)

CR 70-90%

5Y-EFS 60-70%

5Y-OS 60-70%

Raetz E. Pediatr Blood Cancer 2006;47:130-140.

Gökbuget N. Blood 2024;143(19):1903-1930.

Targeted therapy in T-ALL and T-LBL

Study (reference)	ALL subset	Combination treatment	Age (y)	No.	CR (%)	CRD/ RFS (%)	OS (%)	EFS (%)	FUP	Annotations
Nelarabine (T-specific nucleoside analog) MDACC ³⁹	T-ALL/LBL	Hyper-CVAD + nelarabine after course 8 (×2) or 5 and 7 (×1 each)	30 (13-78)	81	NR	—	57	52	5 y	OS non-ETP 63% vs ETP 32% ($P < .001$); non-ETP: OS nelarabine 83% vs no nelarabine 38% ($P = .003$)
UKALL 14 (Phase 3) ⁴⁰	T-ALL	A: SOC B: SOC + nelarabine ×1 after induction II	25-65	75 69	90 87	—	61 65	57 61	3 y	No benefit from single nelarabine course (3 doses), all P values not significant

Nelarabine

Improve survival in 2-course after C8 or after C5,7 (1x each) for non-ETP ALL (when + HyperCVAD)

No survival benefit in 1-course after induction II

4

Conclusion

- MRD status = most important factor driving SCT indication
 - High efficacious Rx achieving MRD negativity is the key
- **Ph neg ALL**
 - Prefer pediatric regimen (+supportive care for regimen's toxicities)
 - Targeting CD20/22/19 (no study combine to pediatric regimen now)
- **Ph pos ALL**
 - Prefer Low inten-induction, High inten-consol + 2G/3G TKI
 - Chemo-free: Blinatumomab + DAS/PON
- **Role of AlloSCT in CR1**
 - Benefit in MRD positive
 - Early CMR (3-month with RQ-PCR <0.01% in Ph+ALL), Blinatumomab = maybe no benefit from AlloSCT in CR1

Ph-like ALL: TKI+MRD guided

T-ALL: as Ph neg ALL

Thank you for your attention