Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA

HEMATOLOGÍA EN 48H [LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

ACTUALÍZATE 48 HORAS

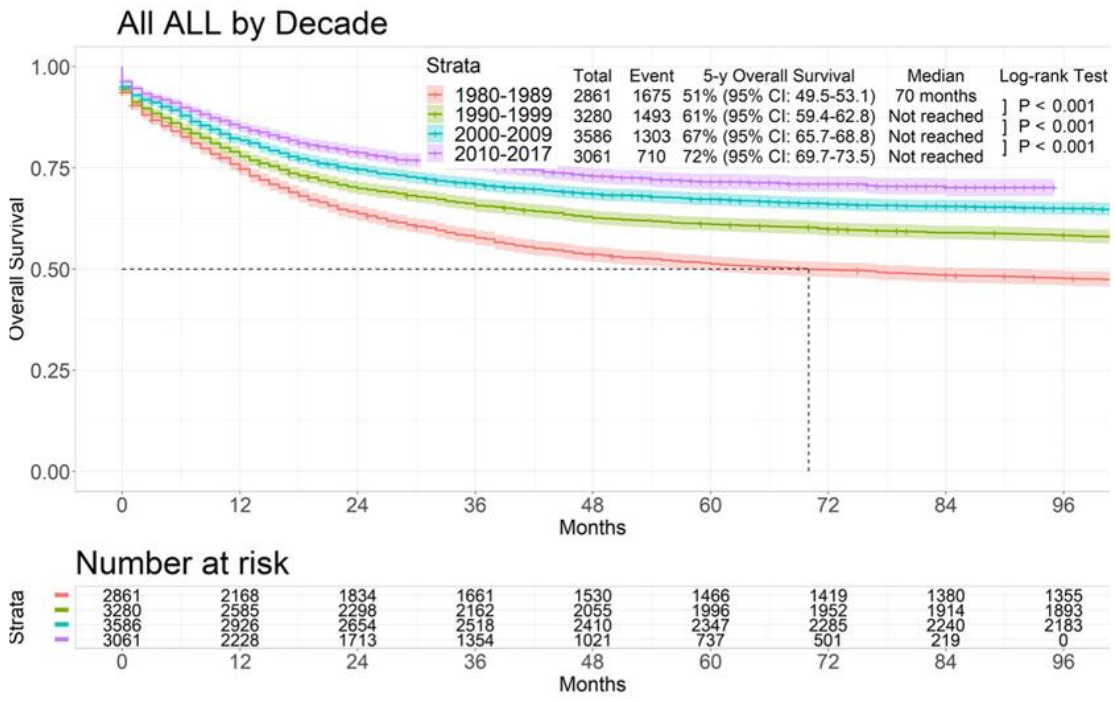
Avances en el Tratamiento de la LLA: De la quimioterapia hacia la Inmunoterapia

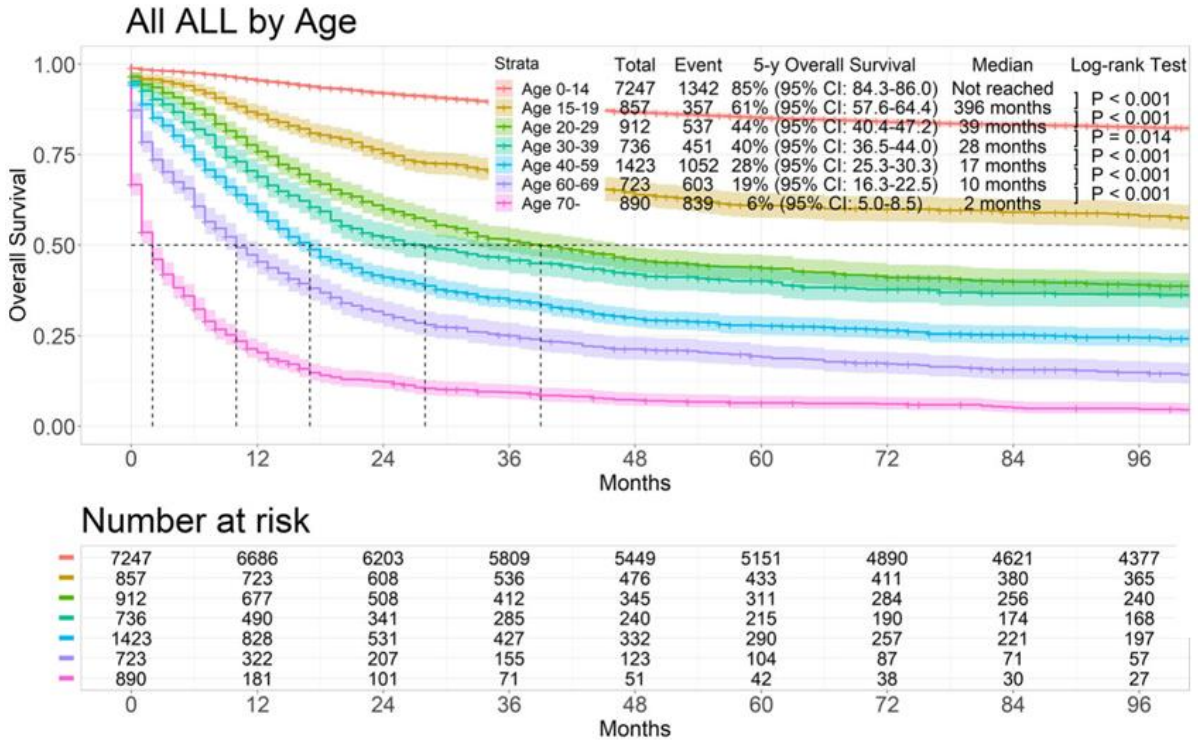
Anna Torrent

ICO Badalona – Hospital Germans Trias i Pujol

Historical survival of patients with ALL

Improved survival of patients with ALL the last 40 years
Limited for patients older than 60 years old

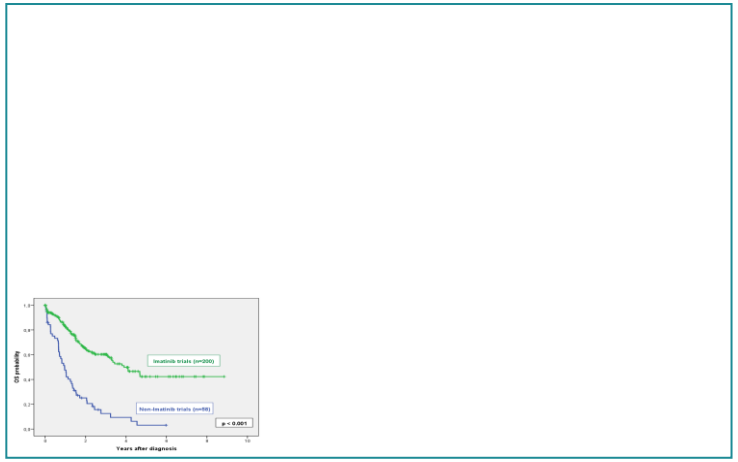




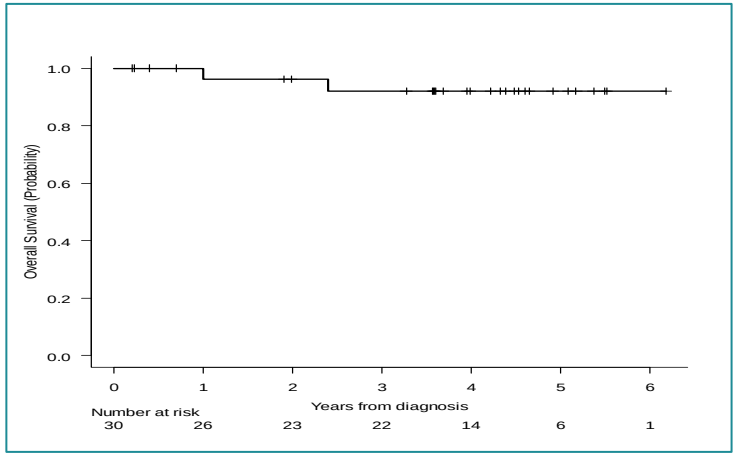
Sasaki K, et al. J Hematol. 2021 Oct 1;96(10):1344.

PETHEMA historical survival overview

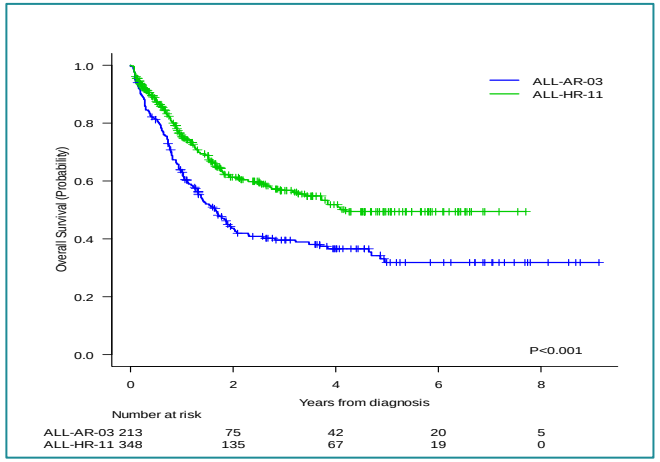
Ph-positive ALL. Imatinib[1]



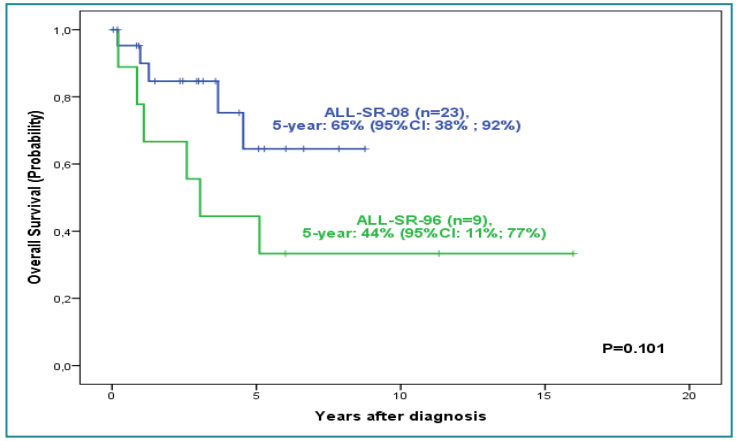
Ph-positive ALL. Ponatinib[2]



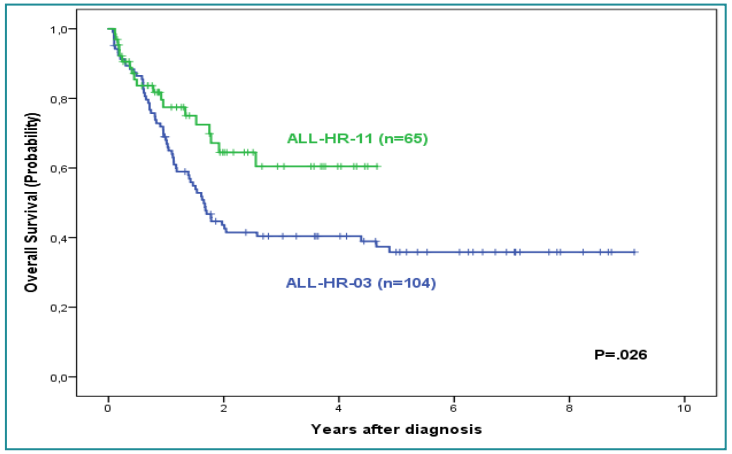
Ph-negative ALL. MRD-oriented[3]



AYA: pediatric trial[4]



T-ALL. Refining CHT[5]



Mature B-ALL. Rituximab[6]

[1]Ribera JM et al Haematologica. 2010; 95. 87-95; [2]Ribera JM et al Hemasphere 2024;8(4):e67; [3]Ribera JM et al Blood. 2021;137:1879-1894;
[4]Ribera JM et al Cancer Med 2020;9:2317-2329; [5]Barba P et al Hemasphere. 2022;7(1):e810; [6]Ribera JM et al Haematologica 2024;109:543-552.

How have we improved these outcomes?

- Better knowledge of the disease: biology, risk factors, genomic classification.
- Technological advances in MRD quantification (MRD by NGF, qPCR, NGS).
- Better therapeutic strategies:
  - Pediatric-based protocols for adult: PEG-ASP.
  - Novel immunotherapy.
  - CAR T-cell.
  - Targeted therapy: 3rd Generation TKI, menin inhibitors…
- Improvement of HSCT (the procedure and supportive care)

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Ph-positive ALL

Where do we come from?

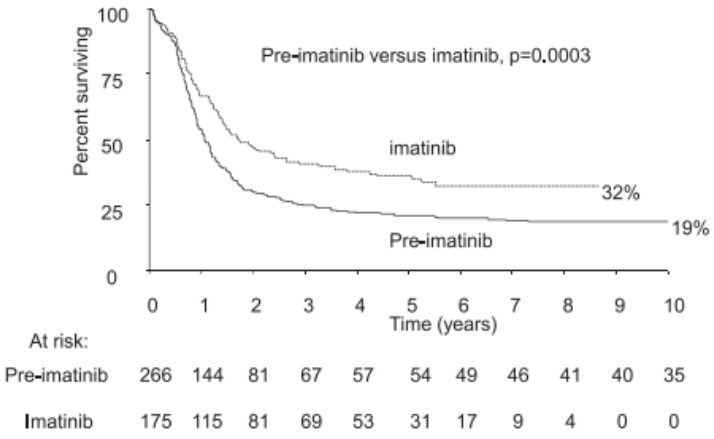
Where we are?

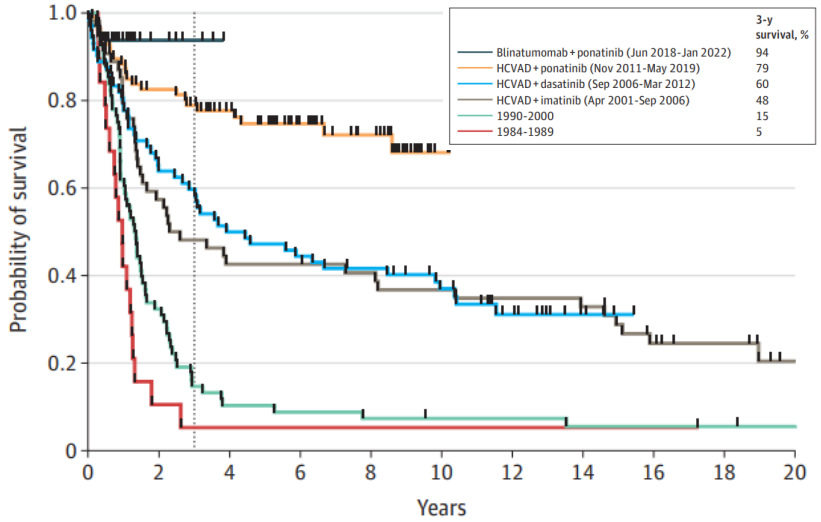
Where we are going?
(where we want to go)

Chemotherapy
(high doses + HSCT)

CR rate <50%
Cure rate <20%
High ED (toxicity)
HSCT only cure

- Ph+ ALL is the most freqüent ALL subtype in adult (>50% of ALL in patients ≥60 years).
- The addition of TKI to chemotherapy has improved outcomes.
- The introduction of MoAb improved outcomes in R/R B-cell ALL





Fielding AK, Am Soc Clin Oncol Educ Book 2015;35:e352-e359 // Secker-Walker LM, et al. Leukemia 1991;5:196-199 // Burmeister T, et al. Blood 2008;112:918-919 // Moorman AV, et al. Blood 2010;115:206-2014 // Jabbour E, et al. JAMA Oncol 2022 – Short NJ, et al. Leukemia 2021 – Kantarjian H, et al. N Engl J Med. 2017 – Kantarjian HM, et al. N Engl J Med 2016 – Martinelli G, et al. Eur J Cancer 2021 – Stock W, et al. Cancer 2021,

Ph-positive ALL

Where do we come from?

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Where we are?

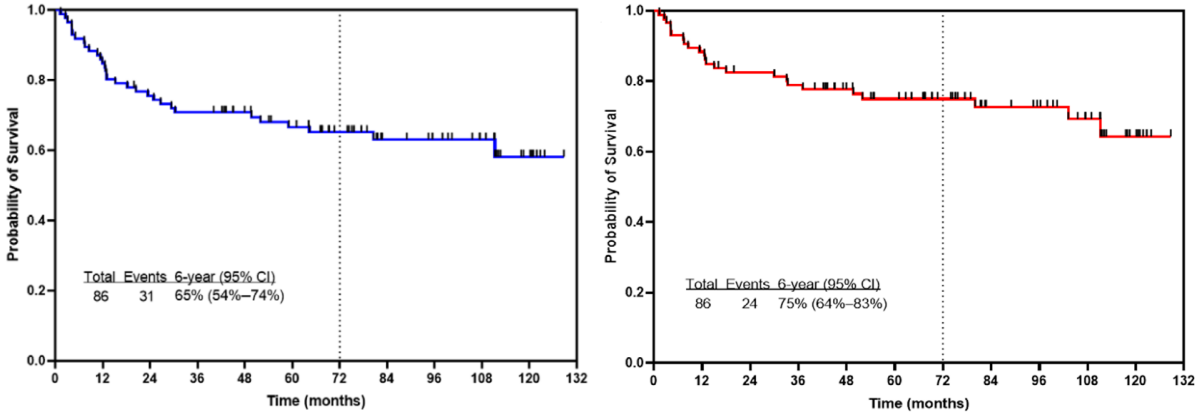
PED-based therapies
Immunotherapy r/r, 1L
2/3G TKI
CAR T-cell

Where we are going?
(where we want to go)

Ph positive ALL: High-dose chemotherapy + 3G TKI + HSCT

Ponatinib 45 mg (C1) + Hyper-CVAD
Long term F/U >6y

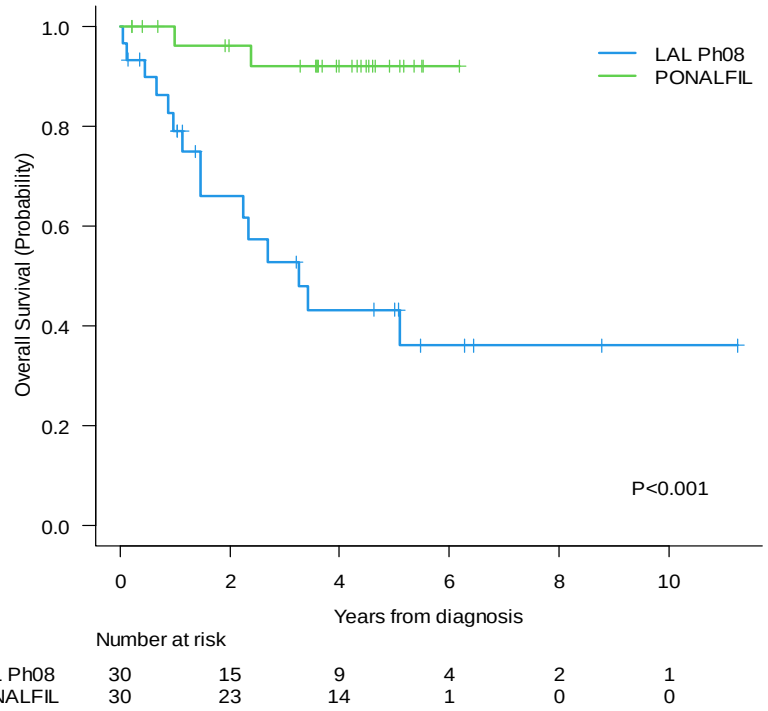
N=86 p, median age 47y (39-61 y); median FU 80 months (6.12-109)
CR 68/68 (100%); FCM-MRD negative 85/86 (99%)
CMR 84%; **6y OS 75%, EFS 65%,** 20 p (23%) HSCT



Kantarjian H, et al. Am J Hematol. 2023 Mar;98(3):493-501.

Ponatinib + Chemotherapy + alloHSCT
PONALFIL TRIAL (PETHEMA)

Median Follow-Up 4 years

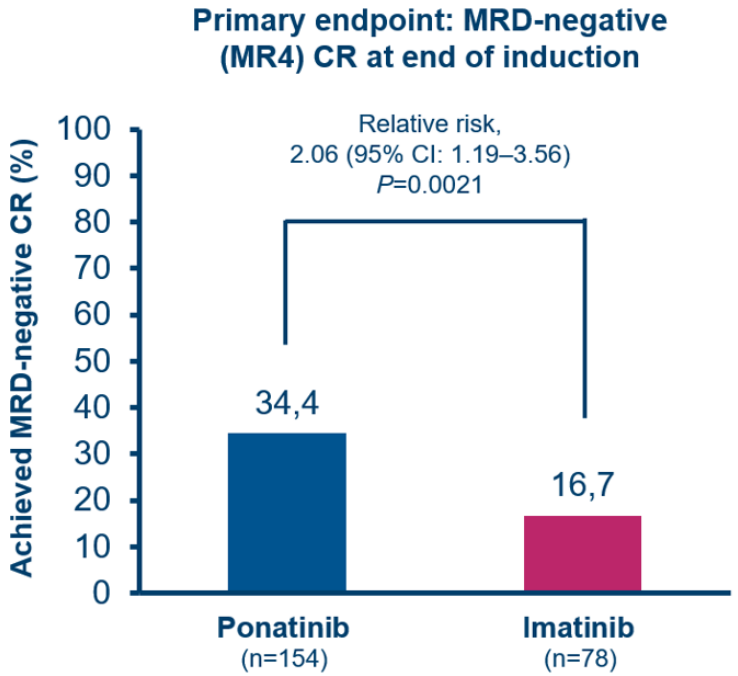


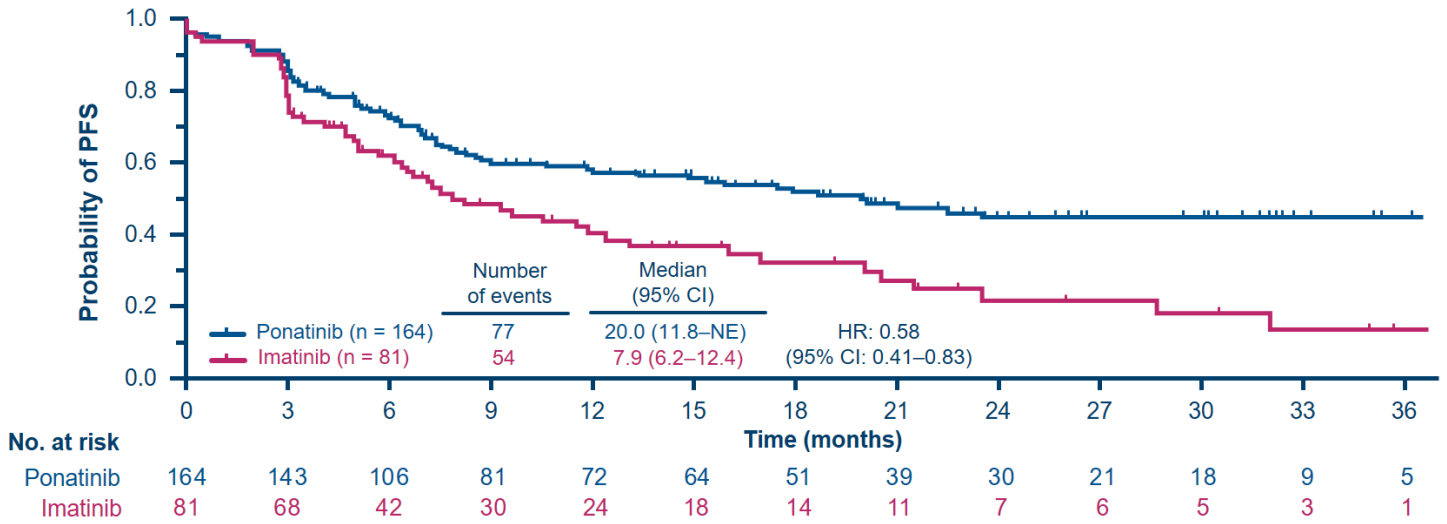
Ribera JM, et al. Blood Adv. 2022 Sep 27;6(18):5395-5402.

Ph positive ALL: Best TKI front-line?

PhALLCON: phase 3 study LD-CHT + **imatinib vs ponatinib** first line therapy

- N= 245 p randomized (2:1) to ponatinib 30 mg/d (n=164) or imatinib (n=81) → median age 54y (19-82y) → **37,1% ≥65 years**
- **Primary endpoint MR4 CR at 90 days: 34,4% vs 16,7% (P=0,002)**

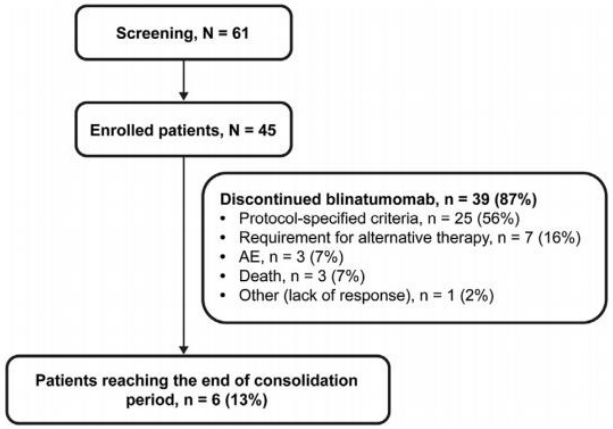




Jabbour E, et al. JAMA 2024;331(21):1814-1823

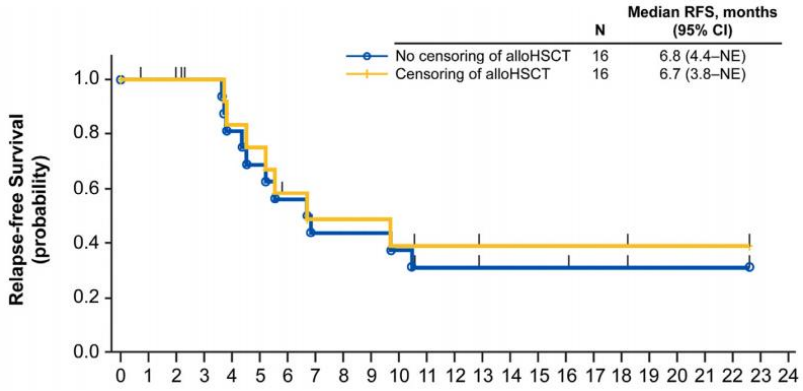
Ph positive ALL: Immunotherapy in R/R

Blinatumomab: Phase 2, single-arm, multicenter **ALCANTARA study**



Outcome	Pts (n/N1)
1ry EP: CR/CRh (two cycles)	16/45 (36%)
- Ph + ACA	10/22 (45%)
- T315I mutation	4/10 (40%)
- No. Prior TKI >2	8/17 (47%)
- Prior Ponatinib	8/23 (35%)
- Prior AlloHSCT	5/20 (25%)
2ry EP: Complete MRD resp	14/16 (88%)
AlloHSCT after Blin	4/16 (25%)

1ry EP: CR/CRh first 2 cycles of blinatumomab

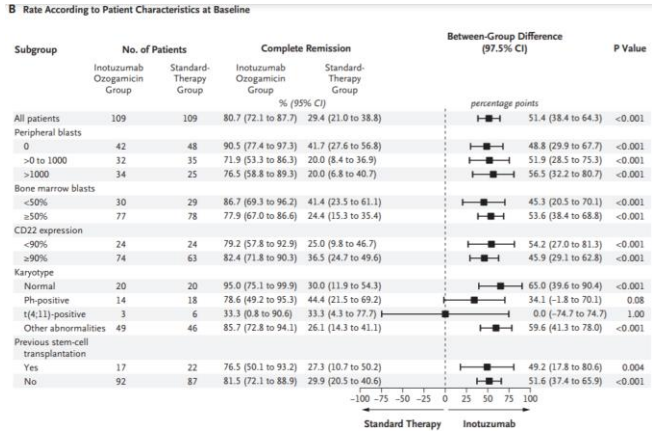


RFS 6.8 m

OS 9 months

OS in RC 23 m

Inotuzumab: Phase 3, randomized, multicenter **INO-VATE study**

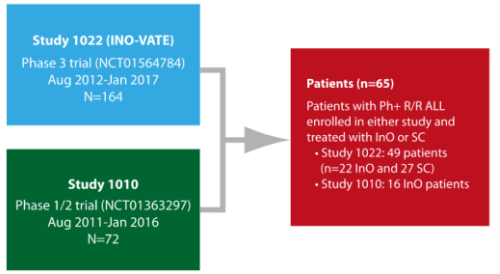


Better CR/CRi in InO vs SCO for all **baseline** characteristics

EXCEPT

Ph-positive

t(4;11)-positive



Inotuzumab is effective in patients with R/R Ph+ ALL, but **overall outcomes were inferior** compared to patients with Ph− ALL

TABLE 1. Efficacy Endpoints

	Study 1022			Study 1010
Efficacy Endpoints	InO (n = 22)	SC (n = 27)	*P*	InO (n = 16)
CR/CRi, n (% [95% CI])	16 (72.7 [49.8-89.3])	15 (55.6 [35.3-74.5])	.1075	9 (56.3 [29.9-80.3])
CR, n (% [95% CI])	10 (45.5 [24.4-67.8])	8 (29.6 [13.8-50.2])	.1265	4 (25.0)
CRi, n (% [95% CI])	6 (27.3 [10.7-50.2])	7 (25.9 [11.1-46.3])	.4577	5 (31.3)
MRD negativity, n (% [95% CI])[a]	13 (81.3 [54.4-96.0])	5 (33.3 [11.8-61.6])	.009	9 (100.0 [66.4-100.0])

Martinelli G, et al. Eur Jour Cancer 2021;146:107-114 - DeAngelo DJ, et al. Blood Adv 2017;1;1167-80 - Kantarijan HM, NEJM 2016;375:740-53 - Stock W, et al. Cancer 2021;127(6):905-913

Ph-positive ALL

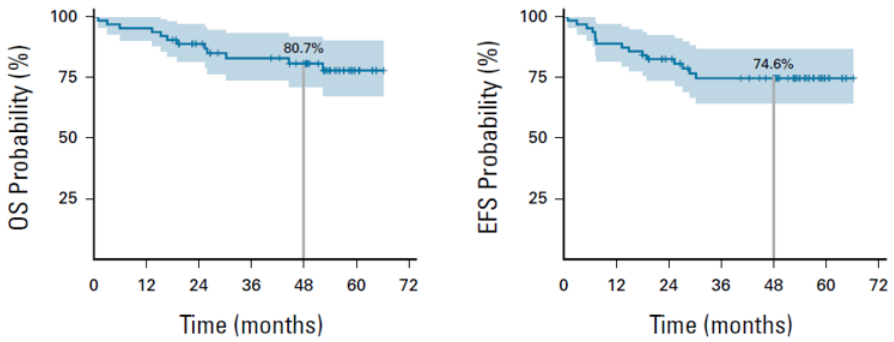
Where do we come from?	Where we are?	Where we are going? (where we want to go)
Chemotherapy (high doses + HSCT)	PED-based therapies Immunotherapy r/r, 1L 2/3G TKI CAR T-cell	
CR rate <50% Cure rate <20% High ED (toxicity) HSCT only cure	CR rate 90-100% HSCT (>MRD neg) Less ED / toxicity	

Ph-positive ALL

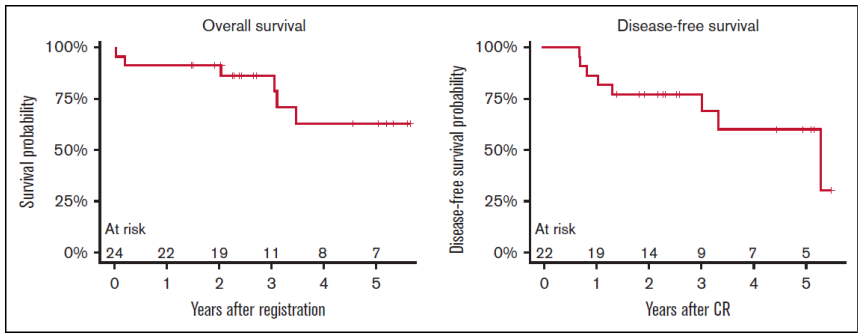
Where do we come from?	Where we are?	Where we are going? (where we want to go)
Chemotherapy (high doses + HSCT)	PED-based therapies Immunotherapy r/r, 1L 2/3G TKI CAR T-cell	Chemo-free strategies? Immunotherapy 1st line CAR T-cell vs HSCT? Less HSCT?
CR rate <50% Cure rate <20% High ED (toxicity) HSCT only cure	CR rate 90-100% HSCT (>MRD neg) Less ED / toxicity	

Ph positive ALL: Immunotherapy-based strategies

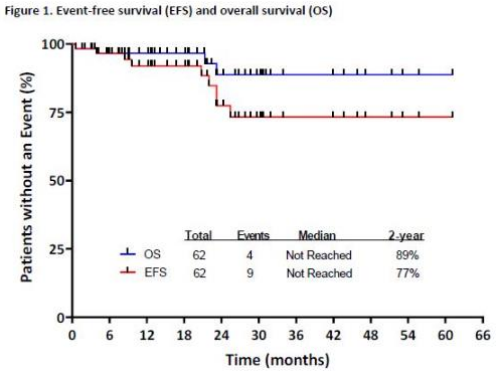
Parameter	MDACC Pona + Blina (n=62; 5 blina)	D-ALBA Dasa + Blina (n=63; 2 + blina)	SWOG 1318 Dasa + Blina (n=24; 3 blina)
Median age (yrs)	58 (38-72)	54 (24-82)	73 (65-87)
% PCR neg	84	93	63
% 4y OS	89	82	75
% allo SCT	3	48	5
Relapses (CNS)	7 (4)	9 (4)	8 [3 T315I]



Jabbour E, et al. Lancet Hematol 2023;10:e24-34
Haddad FG, et al. ASH 2023 #2827



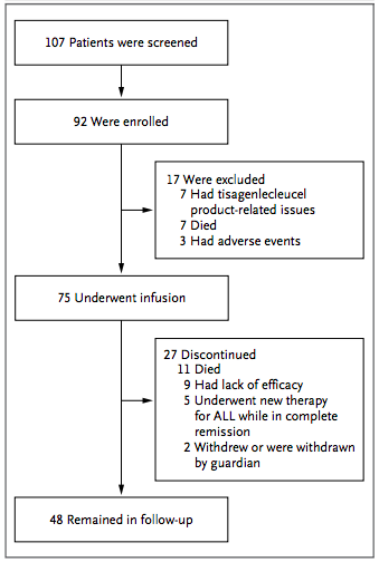
Foà R, et al. N Engl J Med 2022;383:1613 // Foà R, et al. J Clin Oncol 2023;00:1-5



Advani AS, et al. Blood adv 2023;7:1279

Ph positive ALL: CAR T-cell

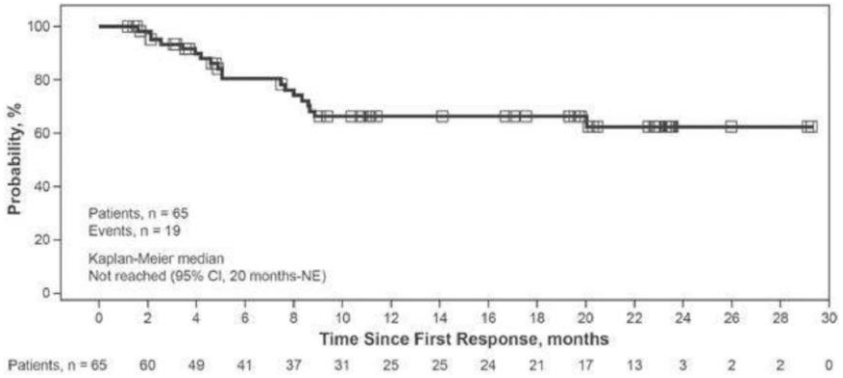
ELIANA: Phase 2, Tisagenlecleucel (Tisa-cel) for R/R B-ALL ped/AYA



Ph-positive ALL included:

- Intolerant TKI, 2 failed lines of TKI or contraindicated TKI therapy
- Ineligible for alloSCT

Some patients enrolled but **no subgroup analysis is available**.



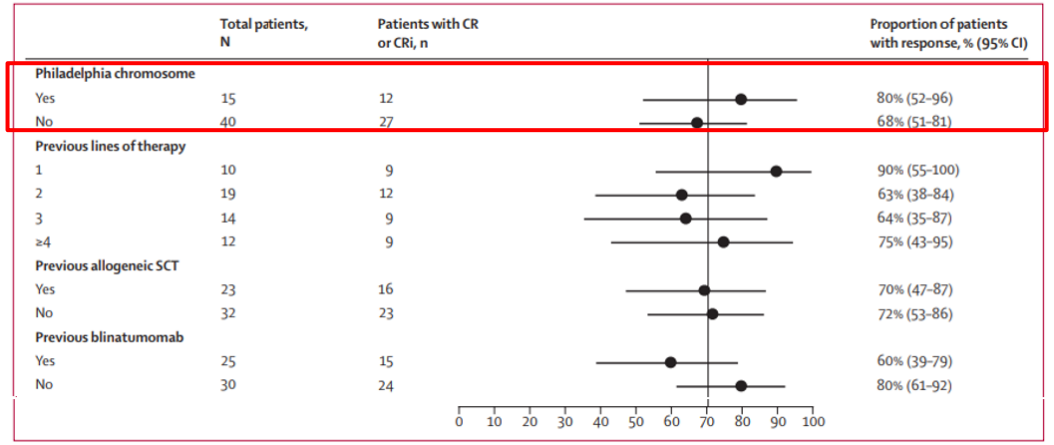
ZUMA-3: Phase 2, BREXU-CEL (TECARTUS)

N=15 (27%) Ph+ ALL treated

RFS-6m 58% (95% CI 43–70)
OS-12 m 71% (57–82),
largely consistent among subgroups.

No specific analysis for Ph+ ALL patients

	Treated patients (n=55)
Overall complete remission or complete remission with incomplete haematological recovery	39 (71%)*
Complete remission	31 (56%)
Complete remission with incomplete haematological recovery	8 (15%)
Blast-free hypoplastic or aplastic bone marrow	4 (7%)
No response	9 (16%)
Unknown or not evaluable†	3 (5%)

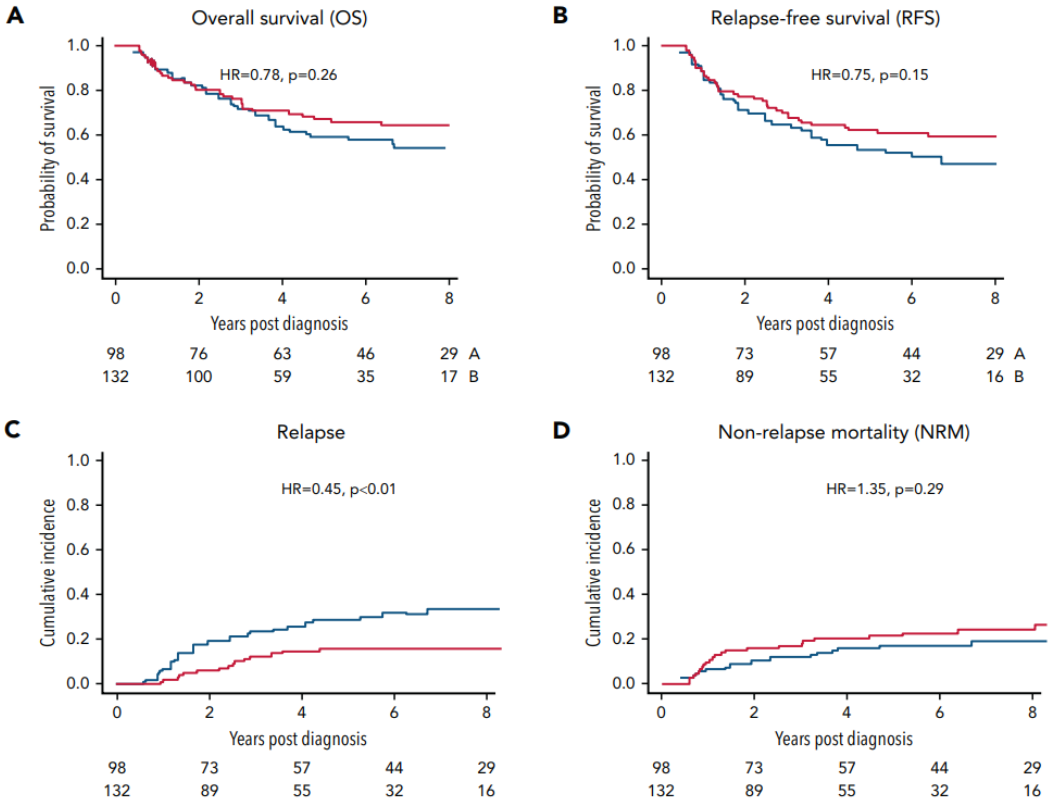


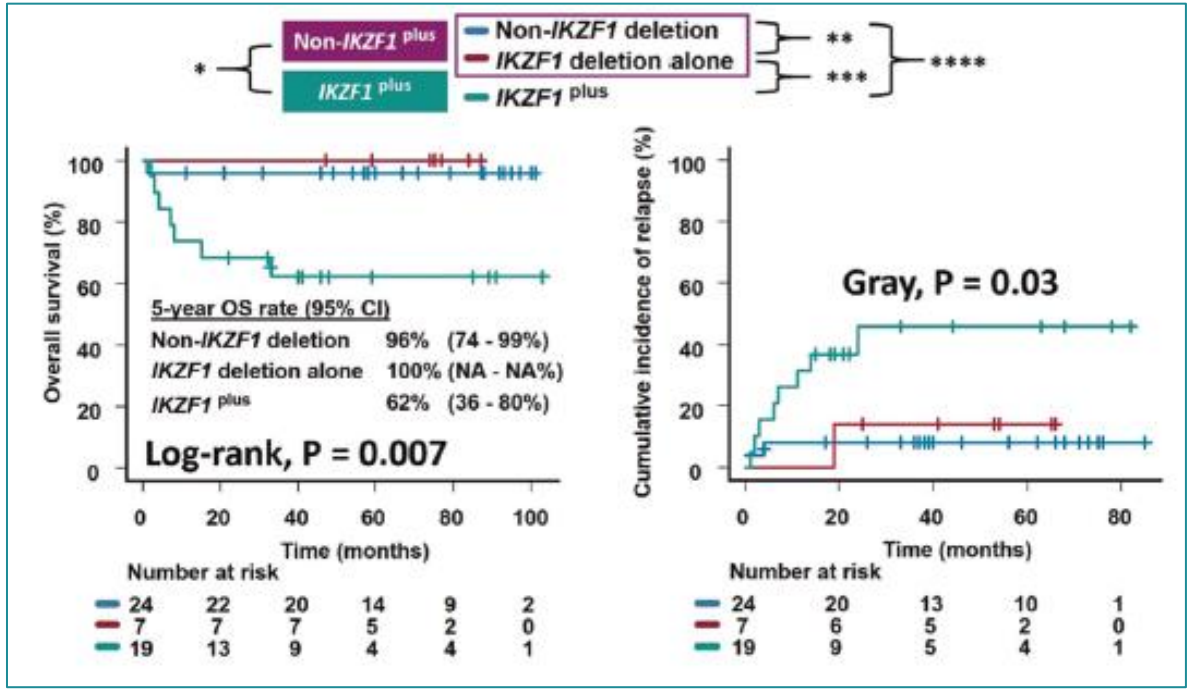
Stephan A. Grupp et al. BBMT 2019, S126-S127 // SL Maude. N Engl J Med 2018;378:439-48 // Shah. Lancet. 2021;398:491 // Shah. EHA 2021. Abstr S117

Ph positive ALL: Role of HSCT

No benefit of alloHSCT in Ph+ ALL patients with **CR1 CMR at 3 months**

Disease status at HSCT and the **genetic background** (IKZF1^{plus}) of ph-positive ALL, are both risk factors for relapse and may benefit of HSCT

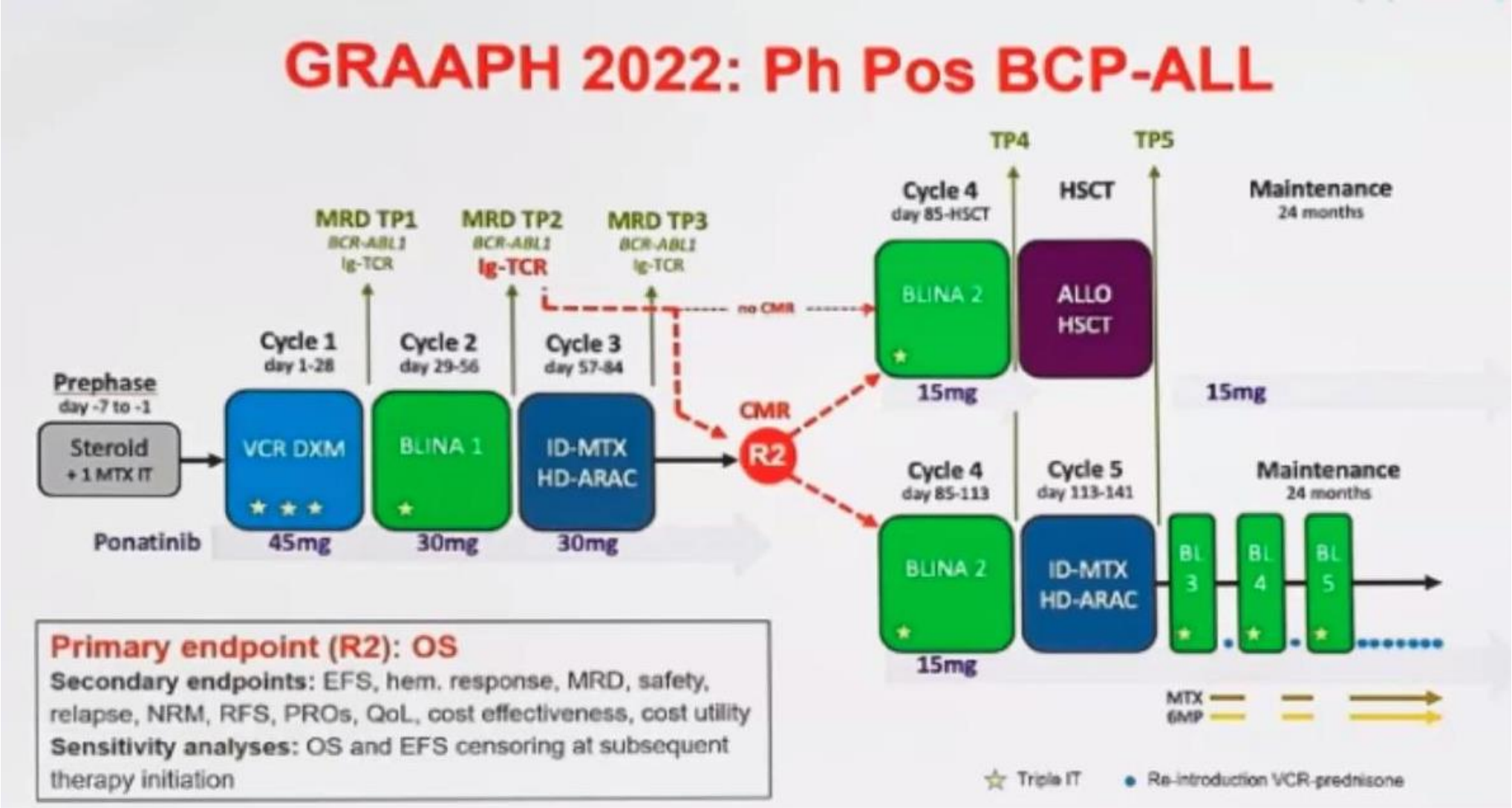




Ghobadi A, et al. Blood 2022;140:2101-2112

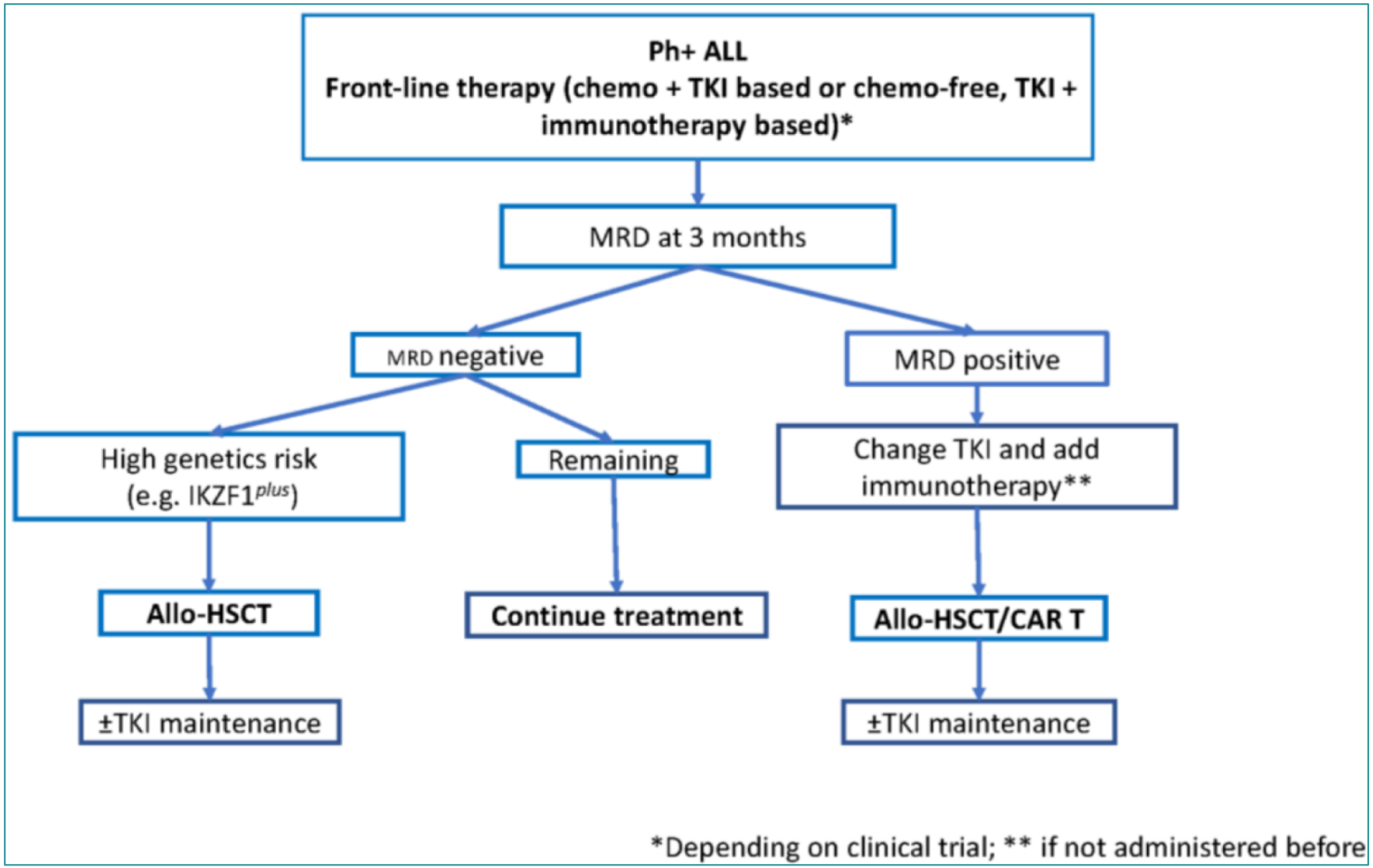
Foà R, et al. N Engl J Med 2022

Ph positive ALL: Role of HSCT



Courtesy of N Boissel

Ph positive ALL: treatment approach



Ribera JM et al. Cancers 2022;14:4554

Ph-negative ALL

Where do we come from?

Where we are?

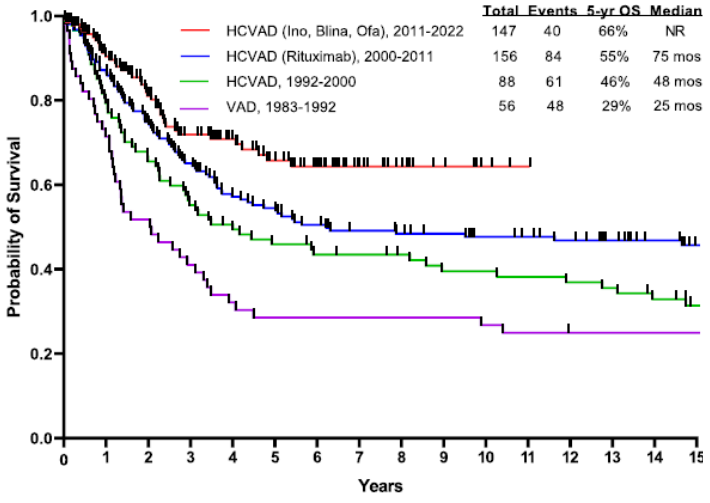
Where we are going?
(where we want to go)

Chemotherapy
(high doses + HSCT)

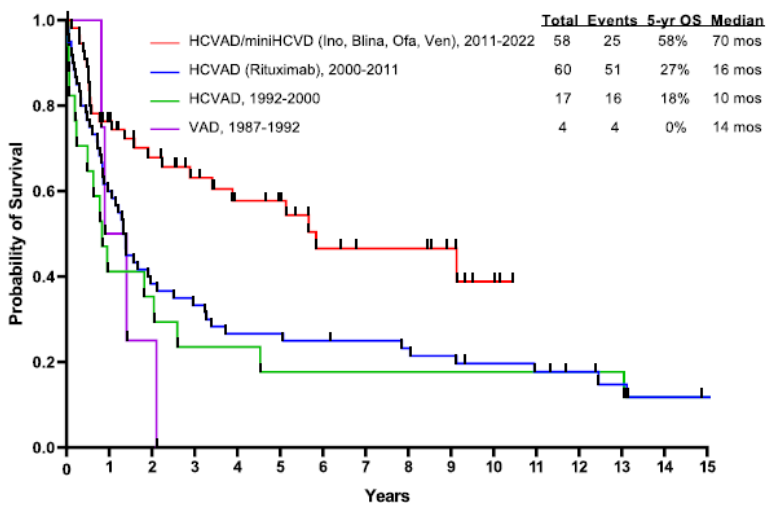
CR rate >90%
Cure rate 40% (18-60y),
<20% >60y
High ED (toxicity)
Many patients did not
receive therapy/HSCT

- OS adults Ph- ALL: 40–50%; older adult ≤20%
- Better understanding of the B-ALL biology → better stratification.
- The introduction of MoAb and CAR T-cell have improved outcomes in R/R Ph-negative B-cell ALL

Ph-negative ALL <60 years



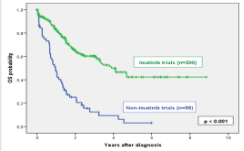
Ph-negative ALL ≥60 years



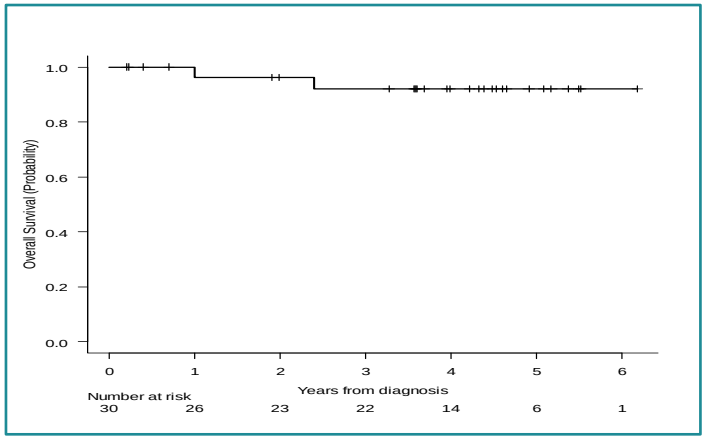
Jabbour E, et al. JAMA Oncol 2022 – Short NJ, et al. Leukemia 2021 – Kantarjian H, et al. N Engl J Med. 2017 – Kantarjian HM, et al. N Engl J Med 2016 – Shah BD, et al. Lancet. 2021 Aug 7;398(10299):491-502 // Maude et al. N Engl J Med. 2018 Feb 1;378(5):439-448.

PETHEMA survival overview: the importance of having a target

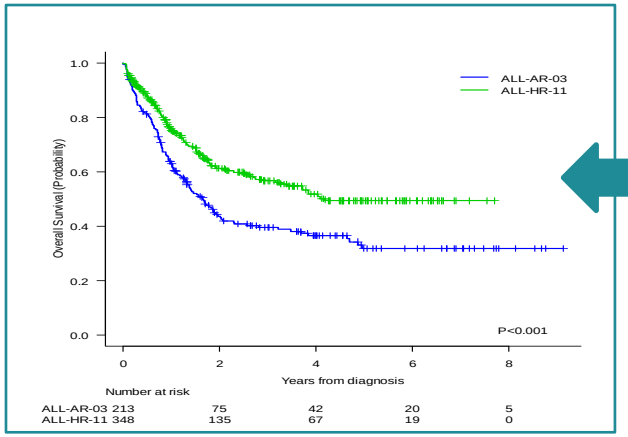
Ph-positive ALL. Imatinib[1]

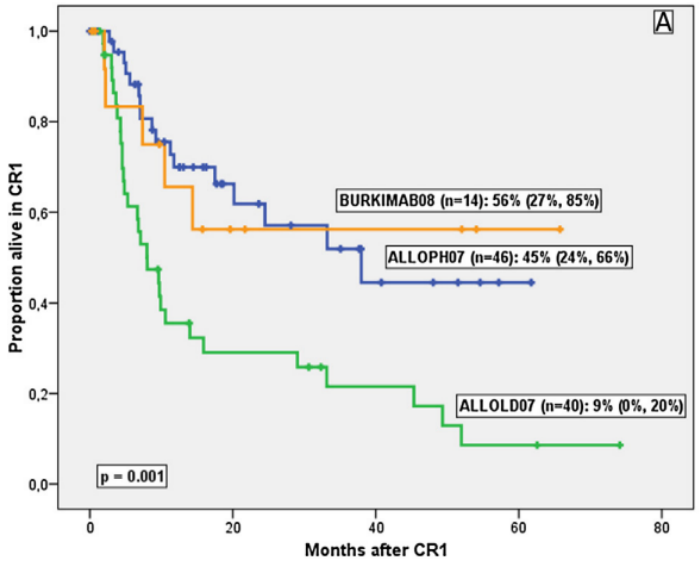


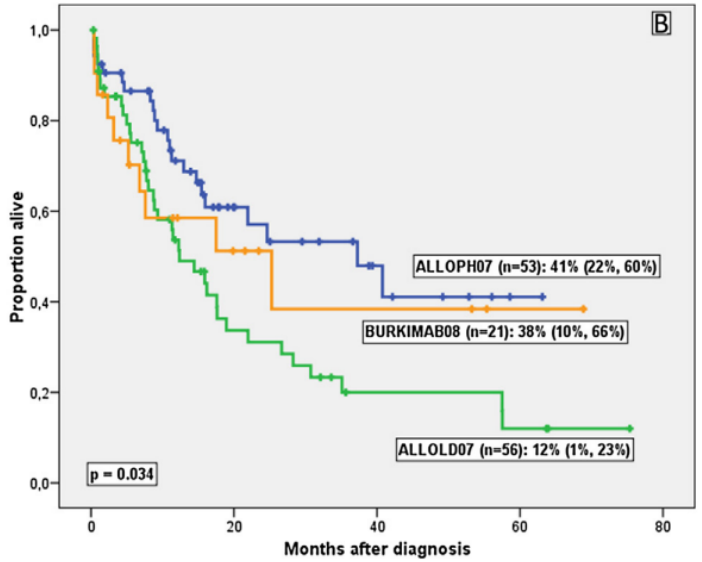
Ph-positive ALL. Ponatinib[2]



Ph-negative ALL. MRD-oriented[3]







[1]Ribera JM et al Haematologica. 2010; 95. 87-95 // [2]Ribera JM et al Hemasphere 2024;8(4):e67 // [3]Ribera JM et al Blood. 2021;137:1879-1894 // Ribera JM; et al. Leuk Res. 2016 Feb;41:12-20

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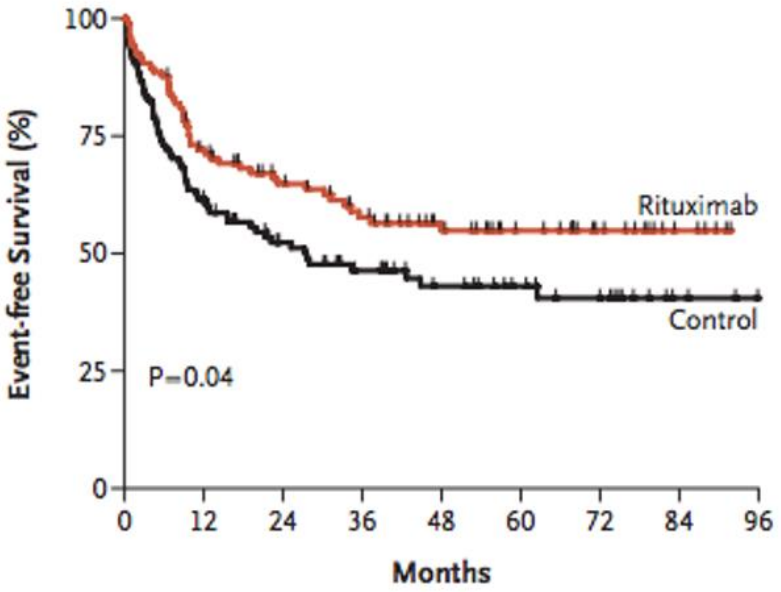
Where we are?

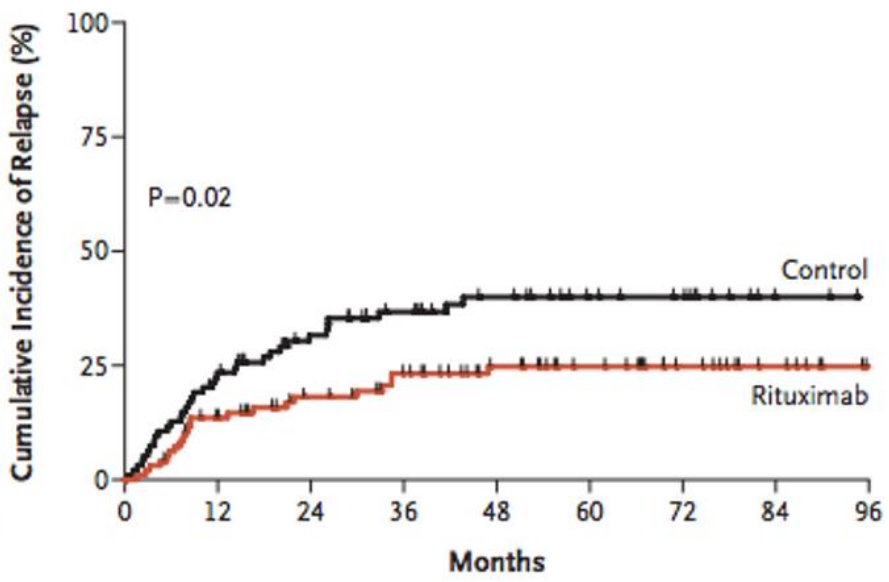
PED-based therapies
Immunotherapy r/r, 1L
Targeted therapies
CAR T-cell

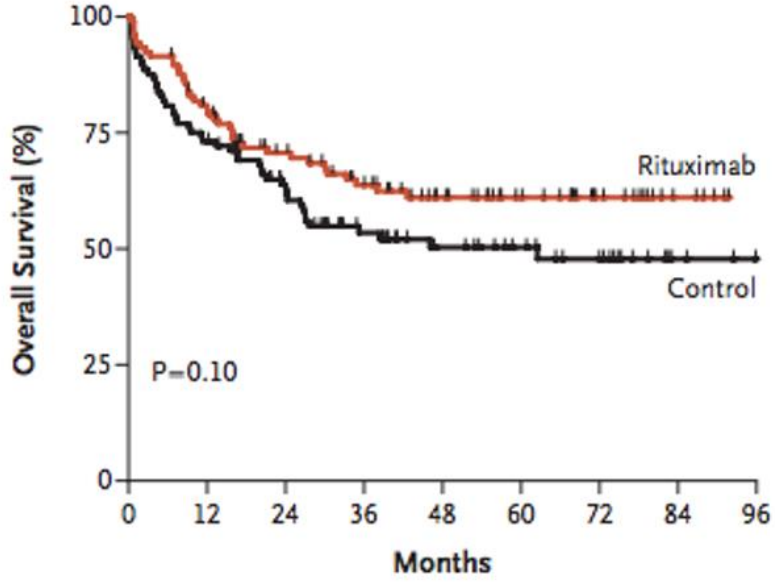
Where we are going?
(where we want to go)

Ph-negative ALL: MoAb anti-CD20

Phase III, randomized, multicenter GRAALL-R 2005 trial
Newly diagnosed B-ALL (18-59 y)







2y EFS **65%** vs 52% (p=0.038)

CIR 25 vs **41%** (p=0.02)

2y OS **74%** vs 63% (p=0.018)

No increased the incidence of SAE, **significant decline in ASP-related allergic reactions** (2% vs 11%, p 0.002)

Maury S et al. NEJM 2016;375:1044-53

Ph-negative ALL: Inotuzumab for R/R ALL

Phase 3 Study: 326 Patients Randomized at 117 Sites in 19 Countries (INO-VATE ALL)

(N = 326)
- R/R CD22+ ALL due for salvage 1 or 2 therapy (Ph− or Ph+)

1:1

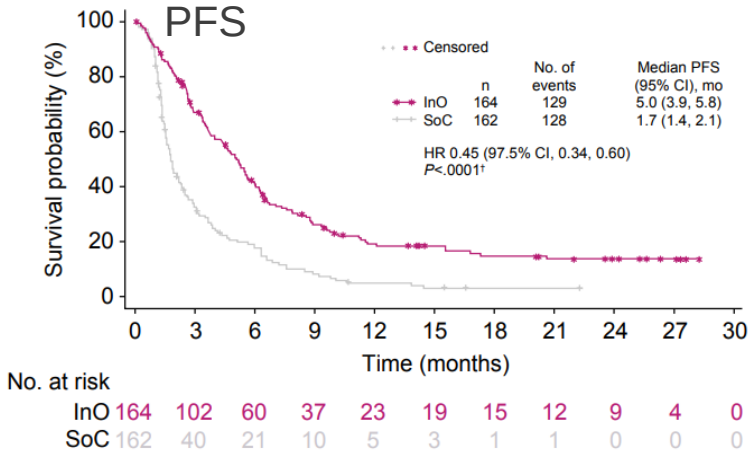
Inotuzumab ozogamicin
- Starting dose 1.8 mg/m²/cycle
- 0.8 mg/m² on day 1; 0.5 mg/m² on days 8 and 15 of a 21-28–day cycle (≤6 cycles)

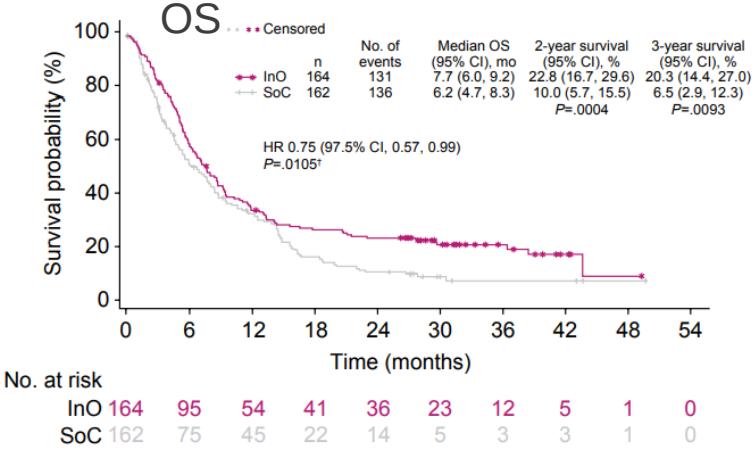
Investigator's choice chemotherapy (≤4 cycles)
- FLAG
- HiDAC
- Cytarabine/mitoxantrone

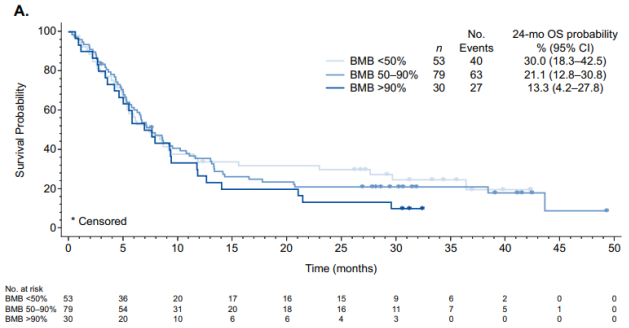
- **Stratifications**
  - Duration of first remission ≥12 vs <12 months
  - Salvage 2 vs 1
  - Aged ≥55 y vs <55 y
- INO dose was reduced to 1.5 mg/m²/cycle once the patient achieved CR/CRi
- **Primary endpoints:** response and OS

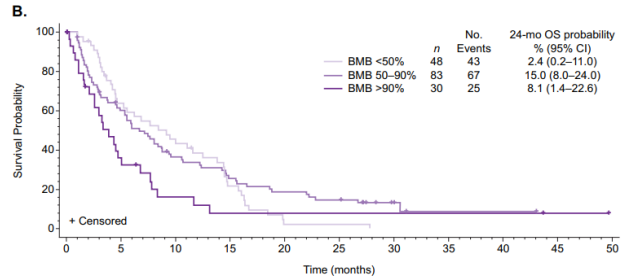
Clinical benefit of **INO** vs SOC in[2]:
- Duration of CR <12m
- Previous HSCT
- Salvage 2 vs 1

No clearly benefit in t(4;11)







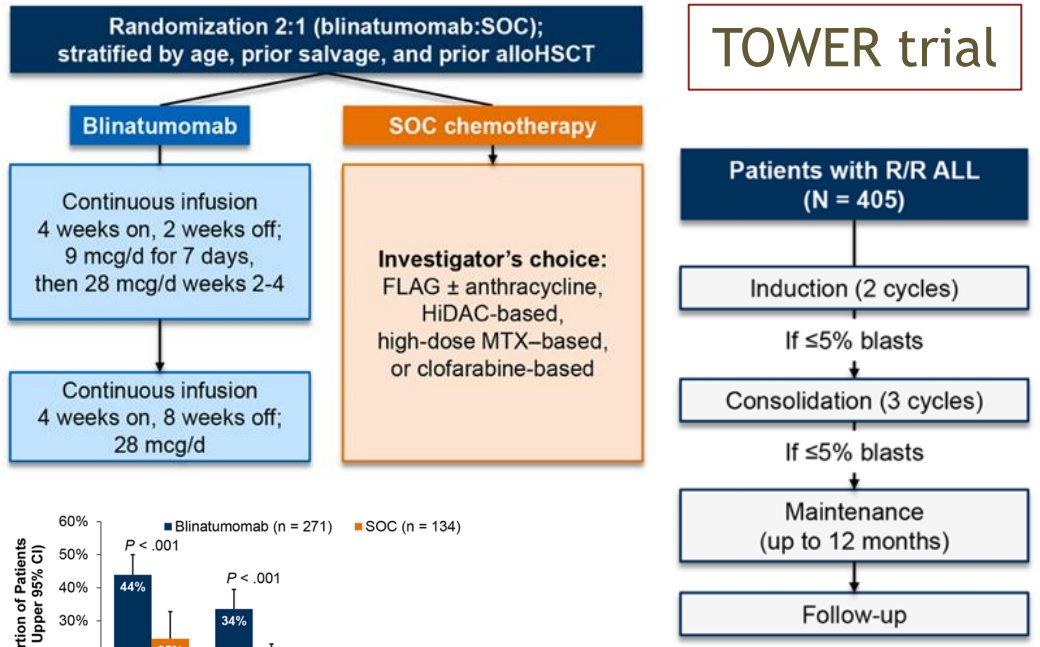


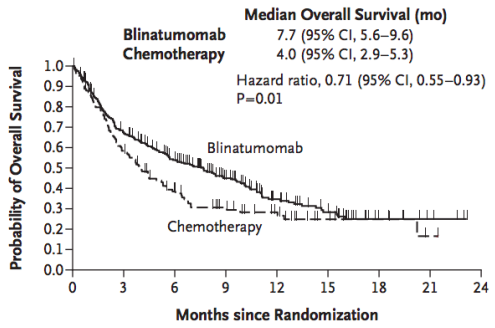
Benefit of INO vs SOC in high tumor burden[1]

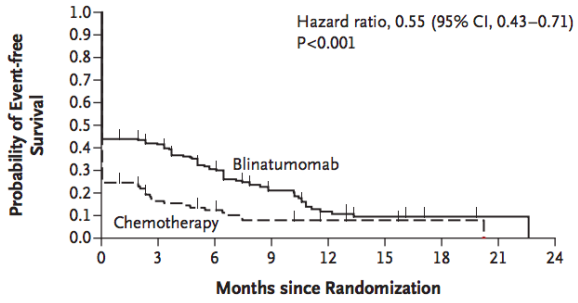
Kantarjian HM, et al. N Engl J Med. 2016 – INOVATE; Kantarjian HM; et al, Cancer 2019 – DiAngelo DJ, Blood Cancer Jour 2020

Ph-negative ALL: Blinatumomab for R/R ALL

TOWER trial

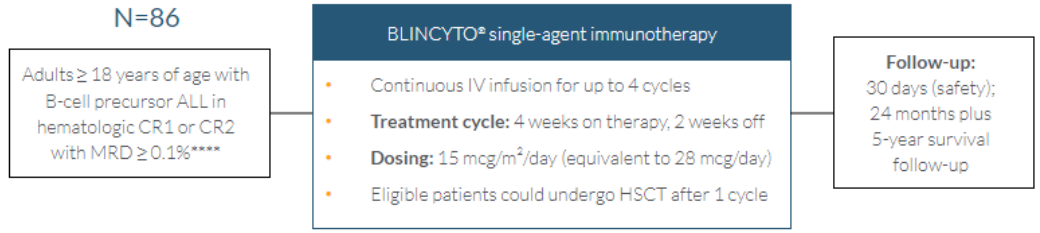






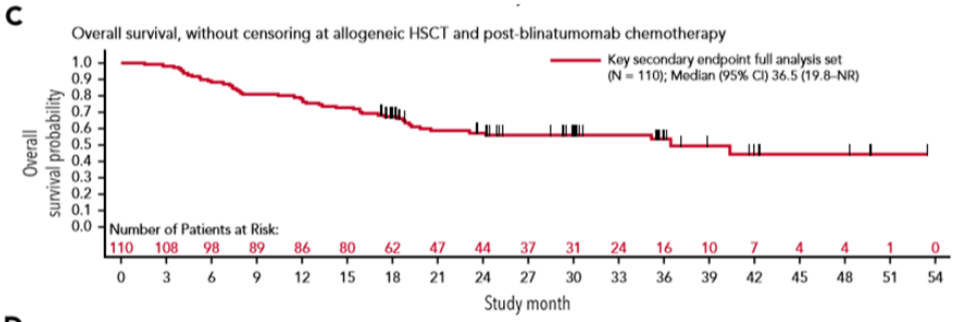
Kantarjian H, et al. NEJM 2017

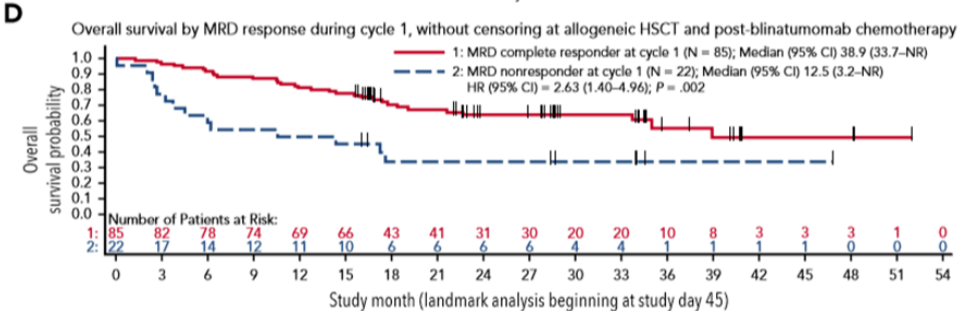
BLAST trial



Median OS 36.5 months

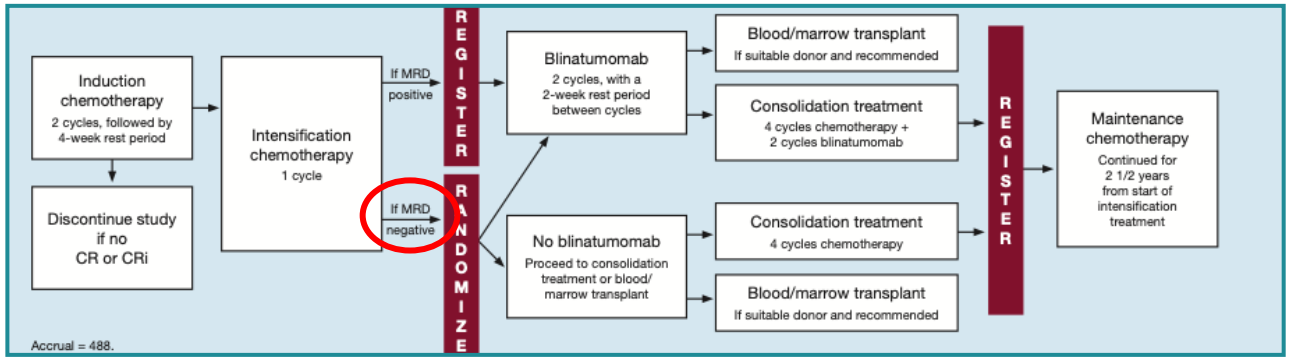
Median OS: MRD neg 38.9 mo vs 12.5 mo





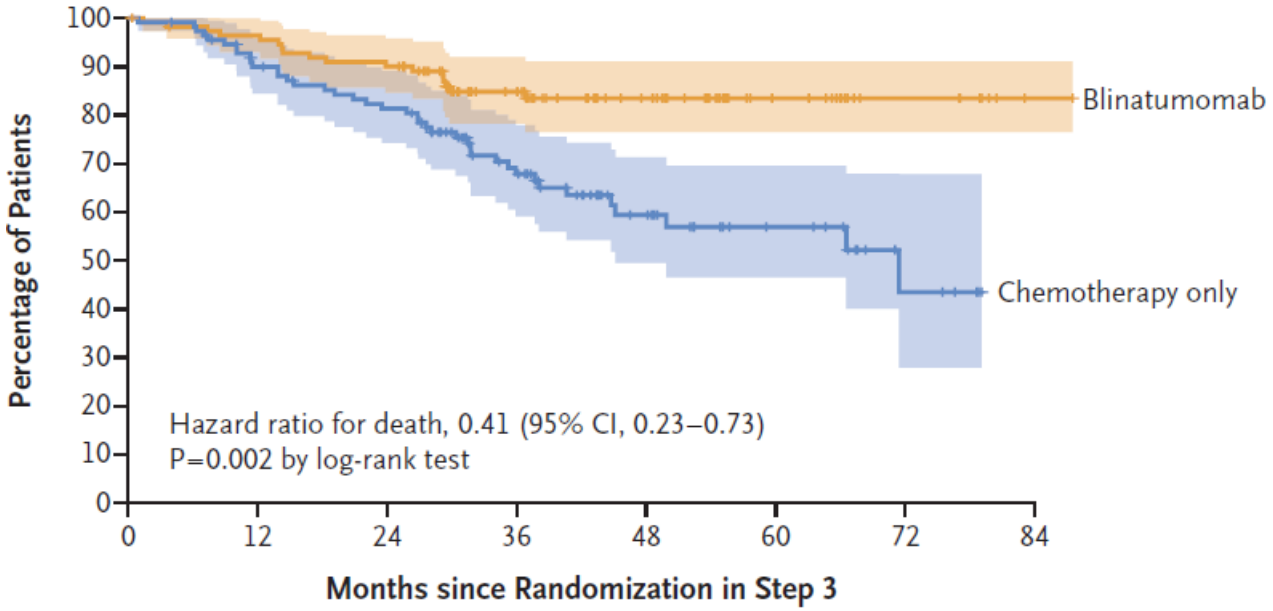
Gökbuget, N, et al. Blood 2018,

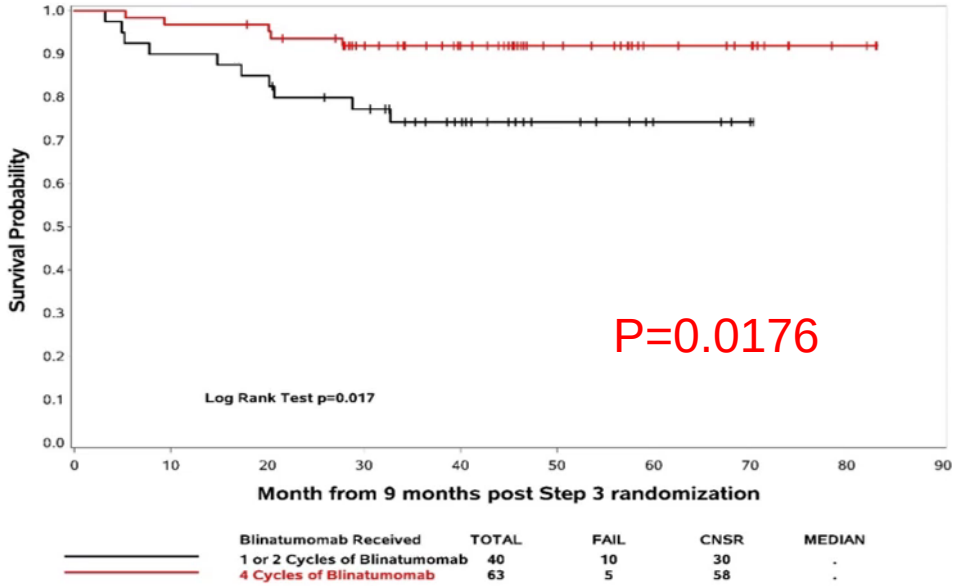
Ph-negative ALL: Blinatumomab 1st line ALL



488 p, median age 51y (30-70y)
225 MDR-neg CR randomized 1:1
Median OS NR vs 71,4 months (P=0,003)

No difference in OS if 1-2 cycles of Blina vs control
OS: 1-2 vs 4 cycles (P=0,017)





Litzow MR, et al. N Engl J Med 2024;391:320-333

Ph-negative ALL: R/R ALL CAR T-cell

18 mo	N*	Age, Median (range)	CR, %	MRD- in CR, %	Relapse (%)	PFS	OS
ELIANA, tisa-cel	97	11 (3-24)	82	95	27%	49% (5y) in CR/CRi	**63% (5y) Plateau**
Upenn, CTL019 (fraccionated)	35	33 (20-70) Single dose, low: 9 Single dose, high: 6 Fractionated dose, high: 20	33 50 90			0% 17% 49% (24 mo)	22% 17% 73% (24 mo)
MSKCC, 19-28z	53	44 (23-74)	83	67	57	Median: 6.1 mo	Median: 12.1 mo
FHCRC	53	39 (20-76)	85	85	49	Median: 7.6 mo	Median: 20 mo
HCB-HSJD, ARI001	27	35 (18-69)	85	85	15	Median: 9.4 mo	Median: 20.2 mo
KTE-X19 Phase 1	45	46 (18-77)	83	100		Median: 17.6 mo	Median: 16.1 mo
KTE-X19 Phase 2, brexu-cel	55	40 (19-84)	71	97		Median 11.6 mo	Median 18.2 mo
KTE-X19 RWE	189	46 (range, 18-81)	90	82		12mo 48%	12mo 63%
AUTO-1, obe-cel	127	47 (20-81)	78	96		12mo 49%	12mo 61%

Kantarjian H, NEJM 2017 (ELIANA)//Laetsch TW, et al. J Clin Oncol. 2023;41:1664-1669 – Frey NV, JCO 2020 (Upenn)– Park JH, N Engl J Med 2018 (MSKCC) - V Ortiz-Maldonado, Mol Ther 2021, 29:636-44 - Shah. Lancet. 2021;398:491. Shah. EHA 2021. Abstr S117 - Stephan A. Grupp et al. BBMT 2019, S126-S127 // SL Maude. N Engl J Med 2018;378:439-48 – Roloff G et al, ASH 2023 – Jabbour E, et al. J Clin Oncol. 2024;24:S6504 // Roddie et al. HemaSphere. 2024;8:S114.

Ph-negative ALL

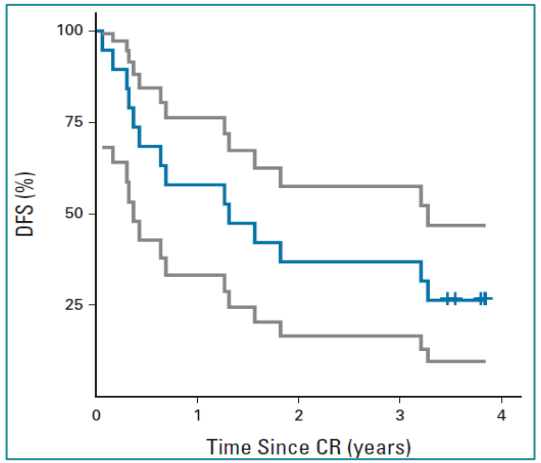
Where do we come from?	Where we are?	Where we are going? (where we want to go)
Chemotherapy (high doses + HSCT)	PED-based therapies Immunotherapy r/r, 1L Targeted therapies CAR T-cell	
CR rate >90% Cure rate 40% (18-60y), <20% >60y High ED (toxicity) Many patients did not receive therapy/HSCT	CR rate 90-100% HSCT (>MRD neg) Less ED / toxicity	

Ph-negative ALL

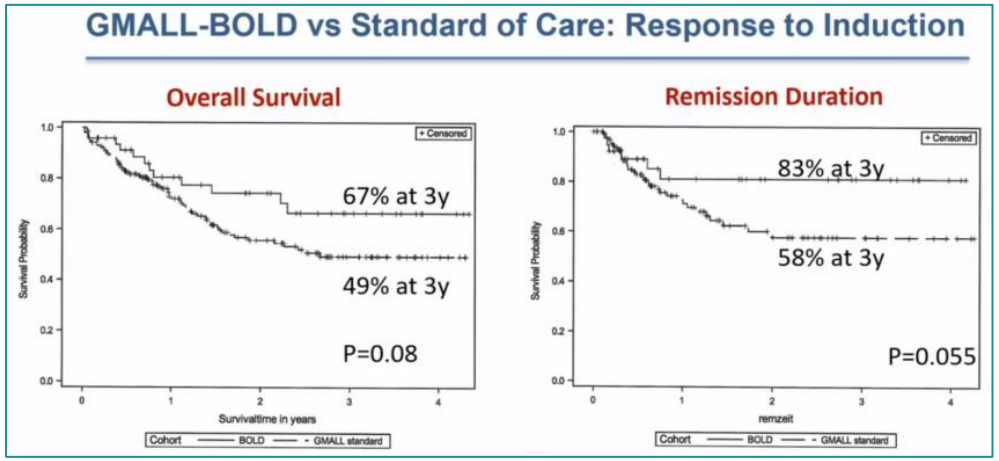
Where do we come from?	Where we are?	Where we are going? (where we want to go)
Chemotherapy (high doses + HSCT)	PED-based therapies Immunotherapy r/r, 1L Targeted therapies CAR T-cell	Chemo-free strategies? Immunotherapy 1st line ImmunoT/CAR in MRD+? CAR T-cell vs HSCT? Less HSCT
CR rate >90% Cure rate 40% (18-60y), <20% >60y High ED (toxicity) Many patients did not receive therapy/HSCT	CR rate 90-100% HSCT (>MRD neg) Less ED / toxicity	

Ph-negative ALL: Front-line Immunotherapy (Phase 2, OLDER)

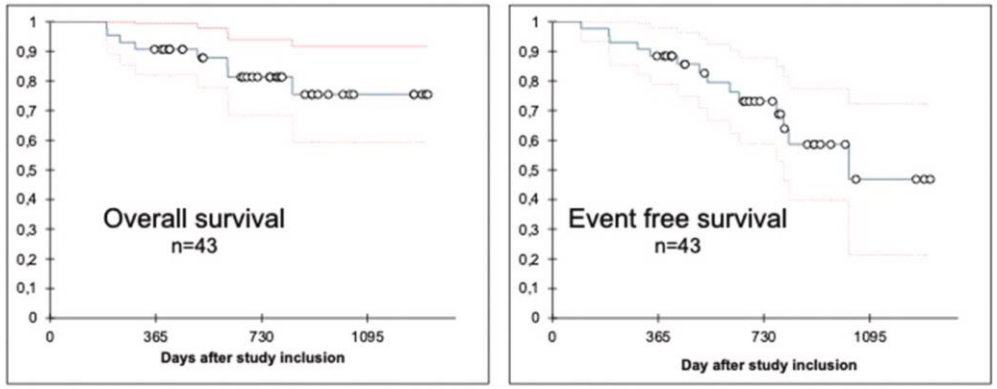
SWOG 1318[1] (≥65 y)
Blin ind/cons
(NO CHT ind/cons)



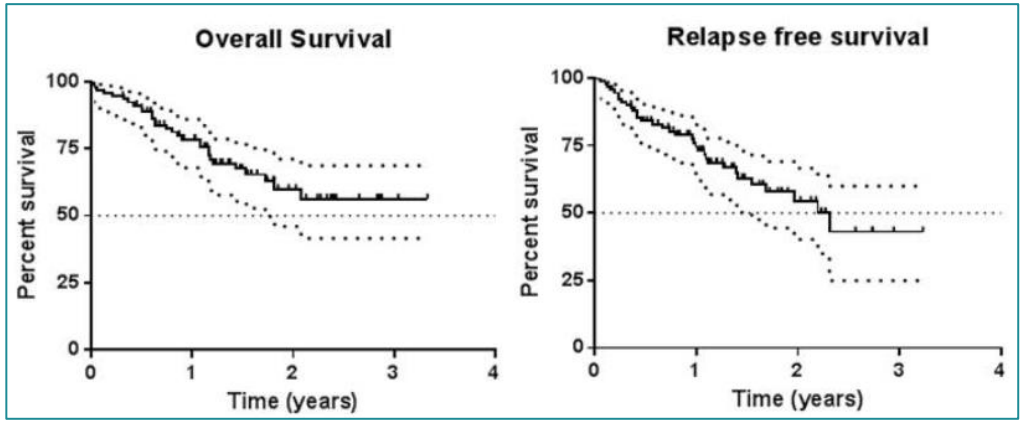
GMALL Bold[2] (56-76y)
LD-CHT + Blin ind/cons



INITIAL-1[3] **(≥55y)**
InO ind (x3) + CHT (cons/reind/maint)
NO CHEMO IN INDUCTION



EWALL-INO[4] **(≥55y)**
LD-CHT + LD-InO x 2 (ind) + CHT (cons/maint)



1. Advani AS, et al. J Clin Oncol 2022;40:1574-82 // 2. Gökbudget N, et al. Blood 2021; 138:3399 and Gökbudget N, et al. ASH 2023 #964 // 3. Stelljes M, et al. Blood 2022;140:510-512 // 4. Chevallier P, et al. Blood 2022 (140);6114

Ph-negative ALL: Front-line Blin + InO (Phase 2, OLDER)

MDACC (≥60 y)
Mini-HyperCVD + **InO** (x4) → **Blin** consol (x4)
→ POMP + **Blin**

ORR 99% (89% CR); MRD-: 94%
2y-PFS 58,2%, 5y 44% // 2y-OS 63,5%, 5y 46%

Fig. 5A

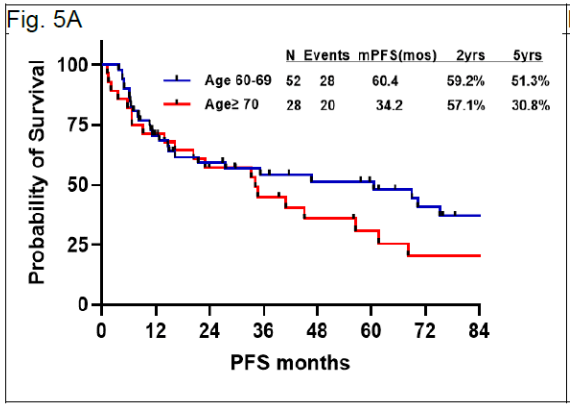
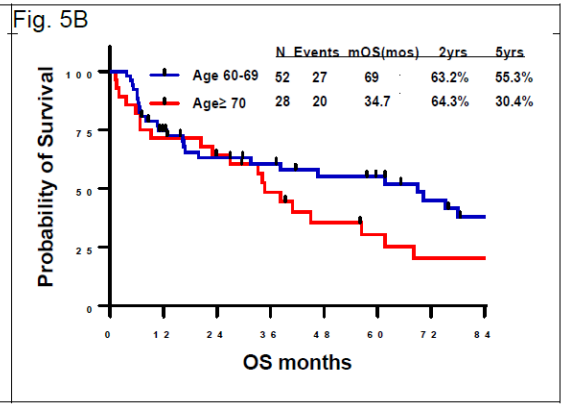


Fig. 5B

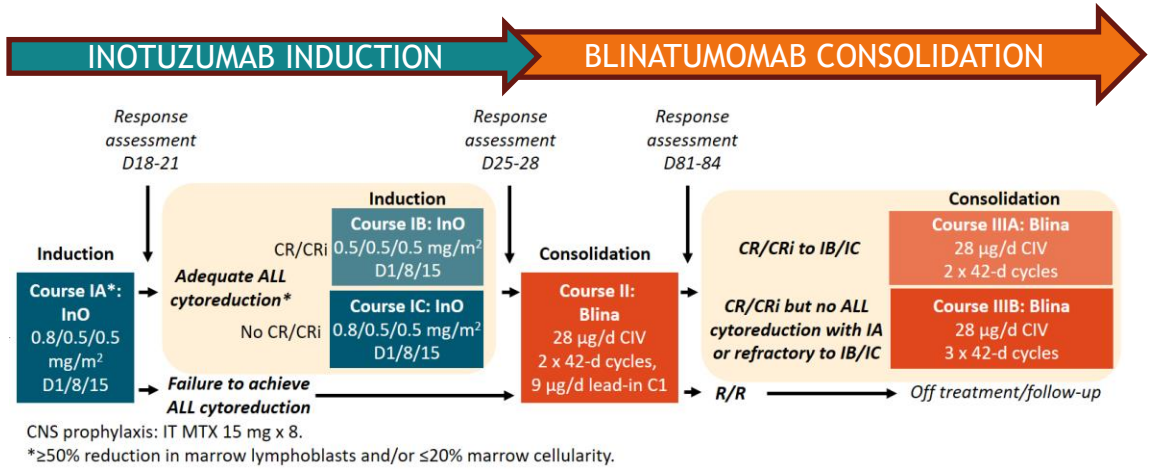


5 CNS relapses!!
47/80 deaths (59%):
- 35/47 (74%) deaths in CR: 9 pts MDS/AML

Jabbour E, et al. Lancet Haematol 2023; 10: e433–44

ALLIANCE A041703: InO ind + Blin cons
CHEMO-FREE STRATEGY

N=33 p; 3 AE deaths // Best CR/CRh/CRi: 85%

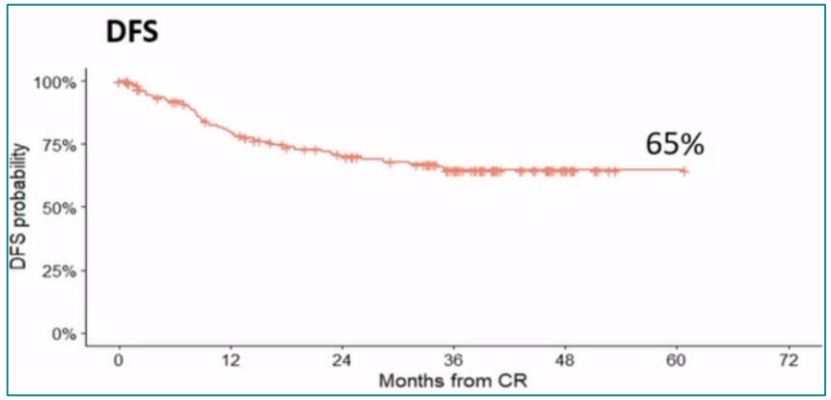


1-yr EFS 75% (2-sided 90% CI: 63%-89%)
Trial met its 1ry EP: effective for further study.

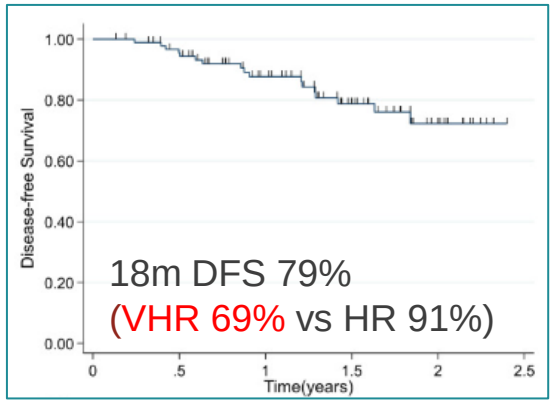
Wieduwilt MJ, et al. ASCO 2023;#7006
Wieduwilt MJ, et al. EHA 2023;7(S3)

Ph-negative ALL: Front-line Immunotherapy (Phase 2, YOUNGER)

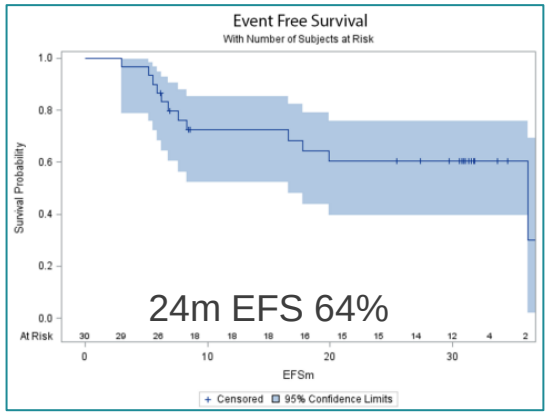
GIMEMA 2317[1]
CHT ind + Blin cons (2) + maint vs HSCT



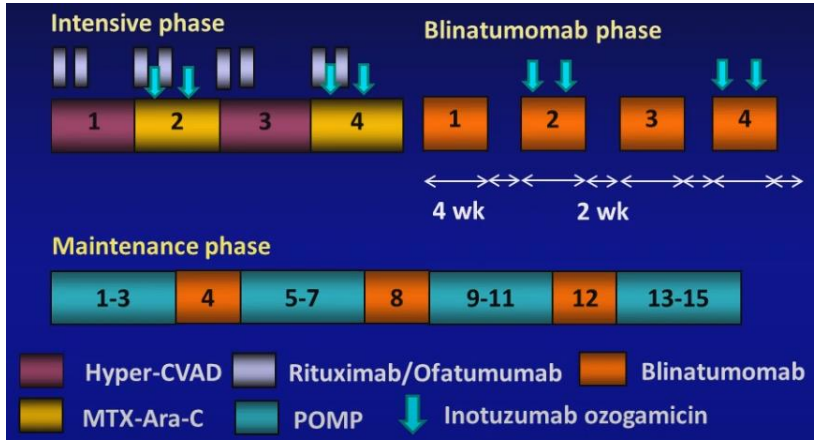
GRAALL-2014 QUEST[2] (HR, ALL)
CHT ind + Blin cons (2) + maint vs HSCT

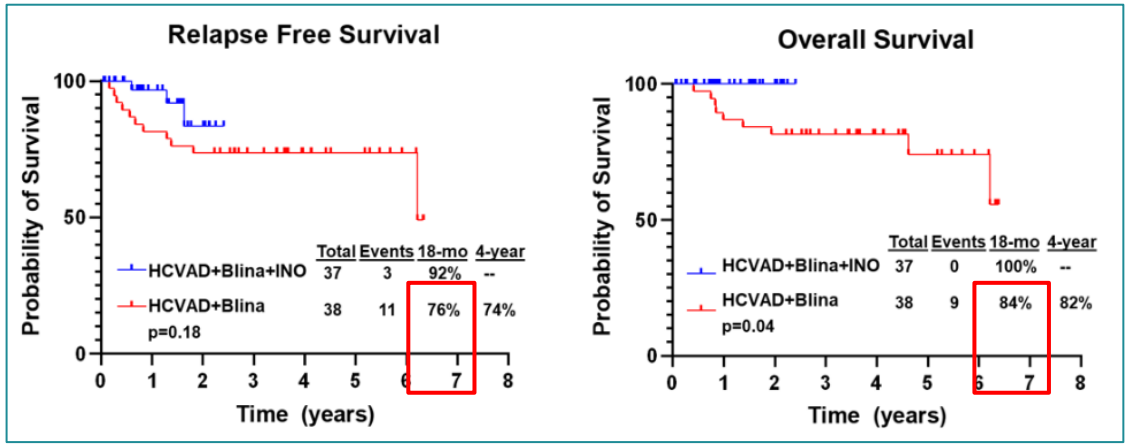


ALL08[3]
CHT + Blin (4) ind + HSCT vs Maint



MDACC[4] **(NCT02877303)**
Hyper-CVAD + InO-ind → Blin consol/maint





1. Chiaretti S, et al. Blood (2023) 142 (Supplement 1): 826 // 2. Boissel N, et al. ASH 2021;#1232 // 3. Fleming S, et al. Hemasphere. 2023 Aug 8;7(Suppl):e811479d // 4. Short NJ et al. ASH 2021, #1233 and Short NJ et al, J Clin Oncol 2023;e19017 and Nguyen D, et al. ASH 2023 #4245

Ph-negative ALL: Front-line Immunotherapy (Phase 2)

Phase 2 trials for Ph-negative ALL patients: Front-line use of MoAb

Study	Schedule	N	Age, median	CR/CRi (%)	MRDneg (responders)	OS (%), y
Young patients (<55-60 years)						
GIMEMA 2317	Blinatumomab consolidation (2 cycles)	149	41 (18-65)	88	93	71, 3y
GRAALL-2014 QUEST	Blinatumomab consolidation for MRD pos	95 (HR)	34 (18-59)	-	74	92, 1,5y
ALLG	Blinatumomab consolidation	30	51 (19-66)	100	83	69, 2y
MDACC	Blinatumomab and Inotuzumab consolidation Blinatumomab maintenance	75	33 (18-59)	100	95	89, 4y
Older patients (>55-60 years of age)						
MDACC	Inotuzumab induction	52	68 (64-72)	85 (ORR)	95	46, 5y
GMALL Initial-1	Inotuzumab induction	43	64 (56-80)	100	71	73, 3y
EWALL-INO	Inotuzumab induction	131	68 (55-84)	88.5	81	72, 1y
A041703	Inotuzumab induction Blinatumomab consolidation	33	71 (60-84)	85 (InO) 97 (Blin)	-	84, 1y
SWOG 1318	Blinatumomab induction and consolidation	29	75 (66-84)	66	92	37, 3y
MDACC	Blinatumomab and Inotuzumab induction Blinatumomab maintenance	80	68 (63-72)	91	94	46, 5y
GMALL Bold	Blinatumomab consolidation	50	66 (56-76)	85	82	67, 3y

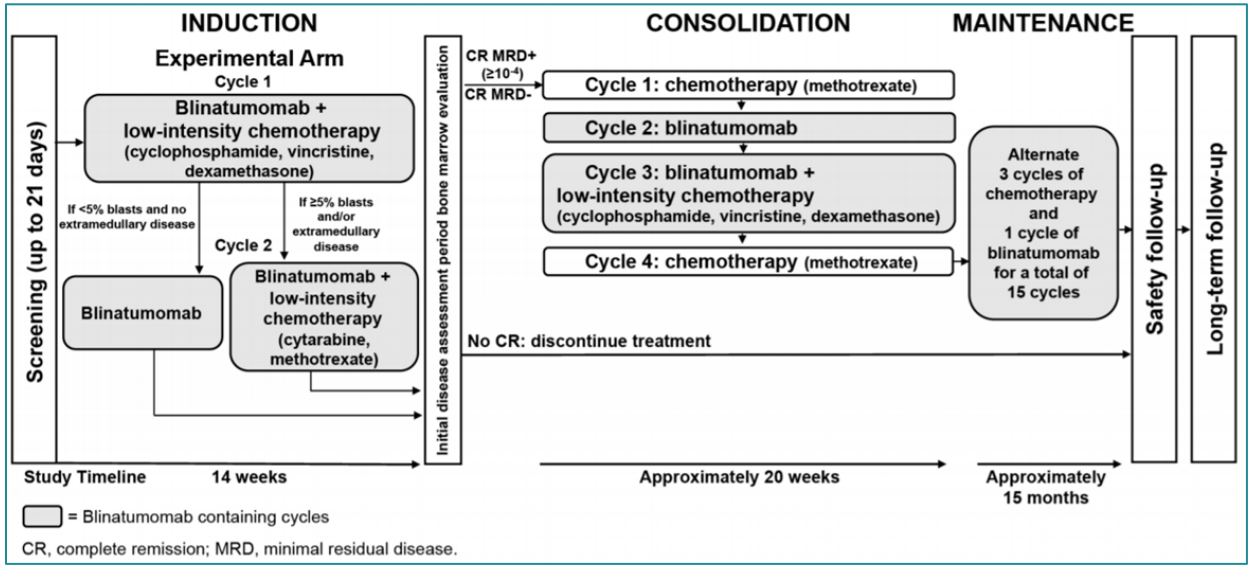
Blinatumomab consolidation

Inotuzumab induction +/- Blinatumomab consolidation

Chiaretti S, et al. Blood 2023;140(Suppl1):826 // Boissel N, et al. Blood 2021;138(Suppl1):1232 // Fleming S, et al. Blood 2021;138(Suppl1):1234 // Jabbour E, et al. Lancet Haematol 2022;9:e878-85 // Kantarjian H, et al. Lancet Oncol 2018;19:240-8 // Stelljes M, et al. J Clin Oncol 2024;42:273-282 // Chevallier P, et al. Blood 2022;140(Suppl1):6114-6 // Wieduwilt MJ, et al. J Clin Oncol 2023;16suppl.7006 // Advani AS, et al. J Clin Oncol. 2022;40:1574-1582 // Göekbuget N, et al. Blood 2023;142(Suppl1):964.

Ph-negative ALL: Front-line MoAb (Phase 3 trials)

GOLDEN GATE STUDY



Newly diagnosed B-ALL (**Older adults**)

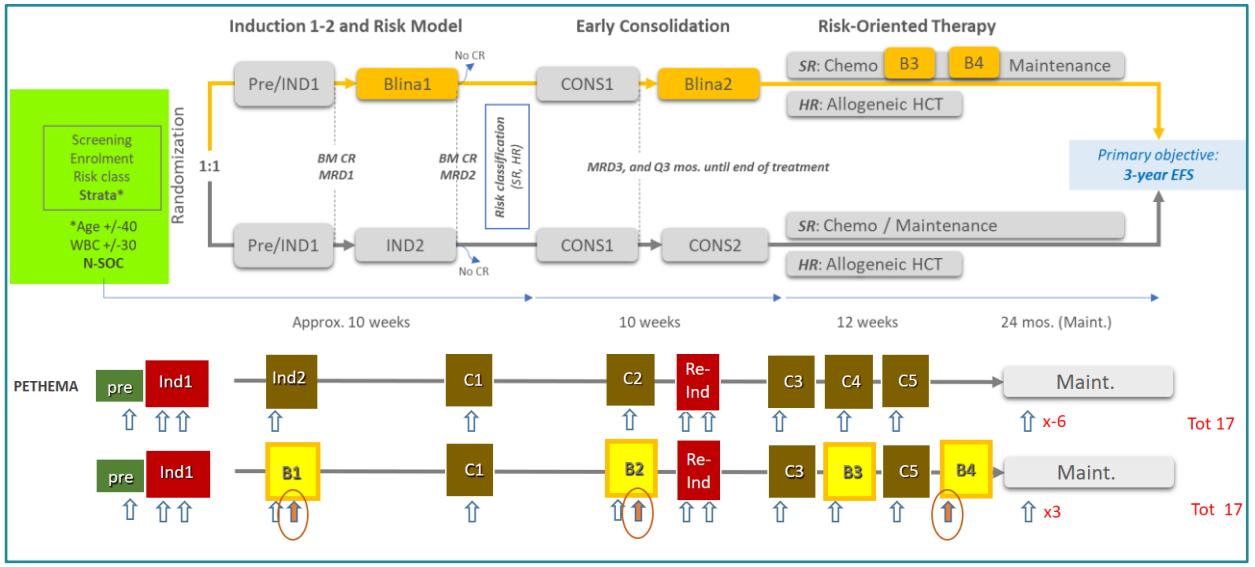
Low-dose chemotherapy + Blinatumomab (induction + consolid)

Safety run-in phase (N=10p) → Published ASH22
Post-ind1: **10/10 CR** (9/10 negative MRD).
Post-ind2: 5/10 negative MRD (no more data).

Randomized ongoing (6 centers in Spain)

Jabbour E, et al. ASH2022 #614

ACCADEMIA TRIAL



Newly diagnosed B-ALL (**Young adults**)

GIMEMA
HOVON
PETHEMA
EWALL

Standard-dose CHT + SC Blinatumomab (induction + consolid)

Clinical proposal approved by EWALL group and by AMGEN.
Budget in evaluation

Ph-negative ALL

Where do we come from?	Where we are?	Where we are going? (where we want to go)
Chemotherapy (high doses + HSCT)	PED-based therapies Immunotherapy r/r, 1L Targeted therapies CAR T-cell	Chemo-free strategies? Immunotherapy 1st line ImmunoT/CAR in MRD+? CAR T-cell vs HSCT? Less HSCT
CR rate >90% Cure rate 40% (18-60y), <20% >60y High ED (toxicity) Many patients did not receive therapy/HSCT	CR rate 90-100% HSCT (>MRD neg) Less ED / toxicity	3y-OS (young) 70% 3y-OS (older) 40-50% Selected patients to HSCT (only HR or VHR patients) No ED / occasional toxicity

T-ALL

Where do we come from?

Where we are?

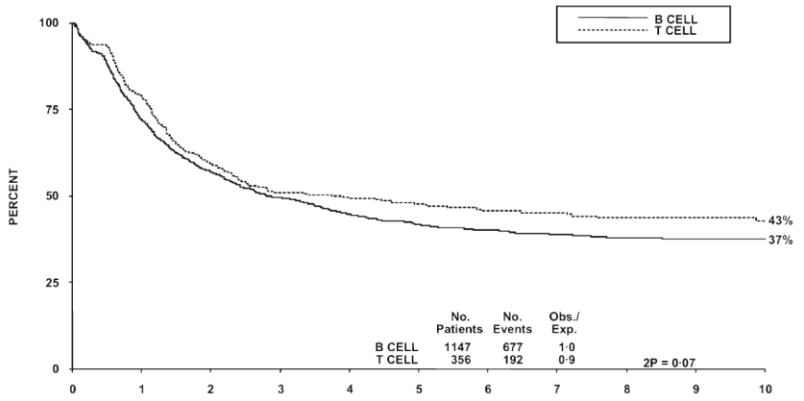
Where we are going?
(where we want to go)

Chemotherapy
(high doses + HSCT)

OS/RFS poor
< HSCT (<MRD neg resposes)
High ED / toxicity

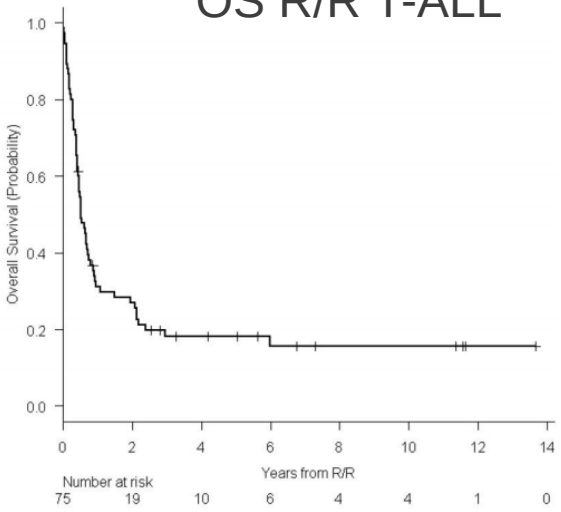
- 15% of childhood and 25% of adult cases of ALL.
- T-ALL has similar (or better) outcomes than B-ALL (except ETP-ALL).
- R/R T-ALL is highly aggressive and often **resistant to steroids and chemotherapy.**

OS



R/R

OS R/R T-ALL



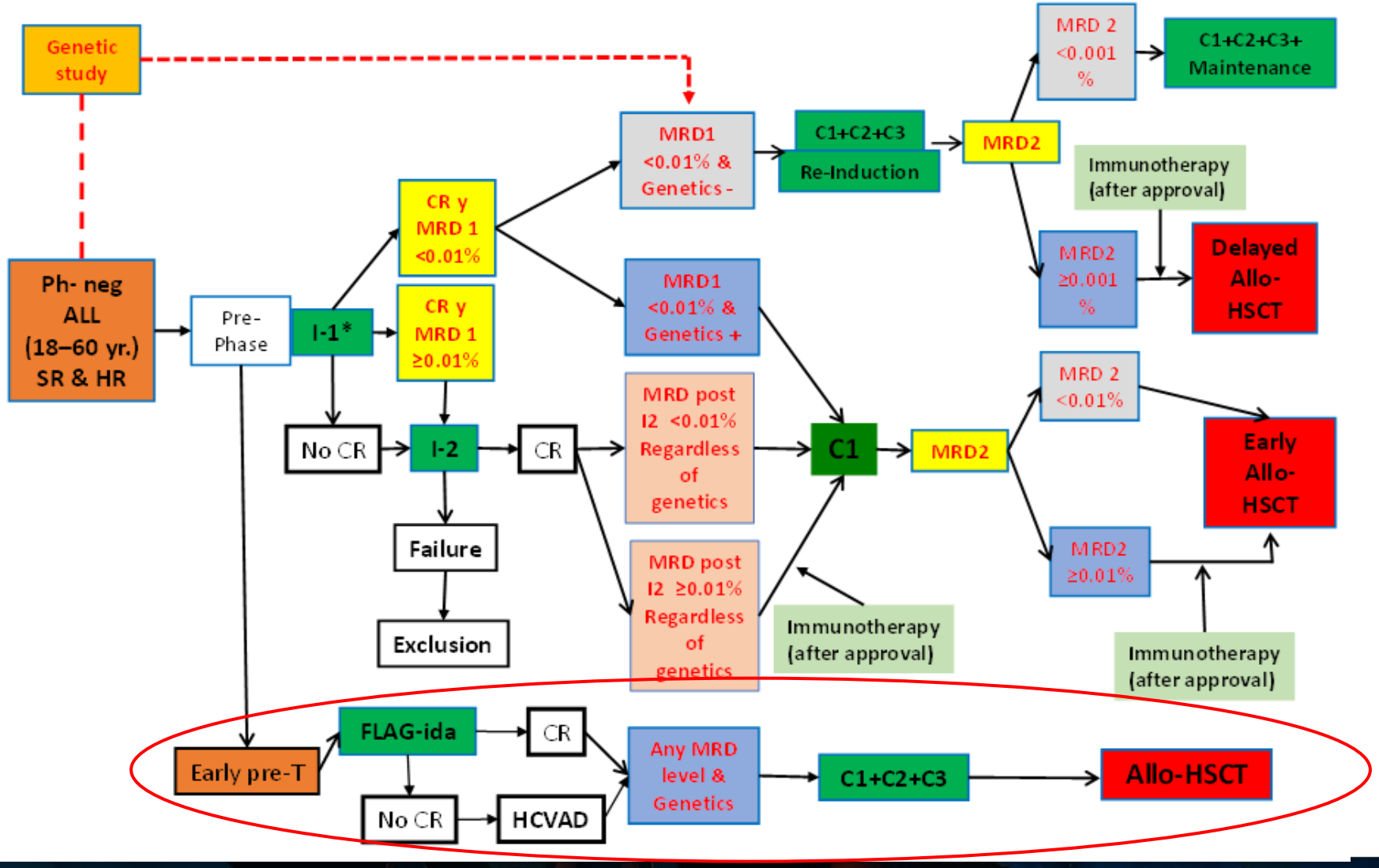
Ribera JM, Hematol Oncol 2021, 39(4):529-538

T-ALL

Where do we come from?	Where we are?	Where we are going? (where we want to go)
Chemotherapy (high doses + HSCT)	PED-based therapies (PEG-ASP) Nelarabine	New therapies 1st line CAR T-cell Personalized targeted therapies?
OS/RFS poor < HSCT (<MRD neg resposes) High ED / toxicity		

T-ALL: Chemotherapy 1st line

PETHEMA LAL19: Guided by subtype, biology and MRD clearance



SR-ALL:
Good MRD clearance +
Mutated NOTCH1
Unmutated PTEN
or NRAS/KRAS

HR-ALL:
Bad MRD clearance **and/or**
Unmutated NOTCH1/FBXW7
and/or
mutated *RAS/PTEN*

ETP-ALL

T-ALL: Nelarabine R/R T-ALL

Nelarabine is the only FDA-approved therapy (in 2005) for relapsed T-ALL specifically as it demonstrated efficacy as a single agent in adults with a CR rate of 31% and a 1-year OS of 28%

WARNING: risk of severe neurotoxicity, dose-limiting.

(A) Response to nelarabine		
Complete remission (CR)	43/118 (36%)	
Partial remission (PR)	16/118 (14%)	
No response (NR)	59/118 (50%)	
Factors affecting nelarabine response		
Factor	**% ORR (CR + PR)**	***P****
Age		.71
18-40 y	20/63 (48)	
>40 y	29/55 (33)	
Diagnosis		.43
T-ALL	41/77 (53%)	
T-LBL	18/41 (44%)	
Phenotype		.83
Early T/Mature	17/32 (53)	
Thymic	42/86 (49)	
Previous lines of therapy		.19
1 line	31/54 (57)	
2 or more lines	28/64 (44)	
Disease status before nelarabine		.008
Relapsed	41/67 (61)	
Refractory	18/51 (35)	

Candoni A, et al. Am J Hematol. 2020 Dec;95(12):1466-1472.

ADULT R/R T-ALL

Nelarabine + Etoposide + cyclophosphamide

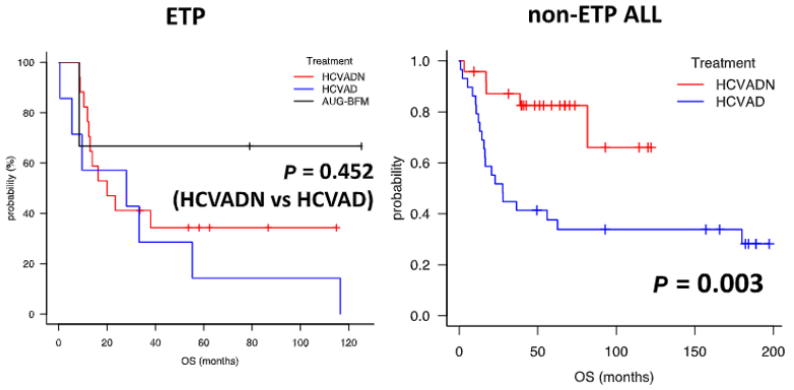
Patient	1	2	3	4	5
Age at relapse (years)	59	58	63	50	57
Sex	Female	Male	Female	Male	Male
Diagnosis*	T-ALL	T-LBL	T-ALL (ambiguous lineage)	T-LBL	T-ALL
Initial regimen	Hyper-CVAD (3 cycles)	Hyper-CVAD (3 cycles)	Idarubicin/ Cytarabine	Hyper-CVAD (4 cycles)	Hyper-CVAD (4 cycles)
Best response to initial therapy	CR	CR	CR	CR	CR
Maintenance/post-remission therapy	No	No	HDAC/allo-SCT	No	No
Time to relapse (days from diagnosis)	189	253	390	2632	215
Relapse regimens prior to NCE	No	Romidepsin	No	No	No
NCE	N days 1–5 C/E days 7–11	N days 1–5 C/E days 7–11	N days 1–5 C/E days 7–11	C/E days 1–5 N days 7–11	C/E days 1–5 N days 7–11
CNS therapy with NCE	No	IT MTX 12 mg day 7	IT MTX 12 mg day 7	IT MTX 12 mg day 2	IT MTX 12 mg days 4, 14 IT-araC 100 mg days 1, 8
NCE best response	CR	CR	N/A	CR	N/A
Cycles to best NCE response	2	1	N/A	2	N/A

N=5 R/R T-ALL → CR 3 patients (after 1-2 cycles of NCE).

Luskin MR, et al. Br J Haematol. 2016;174:332-4

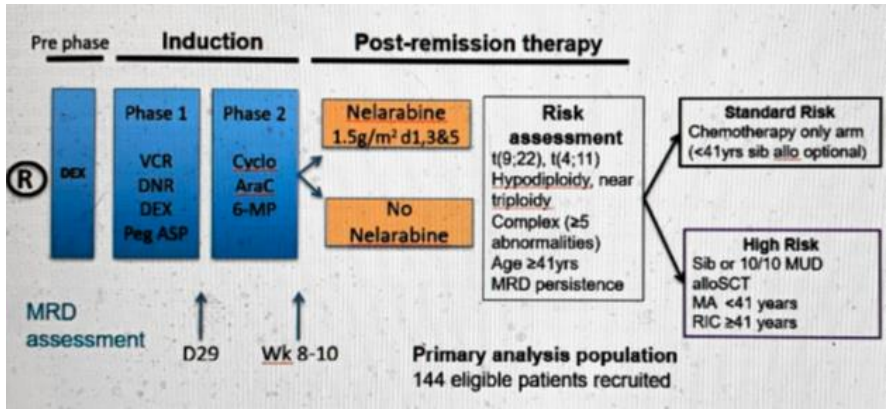
T-ALL: Nelarabine 1st line

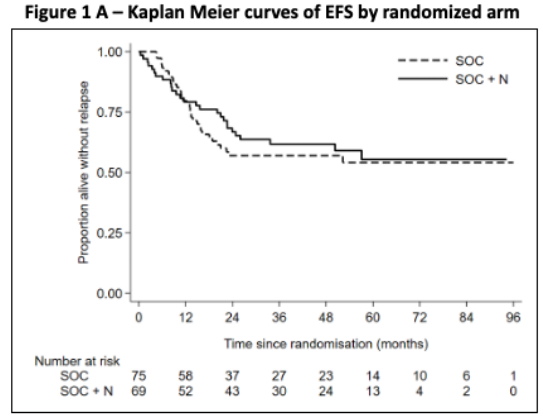
Nelarabine better in non-ETP ALL



Morita K, et al. Am J Hematol. 2021;96:589-598.

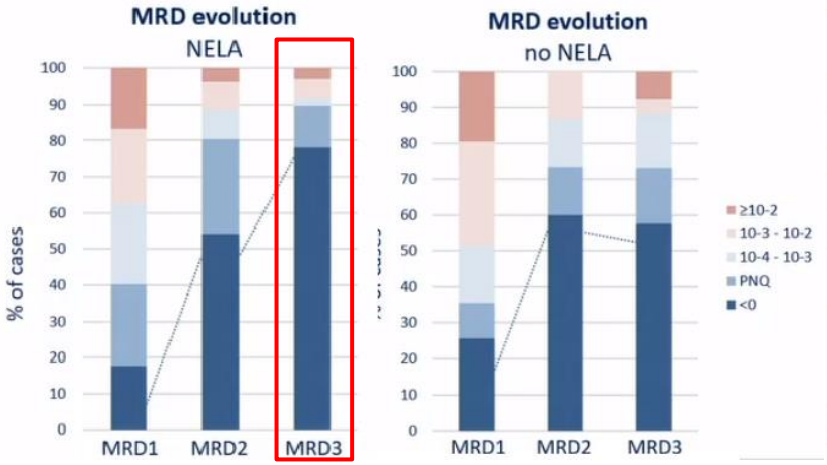
UKALL14: Newly-D T-ALL randomized → No benefit of add NEL



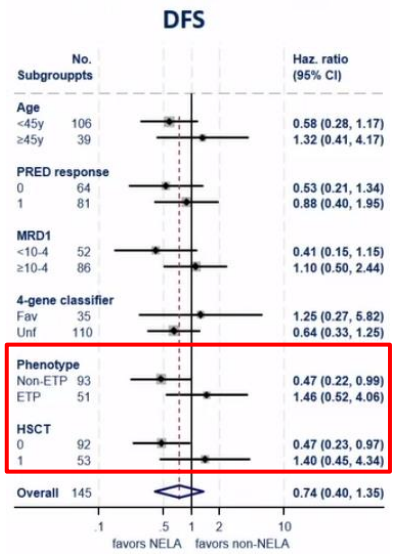


Rowntree C et al. ASH 2021, Blood 138;366.

ATRIALL (GRAALL): Nelarabine consolidation for HR T-ALL



	NELA (ATRIALL) n=112	No NELA N=33	p
MRD response (after conso 2)			
$MRD3_{neg}$, N(%)	75/96 (78)	15/26 (58)	0.05
$MRD3_{neg}$ if MRD1 ≥ 10^{-4} , N(%)	36/55 (65)	5/16 (31)	0.02
Allo-HSCT rate	38/112 (34)	15/33 (45)	0.30
Median follow-up	3.0	5.8	<0.001
3y-CIR (95%CI)	27% (20-37)	47% (31-67)	0.14
3y-CIR, censored at HSCT (95%CI)	29% (20-41)	65% (43-85)	0.045
3y-DFS (95%CI)	67% (56-75)	49% (30-66)	0.32
3y-DFS, censored at HSCT (95%CI)	69% (56-79)	35% (13-57)	0.075
3y-OS (95%CI)	72% (62-80)	76% (56-88)	0.80
3y-OS, censored at HSCT (95%CI)	74% (61-83)	69% (41-86)	0.97



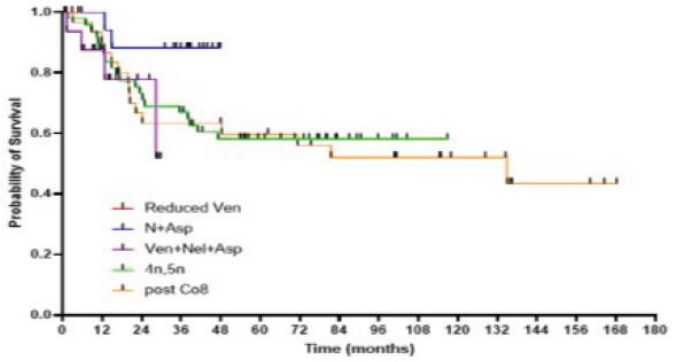
Boissel N, et al. ASH 2023

T-ALL: New strategies and targets

Nelarabine, PEG-Asp, Venetoclax in frontline T-ALL and LBL patients

N=120 p, 35 yrs (range 18-78)
30-day mortality was 0%, CR/CRi 93%, median PFS/OS 135m

	Total N (%)	Cohort 1 N (%)	cohort 2 N (%)	cohort 3 N (%)	cohort 4 N (%)	Cohort 5 N (%)
Number	120	30	49	17	16	8
Median age [Range]	35 [18-78]	38 [19-76]	33 [18-78]	31 [18-65]	38 [18-52]	24 [20-55]
Male	93 (78)	22 (73)	39 (80)	14 (82)	12 (75)	6 (75)
PS 2+	16 (13)	3 (10)	7 (14)	3 (18)	3 (19)	0
T-ALL vs. T-LL	74 (62), 45 (38)	19 (63), 11 (37)	28 (57), 20 (41)	9 (53), 8 (47)	11 (69), 5 (31)	7 (88), 1 (12)
CNS+ at Dx	6 (5)	2 (7)	2 (4)	1 (6)	1 (6)	0
Mediastinal disease	62 (52)	16 (53)	24 (49)	8 (47)	8 (50)	6 (75)
Median WBC [Range]	7.7 [0.5-344.3]	7.6 [0.6-241.4]	7.7 [1.2-309.2]	7.4 [0.5-86.3]	9.3 [1.4-344.3]	12.1 [1.7-150.7]
BM Blast % [Range]	24 [0-97]	19.5 [0-95]	9 [0-96]	30 [1-94]	39 [0-90]	83 [2-97]
Immunophenotype						
Thymic	53 (44)	10 (33)	20 (41)	9 (53)	10 (63)	4 (50)
ETP	23 (19)	6 (20)	10 (20)	5 (29)	2 (13)	0
ETP+CD5	19 (16)	7 (23)	7 (14)	1 (6)	2 (13)	2 (25)
Early, non-ETP	3 (3)	0	1 (2)	0	2 (13)	0
Mature	11 (9)	3 (10)	6 (12)	1 (6)	0	1 (12)
NOS/NA	11 (9)	4 (13)	5 (10)	1 (6)	0	1 (12)



Ravandi F, HemaSphere 2022;6:S3

Venetoclax and navitoclax in R/R T-ALL

N=47 R/R ALL enrolled → N=19 R/R T-ALL

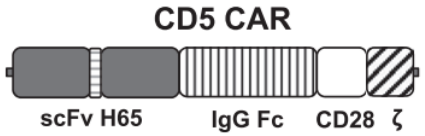
T-ALL (CR/CRi/CRp): 55.6%
ETP (8/12): **66.7%**
Non-ETP (2/6): 33%

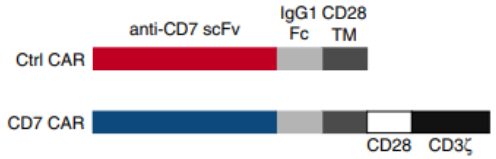
Parameter	B-ALL (*n* = 25)	T-ALL (*n* = 19)	LL (*n* = 3)	All patients[a] (N = 47)
Response[b], *n* (%)				
CR rate (CR/CR$_i$/CR$_p$)	16 (64.0)	10 (52.6)	2 (66.7)	28 (59.6)
PR	3 (12.0)	0	0	3 (6.4)
SD	2 (8.0)	6 (31.6)	0	8 (17.0)
PD	4 (16.0)	3 (15.8)	1 (33.3)	8 (17.0)
Patients with ALL and morphologic CR at baseline, *n*	*n* = 1	*n* = 4	NA	*n* = 5
Response, *n* (%)				
CR rate (CR/CR$_i$/CR$_p$)	0	3 (75.0)		3 (60.0)
SD	0	1 (25.0)		1 (20.0)
NE[c]	1 (100)	0		1 (20.0)
DOR[d] in all responders				
n	19	10	2	31
Median (95% CI), mo	9.1 (1.4–14.6)	4.2 (0.8–12.3)	NE (NE–NE)	4.2 (2.3–11.5)
OS				
Median (95% CI), mo	9.7 (4.0–15.7)	6.6 (3.2–12.5)	NE (2.0–NE)	7.8 (4.0–12.5)
12-month (95% CI), %	33.8 (13.7–55.2)	29.7 (10.4–52.2)	66.7 (5.4–94.5)	35.6 (20.9–50.7)
Bone marrow MRD, *n* (%)				
MRD negative (<10^{-4})	9 (36.0)	6 (31.6)	1 (33.3)	16 (34.0)
MRD positive	10 (40.0)	3 (15.8)	1 (33.3)	14 (29.8)
Other[e]	6 (24.0)	10 (52.6)	1 (33.3)	17 (36.2)

Pullarkat VA, et al. Cancer Discov 2021;11:1440–53

T-ALL: CAR T-cell

Target in T-ALL cells is critical due to fratricide of CAR T cells and *off target* toxicity.
Risk that a CAR T cell product could be contaminated with a patient's malignant T cells.





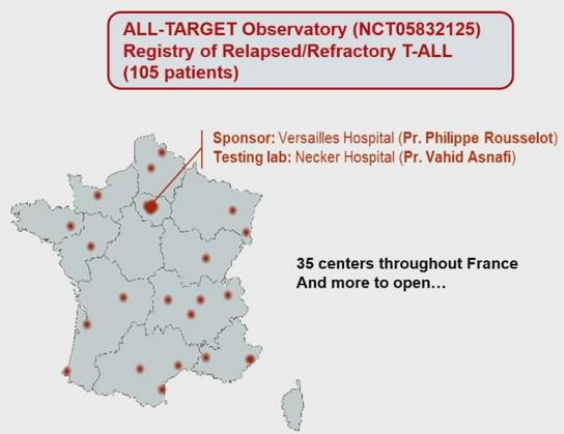
CD5: surface marker 80% of T-ALL and T-LL.
limited fratricide (internalization of CD5).

CD7: >95% of T-ALL, T-LL, peripheral T-cell lymphomas.
Extensive fratricide (incomplete internalization of CD7).
Genome editing necessary.

Author (year)	Type of CAR T	Costimulatory domain	Origin of lymphocytes	Trial phase	N patients	CR
Hill LC, BBMT 2020	CD5	CD28	Autologous	1	9 (adult)	3
Li S, Clin Canc Res 2021	CD7	4-1BB	Off the shelf (alloCAR)	1	2	2
Pan J, JCO 2021	CD7	4-1BB	Donor derived (alloCAR)	1/2	20	18
Zhang M, ASH 2022	CD7	NR	Autologous	1	8	6 (3mo)

Mamonkin M, et al. Blood 2015;126:983-92 - Gomes-Silva D, et al. Blood 2017;130:285-96 - Pan J et al. J Clin Oncol 2021;39:3340-51

T-ALL: Oncogenetic-driven targeted therapy

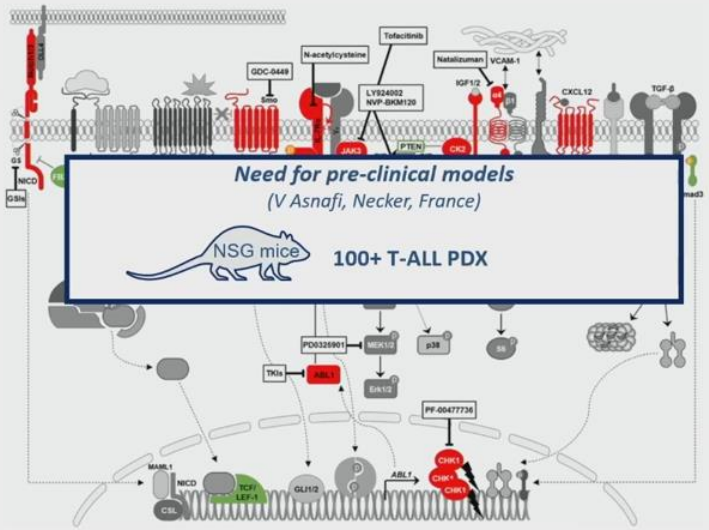


- Can we evaluate **predetermined targeted therapeutic options** validated in preclinical models for R/R T-ALL?
- Can we use a combination of **phenotypic and genotypic information** to decide the best option for a given patient?

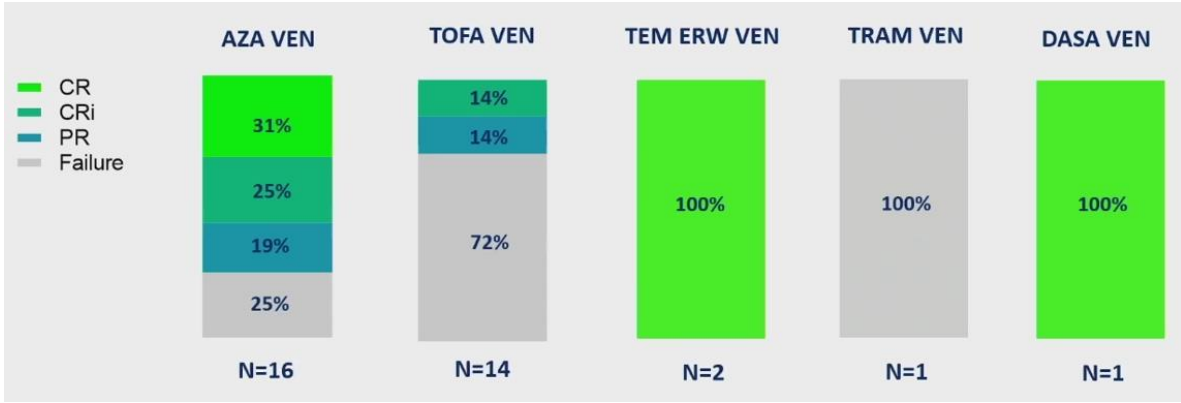
Targeted Therapeutic Option proposed for 34 patients

Targeted Pathways	Validated Combinations	
IL7R-JAK-STAT (IL7R^{ALT}) *Courtois L, Blood 2023*	Venetoclax	14 patients (41%)
	Tofacitinib ou Ruxolitinib	
PI3K-AKT-PTEN (PI3K^{ALT}) *Andrieu G, submitted*	Venetoclax	2 patients (6%)
	Temsirolimus	
	Erwiniase	
METHYLATION (PHF6^{ALT}) *Pinton A, Clin Canc Res 2023*	Venetoclax	16 patients (47%)
	5-Azacytidine	
RAS-MEK-ERK	Trametinib	1 patient (3%)
	Dabrafenib	
FLT3	Giltéritinib	
SRC::ABL1 NUP::ABL1	Dasatinib	1 patient (3%)

A myriad of potential therapeutic targets in T-ALL



Validated Pathways
IL7R-JAK-STAT (IL7R^{ALT}) *Courtois L, Blood 2023*
PI3K-AKT-PTEN (PI3K^{ALT}) *Andrieu G, submitted*
METHYLATION (PHF6^{ALT}) *Pinton A, Clin Canc Res 2023*
RAS-MEK-ERK
FLT3
SRC::ABL1 NUP::ABL1



Cabannes-Hamy A, et al. Blood 2023;142(Supplement1):518

To take home: THE ALL RACE

Where do we come from?	Where we are?	Where we are going? (where we want to go)
Chemotherapy (high doses + HSCT)	PED-based therapies Immunotherapy R/R Targeted therapies (TKI) CAR T-cell	Chemo-free strategies Immunotherapy 1st line CAR T-cell vs HSCT Personalized targeted therapies?
OS/RFS poor ↓HSCT (↓ MRD neg CR) ↑ ED / toxicity	OS/RFS better ↑ HSCT (↑ MRD neg) ↓ ED / toxicity	OS/RFS the best BUT: CNS relapses!! ↓↓ HSCT (only HR or VHR) No ED / occasional toxicity

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Thank you

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