XX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

ROMA,
ERGIFE PALACE HOTEL
7-8 MAGGIO 2026

LLA Ph+ e Ph-like: nuovi farmaci, bersagli molecolari e impatto sul trapianto

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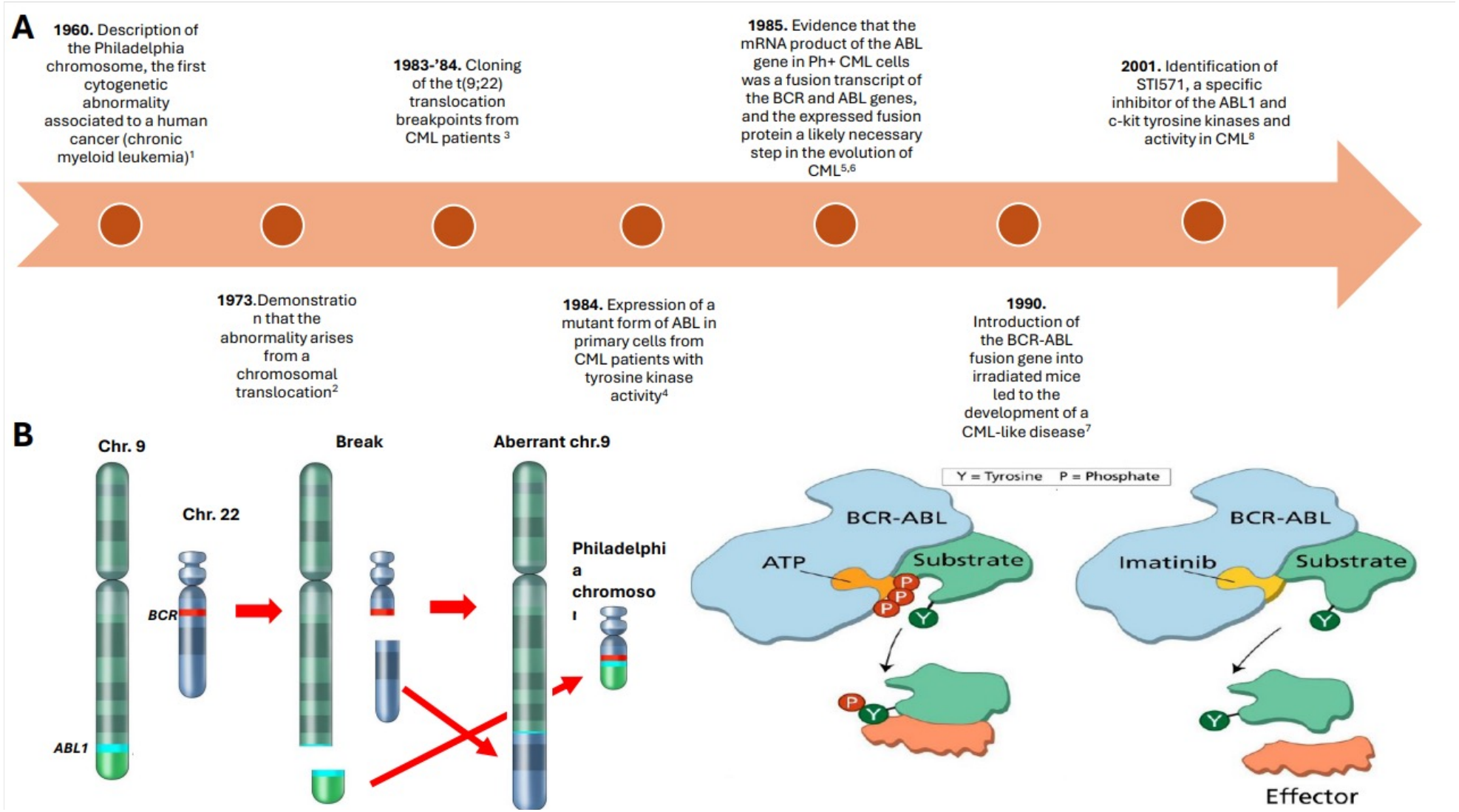
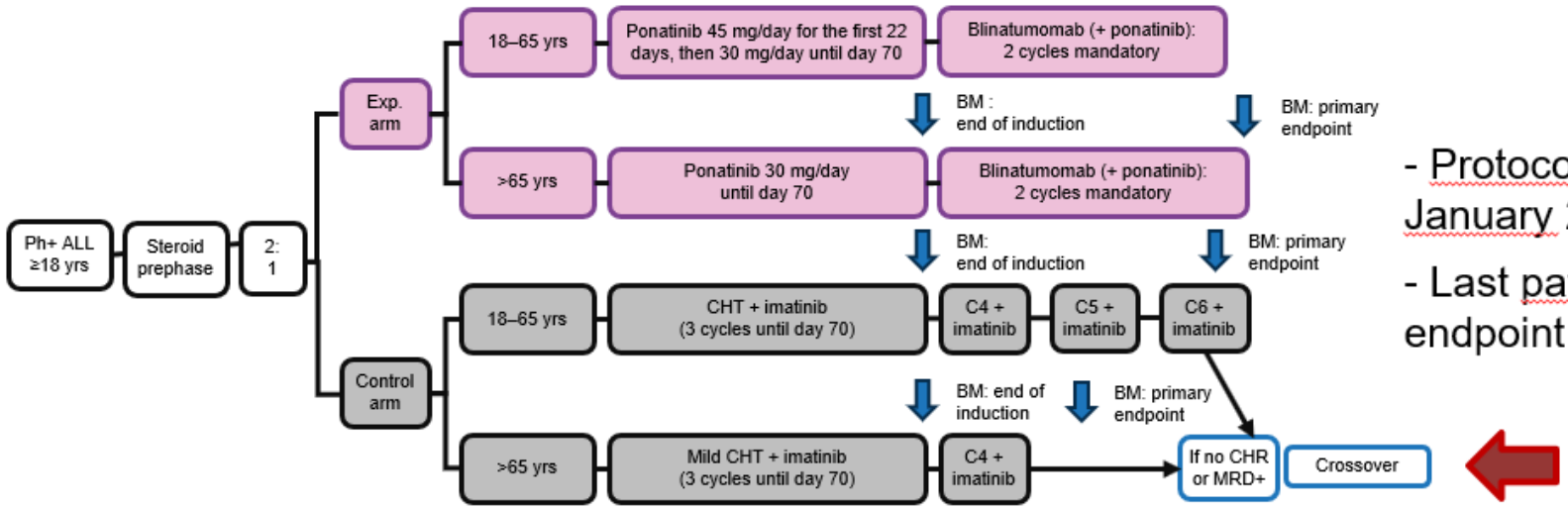
Ph+ ALL



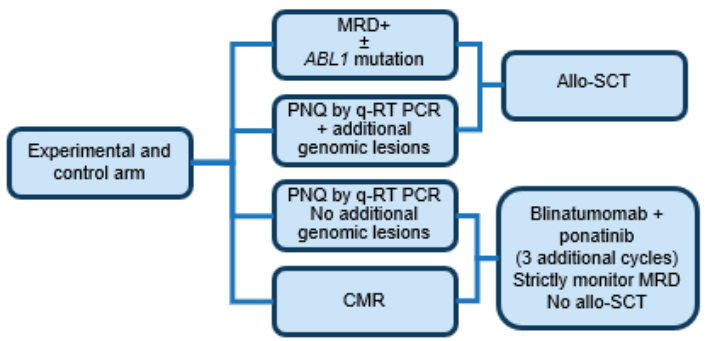
Foà R, Chiaretti S. *NEJM 2022* Jun 23;386(25):2399-2411

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.

Chiaretti et al, ASH 2025 Abs 439; submitted

GIMEMA ALL2820. Features and repsonse to induction

GIMEMA ALL2820. Patients' features (n=236)

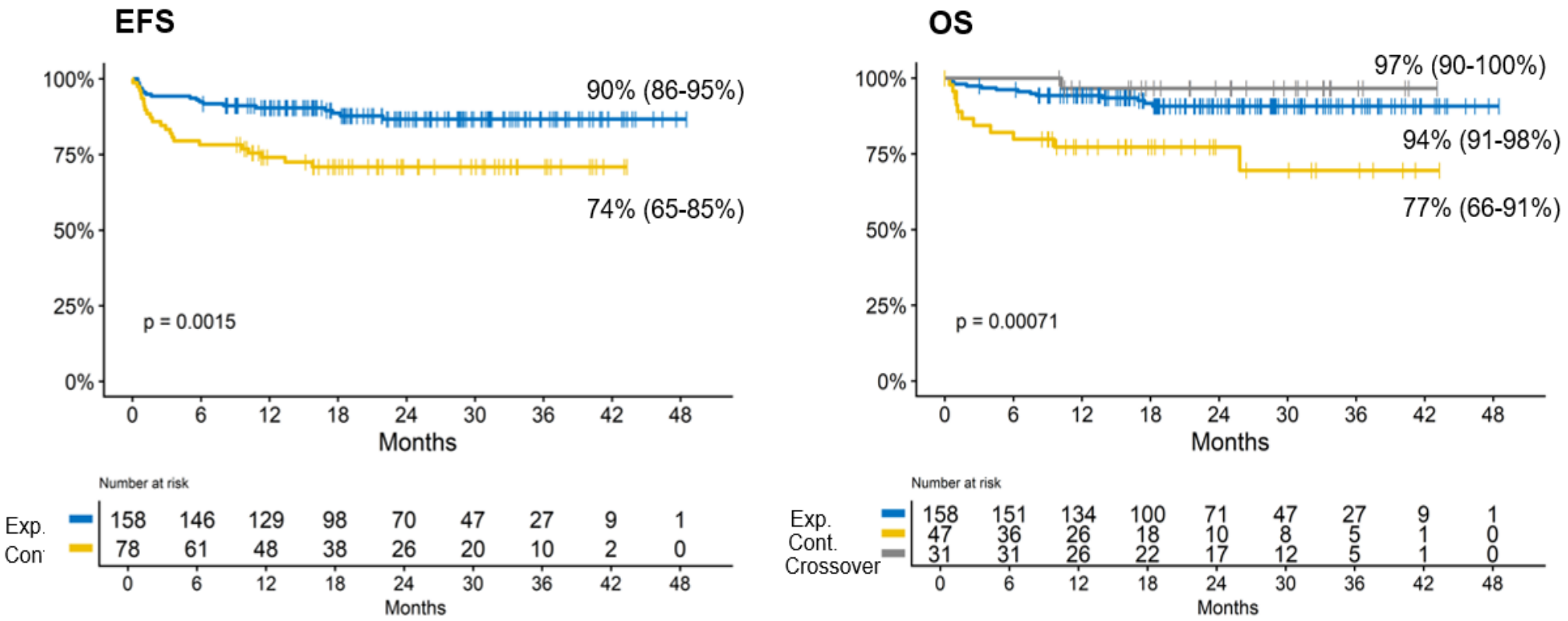
	Experimental arm N=158	Control arm N=78
Age, median (range)	56.5 (19-84)	55 (21-79)
>65 years (%)	44 (28)	21 (27)
Gender: M/F (%)	79/79 (50/50)	48/31(59/41)
WBC x10^9/l, median (range)	10.5 (0.1-244)	13.4 (0.7-231)
≥30x10^9/l (%)	43 (27)	27 (31)
≥70x10^9/l (%)	16 (10)	7 (9.3)
CNS+	15 (9.9)	11(15)
p190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

Chiaretti et al, ASH 2025 Abs 439; submitted

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. EFS and OS



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

Chiaretti et al, ASH 2025 Abs 439; submitted

GIMEMA ALL2820. What is the impact of the chemo-free combination on transplant strategy?

GIMEMA ALL2820. Transplant

	Experimental arm (n=31)	Control arm (n=16)
Ist CHR	29	16
IInd CHR	2	-
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} only	4	2
EOI MRD+	25	8
MRD + after 2 blina cycles/ cycles of chemotherapy	18	10
IKZF1^{plus}+ MRD+ at both time points	11	4
Relapses	-	2
Deaths	4	-

Transplant rate: 19.4% , transplant related mortality rate: 8.5%

Chiaretti et al, ASH 2025 Abs 439; submitted

Blinatumomab and Ponatinib for Adults with Newly Diagnosed Ph+ ALL: Updated Results and Predictors of Relapse

NJ Short, H Kantarjian, N Jain, K Takahashi, K Furudate, J Senapati, FG Haddad, O Karrar, TM Kadia, K Chien, K Sasaki, E Kugler, R Garris, F Ravandi, E Jabbour

Department of Leukemia

The University of Texas MD Anderson Cancer Center, Houston, TX

Short et al, ASH 2024 abs 837

Ponatinib + Blinatumomab in Ph+ ALL: Conclusions

- Chemotherapy-free combination of ponatinib + blinatumomab achieves deep responses in pts with newly diagnosed Ph+ ALL
  - CR/CRi 98%, CMR 83%, NGS MRD negativity 96%
- Durable remissions without HSCT in first remission
  - Estimated 3-year RFS 78%; 3-year OS 88%
  - Only 2 pts (3%) underwent HSCT in first remission
  - 10 relapses to date (13% relapse rate; half in CNS)
- WBC >70K only factor predictive for relapse; ? role of *VPREB1* deletion
  - Very high-risk feature → CIR rate ~50%
- Novel strategies needed for pts with high-risk Ph+ ALL

Short et al, ASH 2024 abs 837

Who to transplant in the chemo-free era (personal opinion)

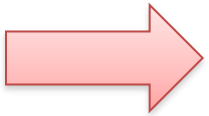
- In the modern era, the number of patients candidate to allo-SCT is significantly decreasing.
- Nevertheless, some should still be considered candidates
- Patients with suboptimal MRD: *BCR::ABL1* and/or *IG/TR*
- *IKZF1*^{plus} patients: most likely.

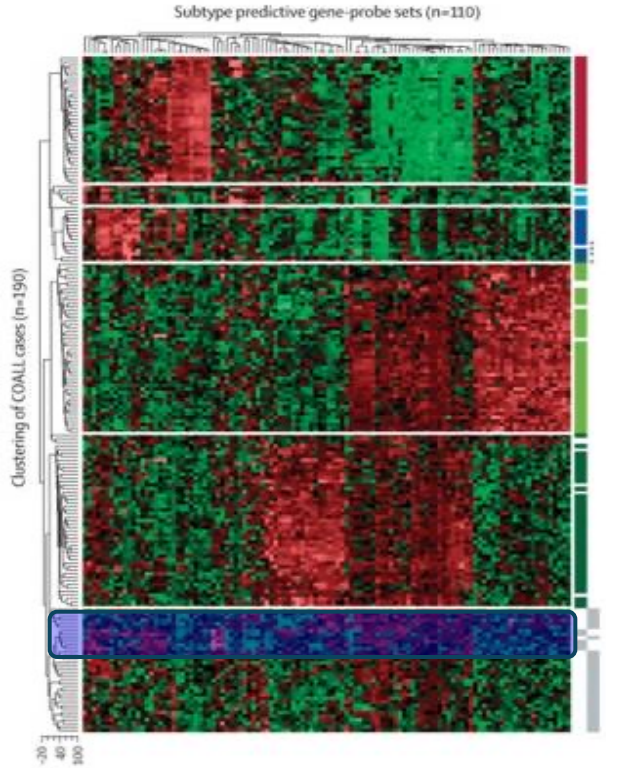
Interaction with WBC count?

WHO ALL classification (2016)

- **B ALL with recurrent genetis abnormalities:**
  a) t(9;22)(q34;q11) BCR/ABL1
  b) t(v;11q23); MLL rearranged
  c) t(12;21)(p13;q22); ETV6-RUNX1
  d) ALL with hyperdiploidy
  e) ALL with hypodiploidy
  f) t(5;14)(q31;q32); IL3-IGH
  g) t(1;19)(q23;p13); E2A-PBX1

Provisional entity: ALL "BCR/ABL1-like"
Provisional entity: ALL with iAMP21

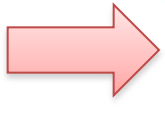


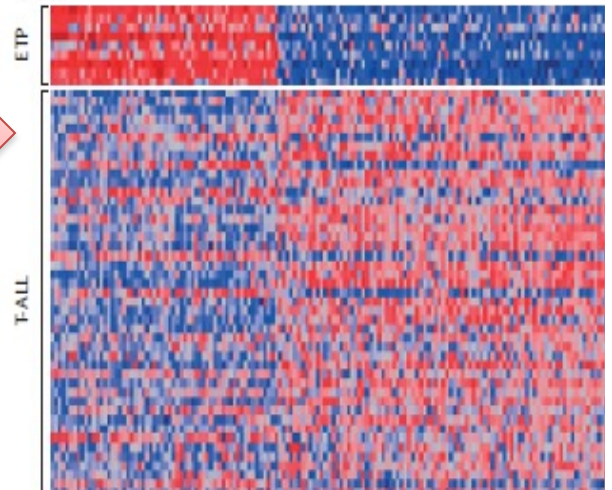


- **B ALL NOS**

- **T ALL**

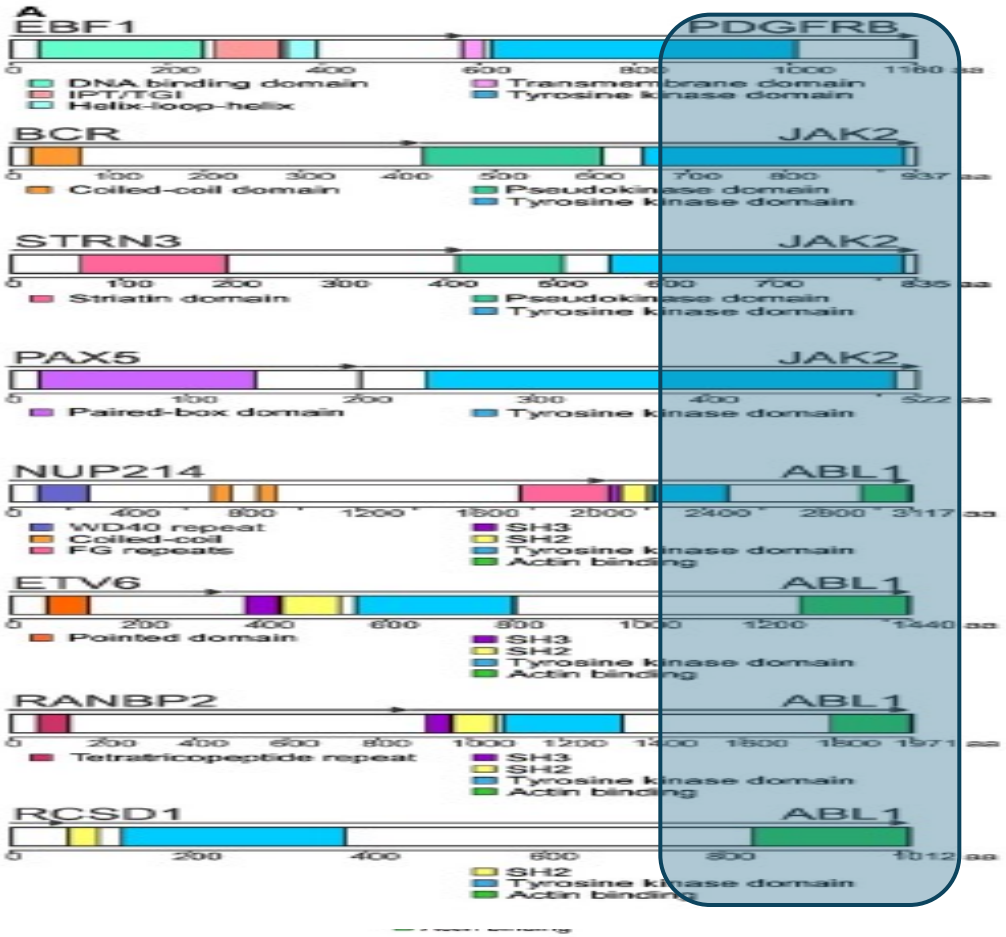
Prov. entity: Early T-cell precursor lymphobl. leukemia
Prov. entity: NK cell lymphobl. leukemia





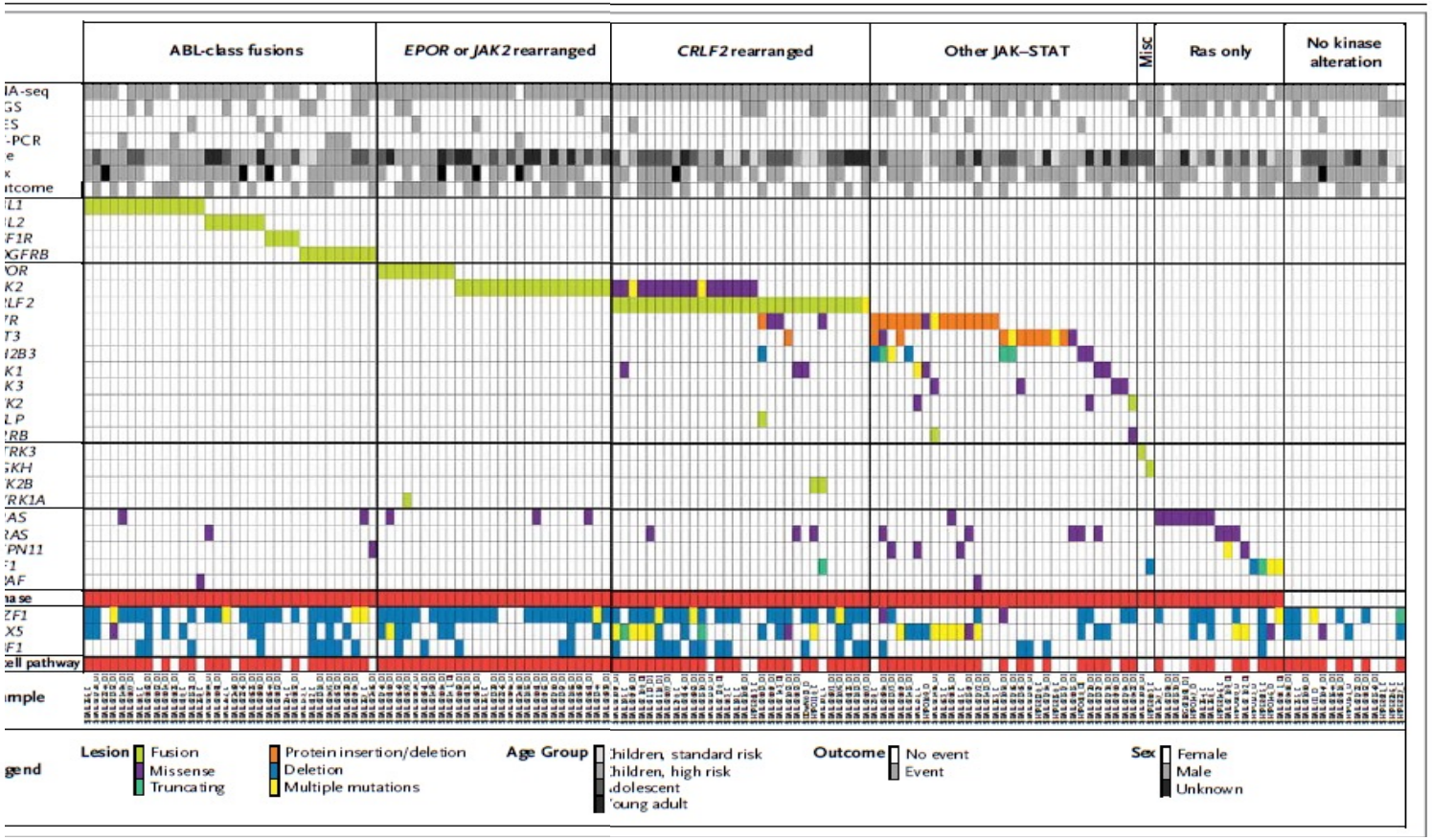
Arber A et al, Blood 2016 127:2391-2405

Genetic Alterations Activating Kinase and Cytokine Receptor Signaling in High-Risk Acute Lymphoblastic Leukemia



Targetable Kinase-Activating Lesions in Ph-like Acute Lymphoblastic Leukemia

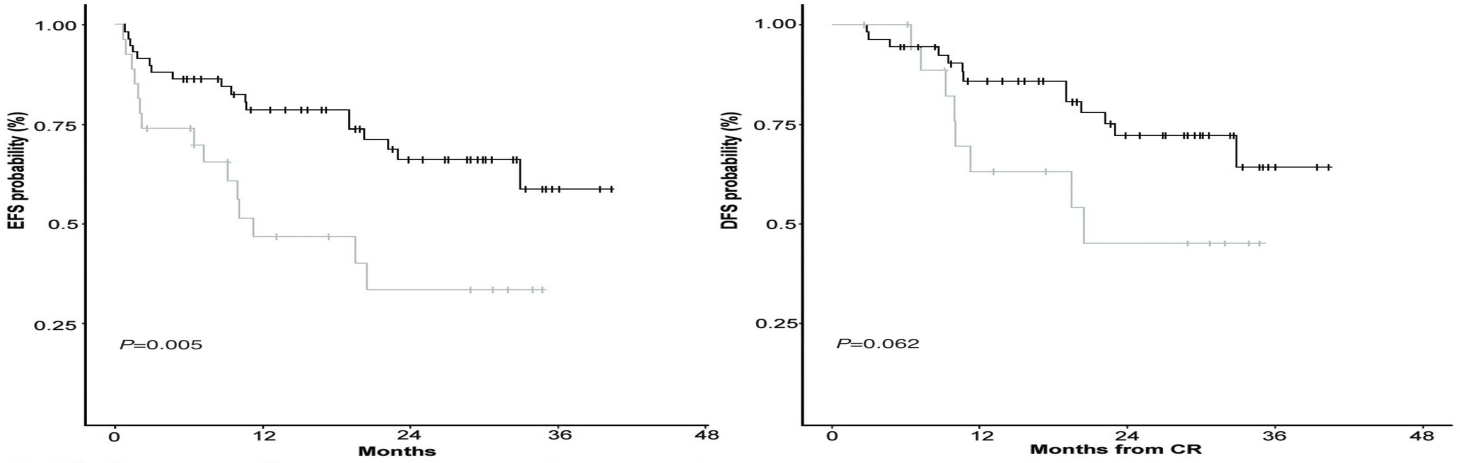
K.G. Roberts, Y. Li, D. Payne-Turner, R.C. Harvey, Y.-L. Yang, D. Pei, K. McCastlain, L. Ding, C. Lu, G. Song, J. Ma, J. Becksfort, M. Rusch, S.-C. Chen, J. Easton, J. Cheng, K. Boggs, N. Santiago-Morales, I. Iacobucci, R.S. Fulton, L. Wen, M. Valentine, C. Cheng



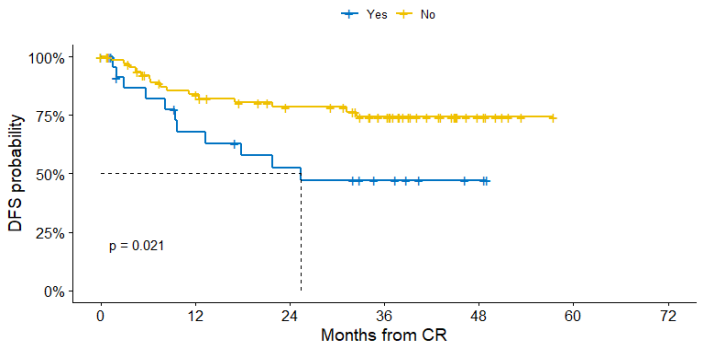
In high risk ALL, RNA-seq has identified novel mutations that involve TKs in the majority of cases. They appear to have transforming capability and to respond to TKIs.

Roberts KG. *Cancer Cell* 2012; 22:153-66 Roberts KG, *et al. N Engl J Med* 2014;371:1005–1015

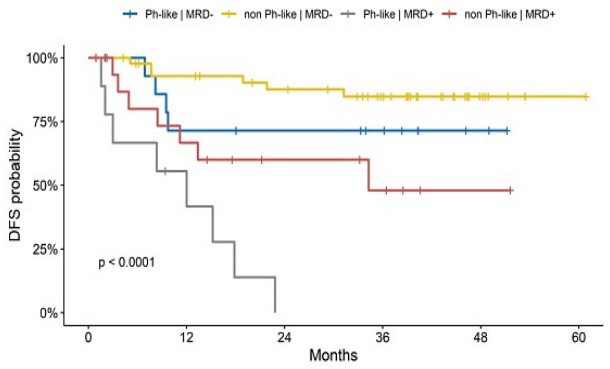
Ph-like ALL: among the black sheeps, the more investigated



Chiaretti S, et al. Haematologica, 2021

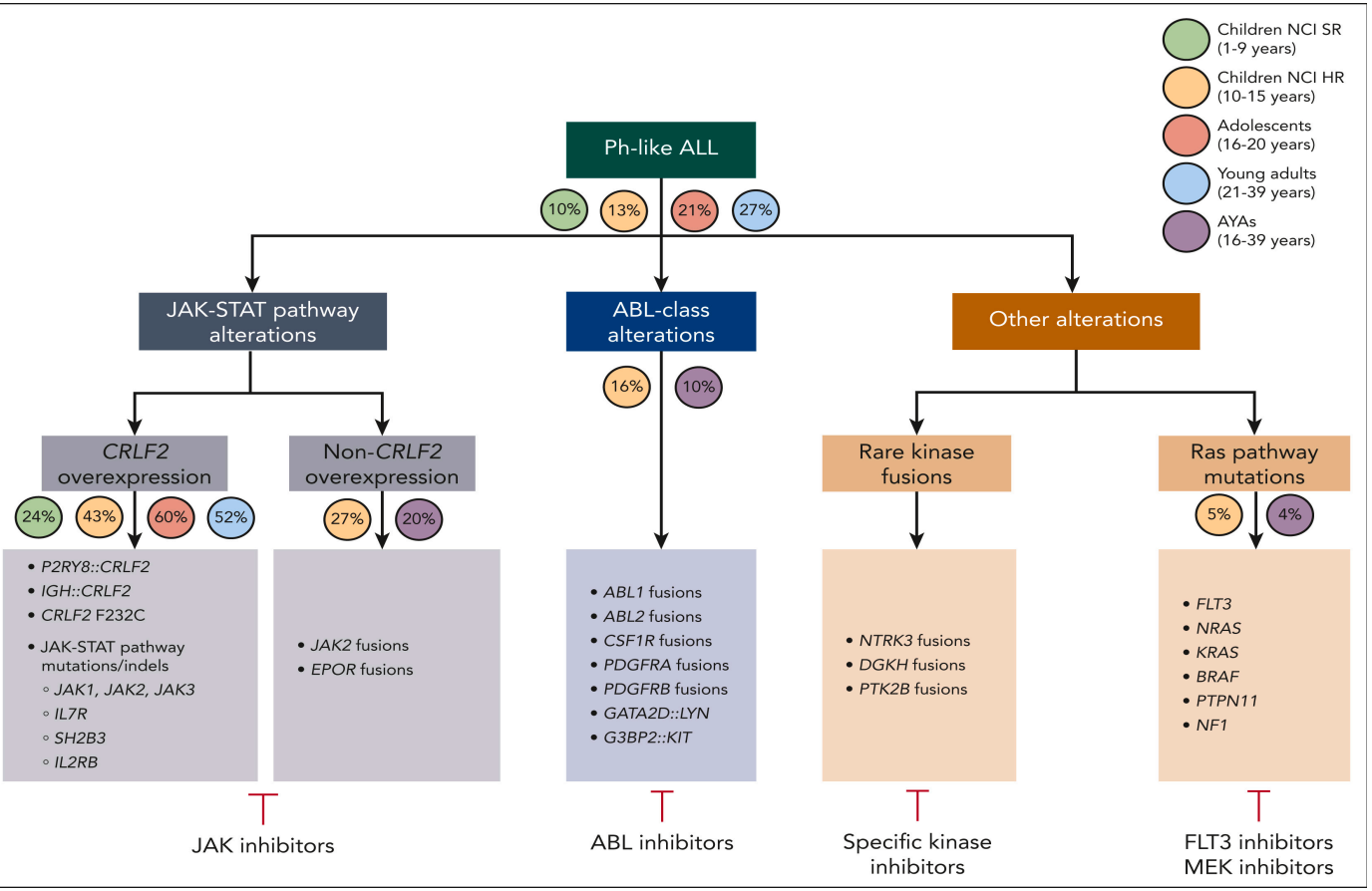


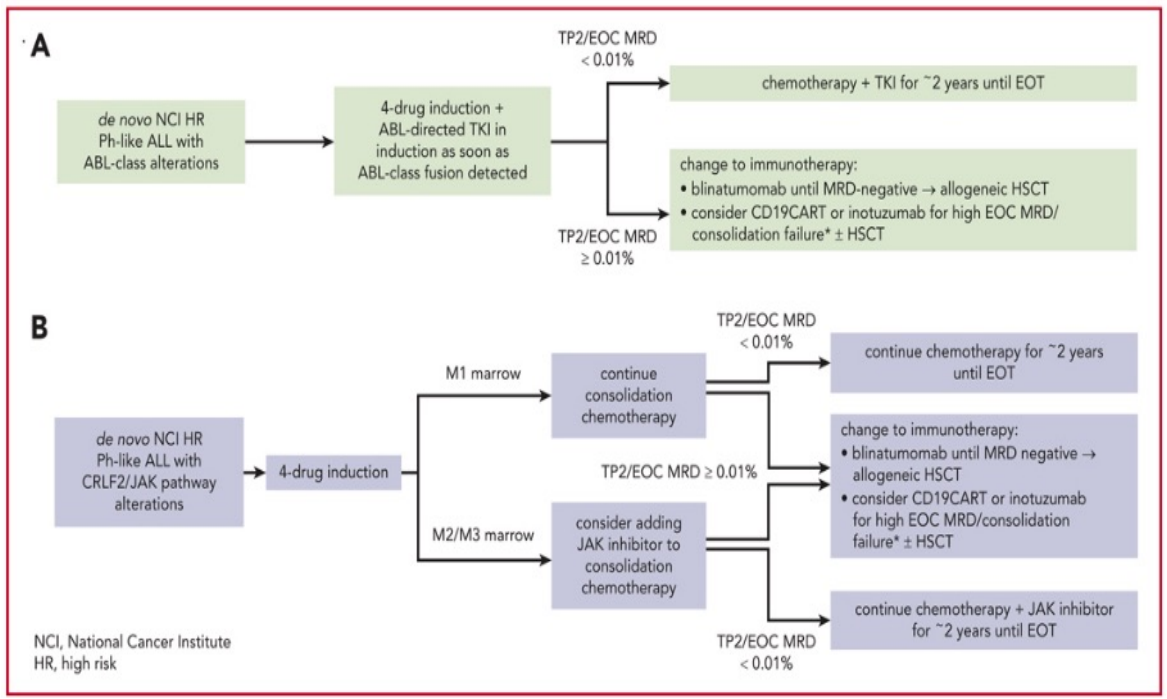
Chiaretti S, et al. ASH 2023



Bassan R, et al. Blood. 2025

Ph-like ALL diagnostic and therapeutic algorithm





Tran TH, Tasian SK. Blood. 2025

Ph-like status in GIMEMA LAL2317 trial: relapse and MRD

No relapse (n=10)	Relapse (n=7)	Relapse (n=5)
• Tp2 neg • Tp3 neg • Fusion detected in 2 patients	• Tp2 pos* • Tp3 neg* • Fusion detected in 6 patients	• Tp2 neg • Tp3 neg • Fusion detected in 3 patients§

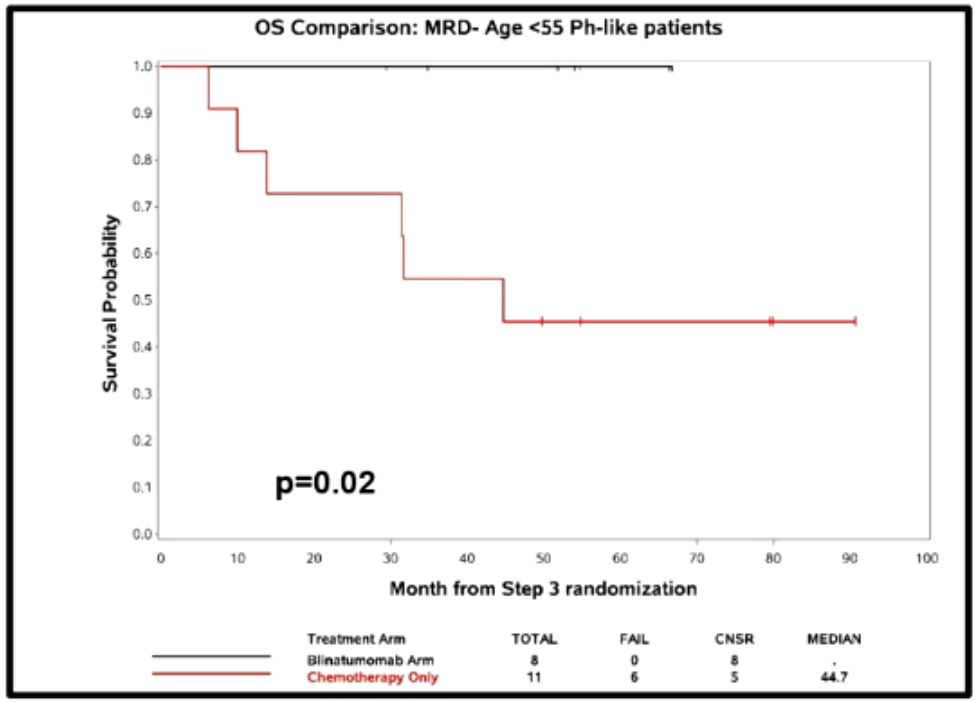
* MRD not evaluable in 2

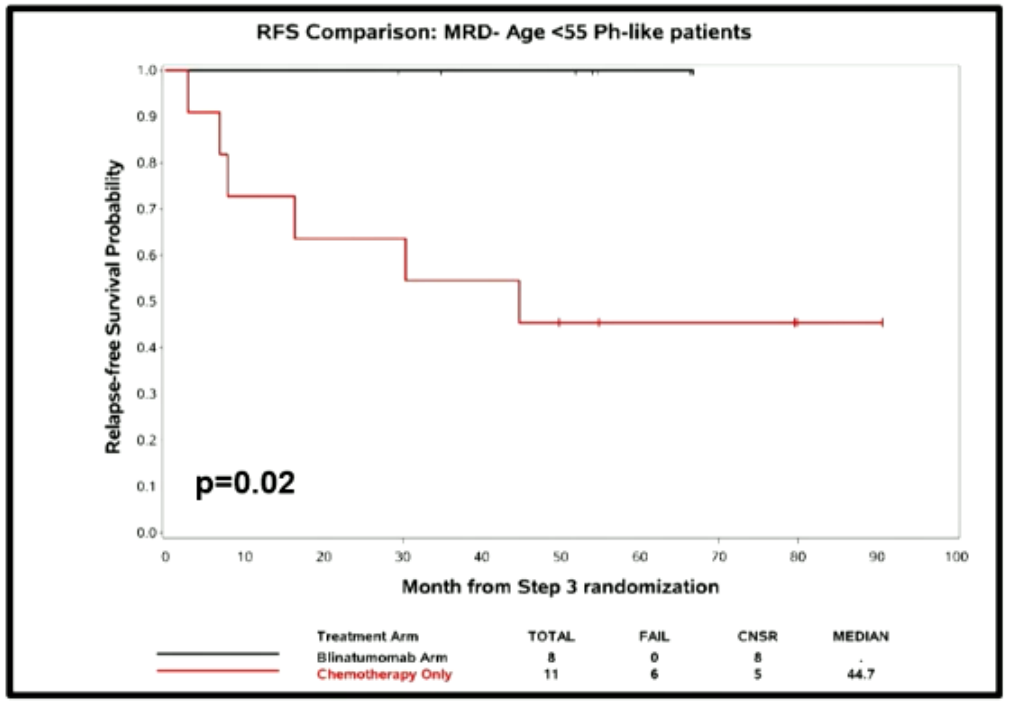
§1 pt not evaluable for fusion gene

Plus 3 refractory cases, 2 deaths, 1 lost, *3 in follow-up (2 with fusions)*

Cardinali et al, ASH 2022

ECOG E1910; Subanalysis on Ph-like ALL



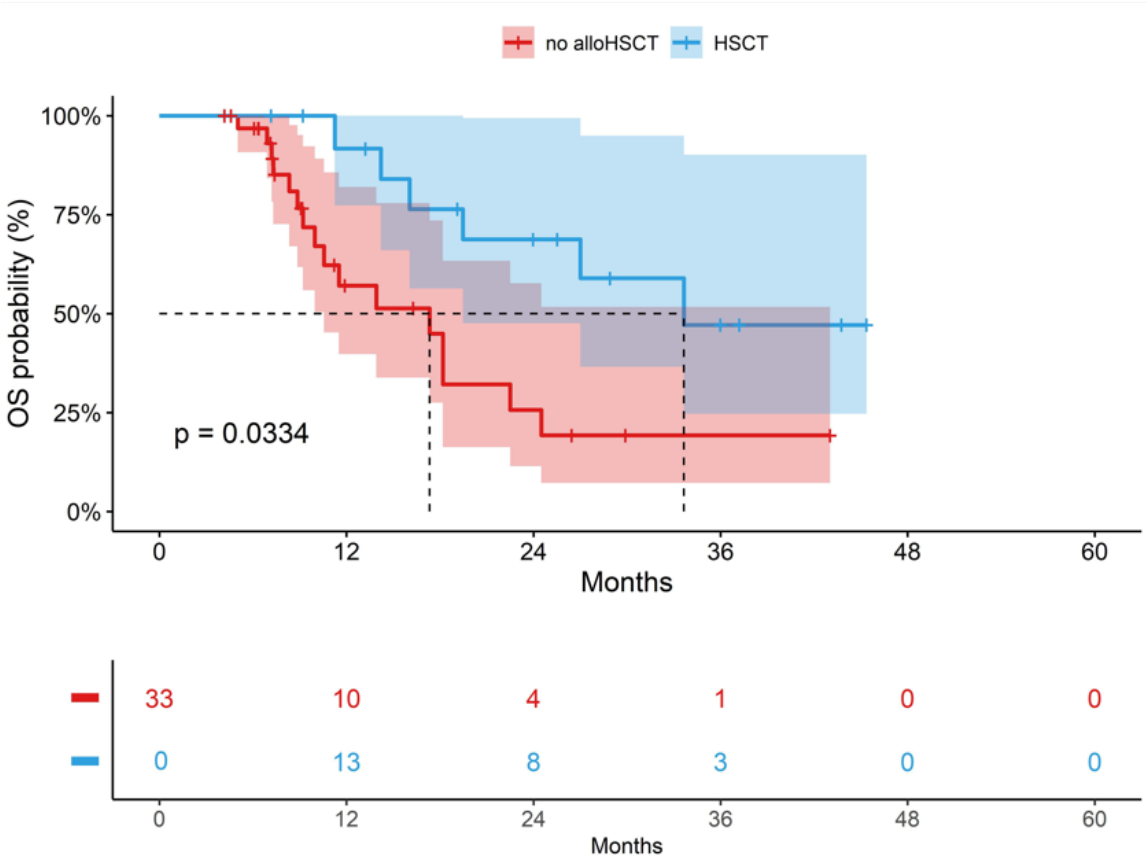


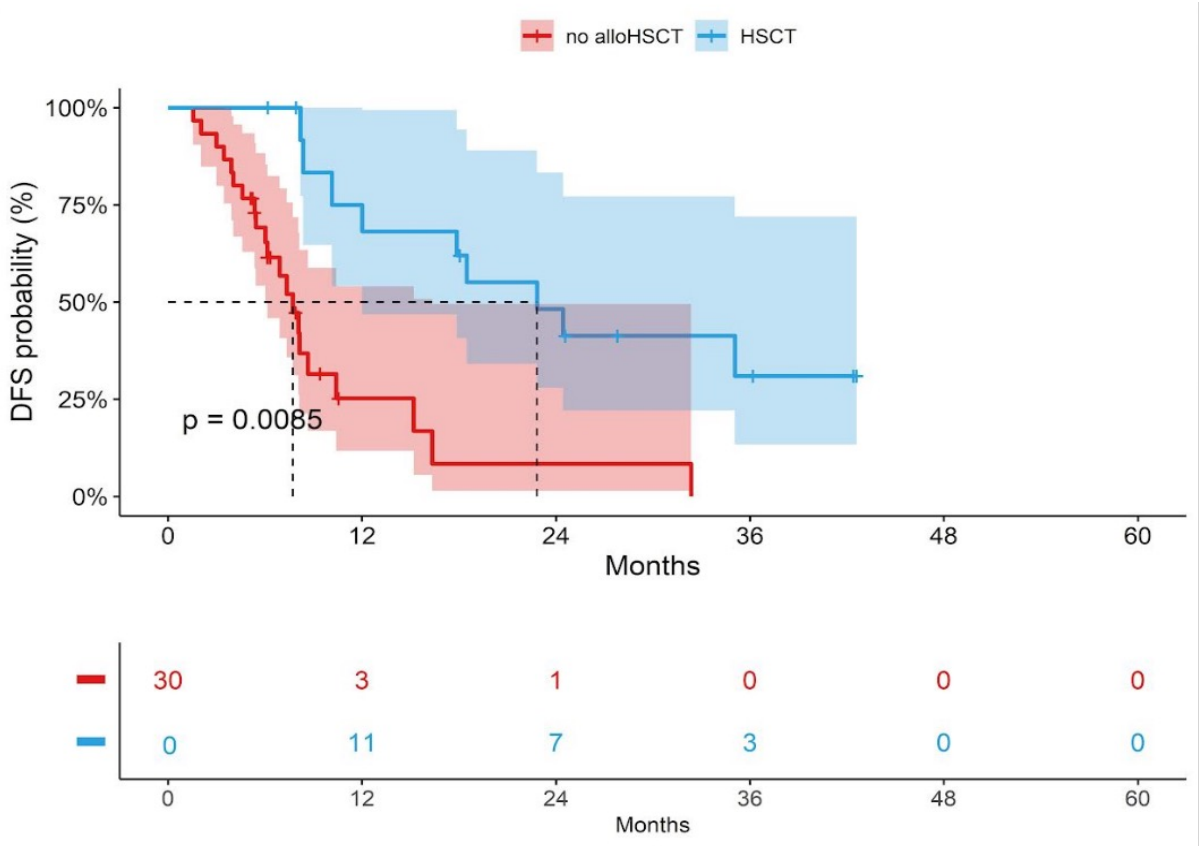
	3 Year Overall Survival
Blinatumomab	100%
Chemotherapy	45%

	3 Year Relapse Free Survival
Blinatumomab	100%
Chemotherapy	45%

Roughly 40% of patients received allo-SCT

Role of allo-sct in Ph-like ALL patients enrolled in GIMEMA trials





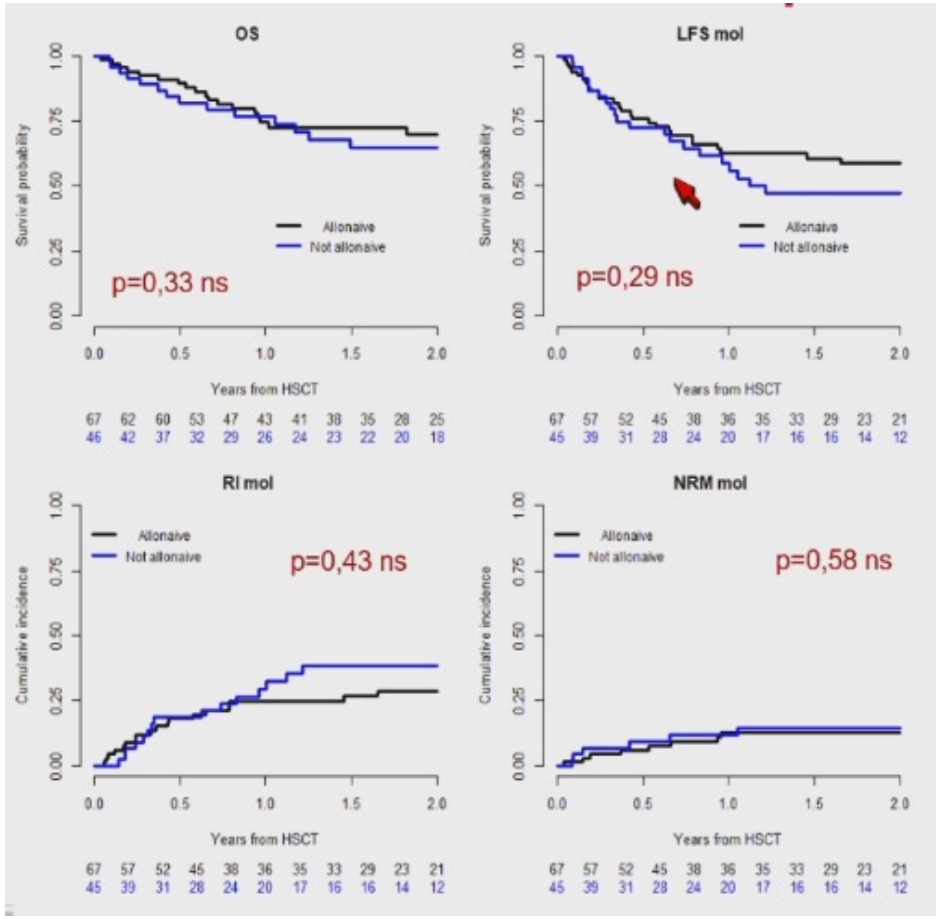
Lussana F, et al; under revision

What about other strategies?

- CAR-T
- Surovatamig

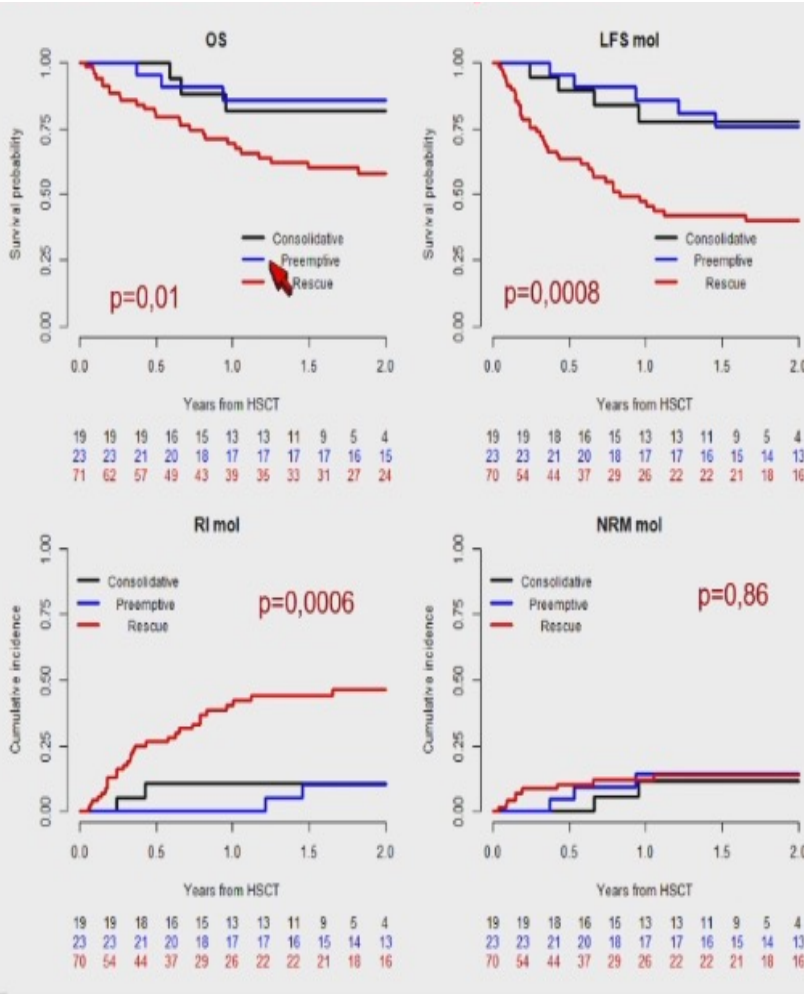
Role of prior and subsequent transplant: GoCART

Prior transplant



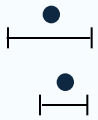
Consecutive transplant

		Consolidative (N=19)	Preemptive (N=23)	Rescue (N=71)
Age at this HSCT	median [IQR]	13 [8.3-23.3]	13.6 [8.4-17]	15.9 [8.4-23.2]
Age at this HSCT	Adult	7 (36.8)	5 (21.7)	26 (36.6)
	Child	12 (63.2)	18 (78.3)	45 (63.4)
Allo HSCT before CART	No	17 (89.5)	17 (73.9)	33 (46.5)
	Yes	2 (10.5)	6 (26.1)	38 (53.5)
CART1	Kymriah	15 (78.9)	15 (65.2)	50 (70.4)
	ARI-0001	0 (0)	6 (26.1)	15 (21.1)
	BREYANZI	0 (0)	1 (4.3)	2 (2.8)
	Sheba CART	2 (10.5)	0 (0)	2 (2.8)
	Tecartus	2 (10.5)	1 (4.3)	1 (1.4)
	Tuebingen CART	0 (0)	0 (0)	1 (1.4)
Months first CART to HSCT	median [IQR]	3.5 [2.7-4.2]	4.4 [3.3-5.7]	9.7 [5.8-17.5]
Response after CART1	CR MRD neg	19 (100)	23 (100)	59 (84.3)
	CR MRD pos	0 (0)	0 (0)	8 (11.4)
	No CR	0 (0)	0 (0)	3 (4.3)
	missing	0	0	1
Myeloablative regimen	No	1 (5.3)	4 (18.2)	17 (25)
	Yes	18 (94.7)	18 (81.8)	51 (75)
	missing	0	1	3
TBI in conditioning regimen	No	1 (5.3)	9 (40.9)	32 (46.4)
	Yes	18 (94.7)	13 (59.1)	37 (53.6)
	missing	0	1	2



Ottaviano G, et al. Abs 112. ASH 2024

Role of prior and subsequent transplant: CIBMTR

			Univariable analysis	Multivariable analysis[b]	
Outcome	Subgroups (n)	n Evaluable[c]	6-month rate, % (95% CI)	HR (95% CI)	
DOR*	**Post alloSCT** No (n=164) Yes (n=76)	 128 62	 55 (42-66) 85 (71-92)		 Reference 0.22 (0.10-0.49)
RFS*	**Post alloSCT** No (n=164) Yes (n=76)	 164 76	 47 (37-56) 67 (55-77)		 Reference 0.62 (0.40-0.96)
	MRD status prior to LD chemotherapy CR/CRi, MRD negative CR/CRi, MRD positive Not in CR/CRi	 59 16 148	 67 (52-78) 49 (19-74) 47 (38-55)		 Reference 1.44 (0.60-3.45) 2.08 (1.25-3.45)
	Ongoing infection at infusion No (n=220) Yes (n=22)	 220 22	 58 (50-65) 27 (8-50)		 Reference 1.80 (1.02-3.19)
OS	**ECOG PS** ECOG PS <2 (n=200 ECOG PS ≥2 (n=17)	 200 17	 80 (74-85) 63 (36-82)		 Reference 2.05 (1.00-4.21)
	Ongoing infection at infusion No (n=220) Yes (n=22)	 220 22	 82 (76-87) 53 (30-71)		 Reference 2.67 (1.40-5.10)

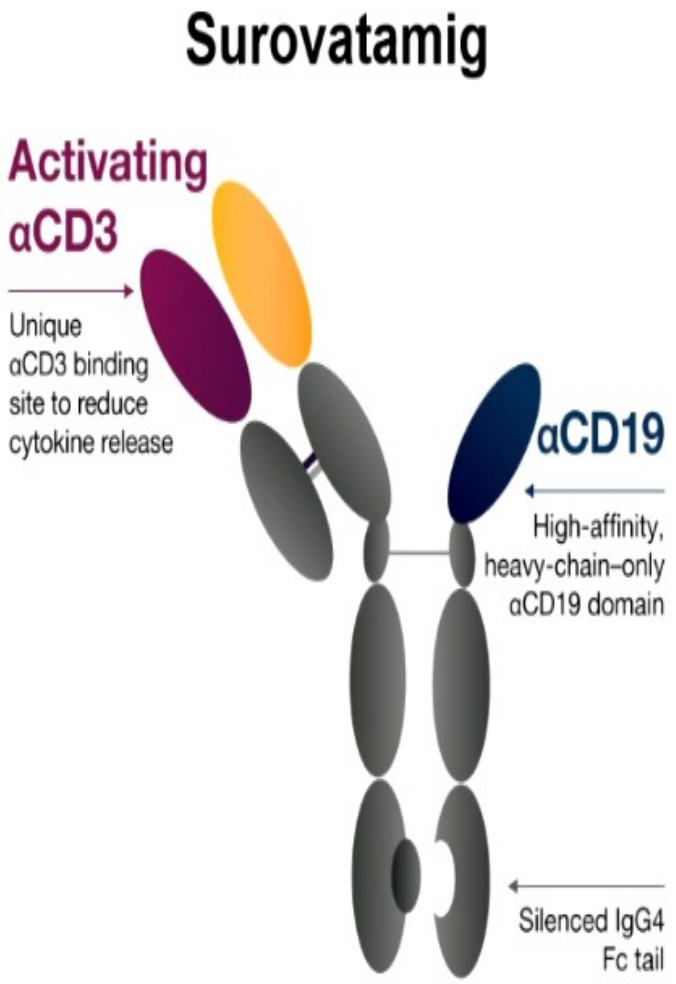
Apparently mild impact of post allo-SCT

Wudhikarn *et al.* ASH 2024 (Abstract 5092; poster/oral presentation)

Safety and Efficacy of AZD0486 in Adolescent and Adult Patients With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia: Early Results From the Phase 1/2 SYRUS Study

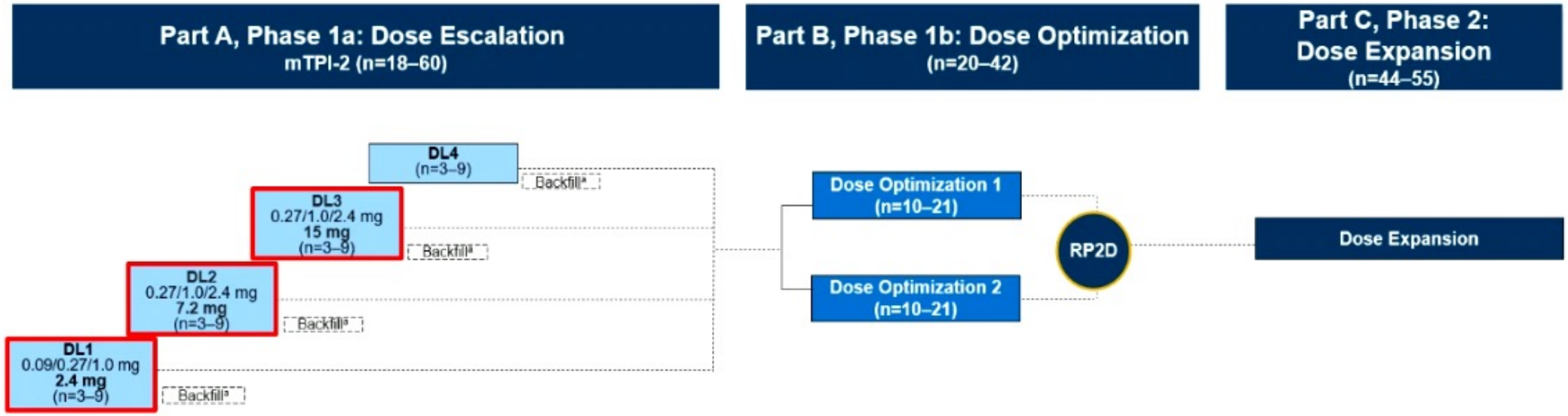
Ibrahim Aldoss, MD,[1] Jae-Ho Yoon, MD,[2] Pere Barba, MD, PhD,[3] Laura Torres Miñana, MD,[4] Depei Wu, MD,[5] Dong-Yeop Shin, MD, PhD,[6] Chieh-Lin Teng, MD, PhD,[7] Gautham Borthakur, MD,[8] Ming Yao, MD,[9] Cristina Papayannidis, MD, PhD,[10] Anna Castleton, MBBS, PhD,[11] Bijal Shah, MD, MS,[12] Shaun Fleming, MBBS, FRACP, FRCPA,[13] Makhdum Ahmed, MD, PhD,[14] Robin Lesley, PhD,[15] Yuyin Liu, PhD,[16] Damilola Olabode, PhD,[16] Margaret Wey, PhD,[14] Marcio Andrade-Campos, MD, PhD,[17] Nicola Gökbuget, MD,[18] Hagop Kantarjian, MD,[8] Max S. Topp, MD[19]

- Surovatamig, previously known as AZD0486, is a novel IgG4 fully human CD19×CD3 bispecific T-cell engager[1] designed for low-affinity CD3 binding to reduce cytokine release from T-cell activation while preserving T-cell cytotoxicity against malignant B cells
- A phase 1, FIH trial in patients with B-NHL (NCT04594642) demonstrated activity and tolerability of surovatamig in R/R FL and DLBCL[2,3]
- Here, we present the preliminary results from a dose-escalation study of surovatamig in patients with R/R B-ALL (SYRUS; NCT06137118)



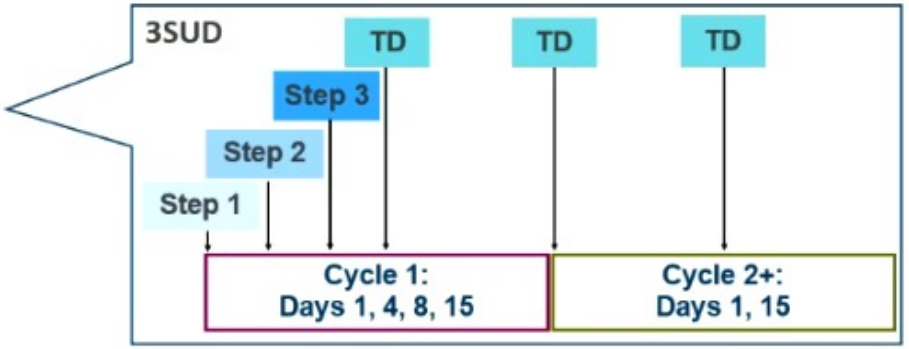
Aldoss,et al. EHA 2025

SYRUS: study design



Treatment Schedule – 28d cycles

- **Triple step-up dosing (3SUD):**
  Surovatamig (2h IV infusion) on first cycle: C1D1, C1D4, and C1D8
  - SUD1: 0.09 mg, 0.27 mg, and 1.0 mg – DL1
  - SUD2: 0.27 mg, 1.0 mg, and 2.4 mg – DL2 & DL3
- **Target doses (C1D15): DL1: 2.4 mg; DL2: 7.2 mg; DL3: 15 mg**
  - Cycles 2+: administered every 2 weeks (D1 and D15)
- Patients with high tumor burden (>50% BM blasts or >15,000/mL PB) received dexamethasone (10–24 mg/d) 4–7 days ± 1 dose of vincristine 2 mg prior to D1



[a]Backfill slots into the SRC-declared safe dose levels may open at SRC approval

BM, bone marrow; C, cycle; D, day; DL, dosing level; mTPI-2, modified Toxicity Probability Interval; IV, intravenous; PB, peripheral blasts; RP2D, recommended phase 2 dose; SRC, safety review committee; SUD, step-up dosing; TD, target dose

SYRUS: responses

Response, n/N (%)	DL1 (SUD: 0.09/0.27/1.0; TD: 2.4 mg) (n=13)	DL2 (SUD: 0.27/1.0/2.4; TD: 7.2 mg) (n=12)	DL3 (SUD: 0.27/1.0/2.4; TD: 15 mg) (n=6)
ORR EoC1 (CR/CRi) (ITT)	**6/13 (46)**	**7/12 (58)**	**5/6 (83)**
CR/CRi MRDneg (local flow [10^{-4}])	5/6 (83)	7/7 (100)	5/5 (100)
Disease relapse	2/6 (33)	0/7	0/5
ORR (CR/CRi) by prior therapy subgroup[a,b]			
Blinatumomab-exposed	4/9 (44)	1/4 (25)	3/3 (100)
CAR-T-exposed	1/3 (33)	2/3 (67)	4/5 (80)
Double-exposed	1/3 (33)	1/2 (50)	3/3 (100)
Triple-exposed (+Inotuzumab)	0/2 (0)	1/2 (50)	3/3 (100)
ORR (CR/CRi) (in patients with EMD)[a]	**2/3 (67)**	**2/2 (100)**	**0/0**

Adverse Events, N=31, n (%)	G3	G4	G5
Non-Hematologic			
Infection	6 (19)[a]	1 (3)[b]	3 (10)[c]
Febrile neutropenia	6 (19)	-	-
ALT/AST increased	2 (6)	-	-
Hematologic			
Neutropenia	3 (10)	7 (23)	-
Lymphopenia	2 (6)	4 (13)	-
Thrombocytopenia	2 (6)	5 (16)	-
Anemia	2 (6)	-	-

- 2 patients experienced DLTs:
  - Both had prolonged cytopenia in the context of MLFS; 1 also had grade 3 AST increased with concomitant use of posaconazole
  - Both continue to receive the target dose without significant cytopenia
- AEs leading to treatment discontinuation were reported in 4 (13%) patients and were deemed unrelated to surovatamig

Dash (-) indicates no patients with an event
[a]Sepsis, COVID-19, corynebacterium infection, hepatitis candidiasis, herpes zoster disseminated, oral herpes, pneumocystis jirovecii pneumonia, pneumonia, systemic candida (n=1 each). [b]Sepsis (n=1). [c]Sepsis, septic shock, and COVI (n=1 each). AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; G, grade; MLFS, morphologic leukemia-free state

	During SUD		After TD		
IR-AEs, n (%)	During SUD1 n=13	During SUD2 n=18	After 2.4 mg n=10	After 7.2 mg n=12	After 15 mg n=6
CRS Any	4 (31)	13 (72)	3 (30)	3 (25)	-
CRS G2	2 (15)	5 (28)	1 (11)	1 (8)	-
CRS G3	-	**1 (6)**	-	-	-

- No G4+ CRS events were reported

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Conclusions

- In Ph+ ALL, in the optimal situation of drug availability, allo-SCT can be spared to most , but NOT all, patients

- In Ph-like ALL, patients should still be allografted at earliest convenience, after POSSIBLY a chemo-targeted-immunotherapy

- Nevertheless, in Ph-like ALL it must be kept in mind that several subsets do exist, and might require different intensification strategies

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