Thursdays Webinars

EuroBloodNet

Management of Relapsed/Refractory Acute Lymphoblastic Leukemia in Adult

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PARIS – FRANCE
6 February 2025

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for rare or low prevalence complex diseases
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Conflicts of interest

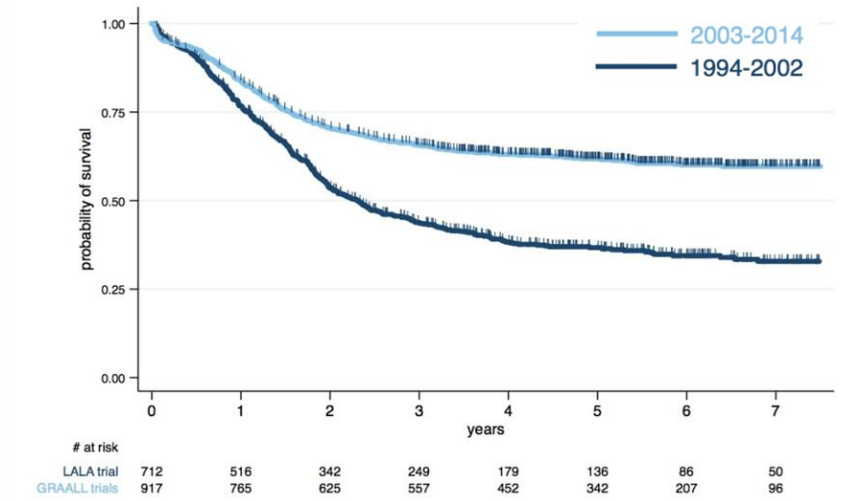
Honoraria (Consulting, advisory role)	Amgen Advesya Ariad-Incyte Autolus Clinigen Gilead	Medac Novartis Jazz Pharma Pfizer Sanofi Servier
Research funding	Amgen Novartis Incyte	Jazz Pharma Miltenyi

Treatment of B-ALL in adults

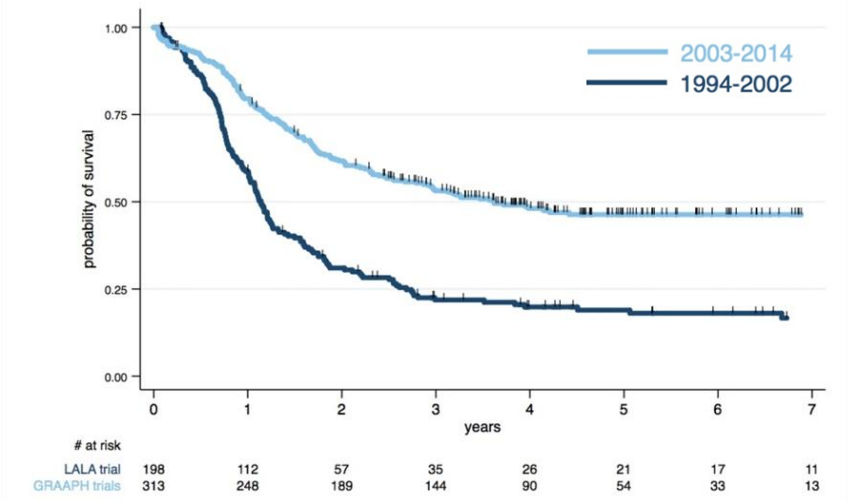
Progress and limits of conventional therapies

- Two major progressions accomplished in the last 15 years:
  - Paediatric-like approaches in young adults with Ph-negative ALL[1]
  - TKIs in Ph-positive B-ALL[2]
- Limitations:
  - Increased toxicity in patients >45 years[1]
  - About 30% of patients still relapse with very poor outcome (median survival of 3–6 months)[1,3]

Ph-negative ALL (ages 18–59 years)[4]



Ph-positive ALL (ages 18–59 years)[4]

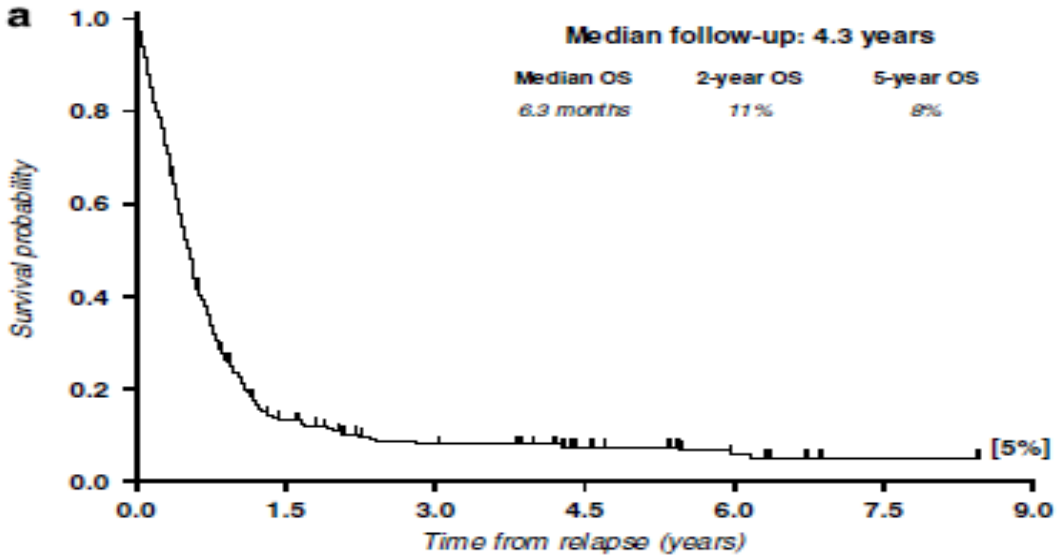


1. Huguet F, et al. J Clin Oncol 2018;36:2514–23;
2. Chalandon Y, et al. Blood 2015;125:3711–9;
3. Gökbuget N, et al. Haematologica 2016;101:1524–33; 4. GRAALL, unpublished data on file.

Adult B-ALL at relapse

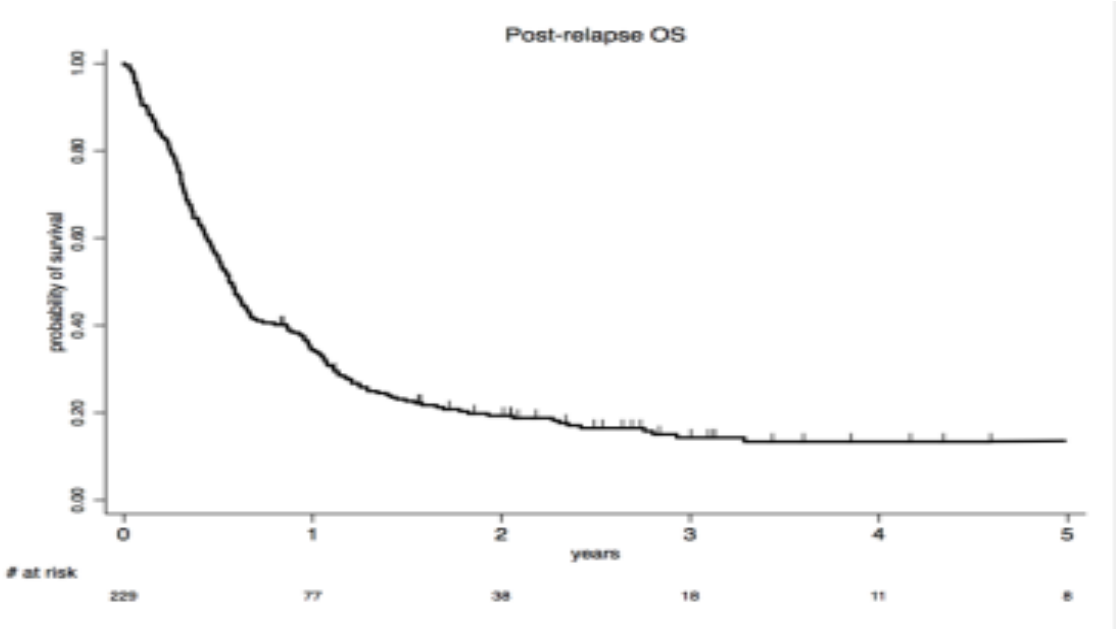
Post-relapse survival

LALA 94[1]



- Median OS: 6.3 mois
- 2y OS : 11%
- 5y OS : 9%

GRAALL 2003 & 2005[2]



- Median OS : 6.7 mois
- 2y OS : 19.3%
- 5y OS : 13.3%

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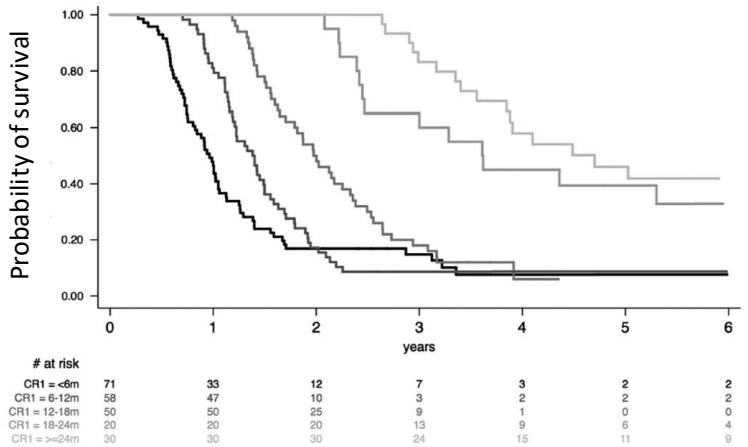
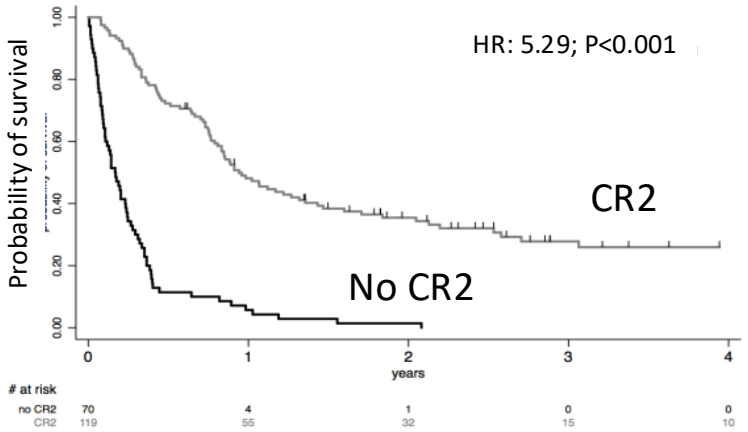
1. Tavernier E. et al. Leukemia. 2007 Sep;21(9):1907-14.
2. Desjonquères A. et al. Blood Cancer J. 2016 Dec 9;6(12):e504

Prognostic factors at relapse

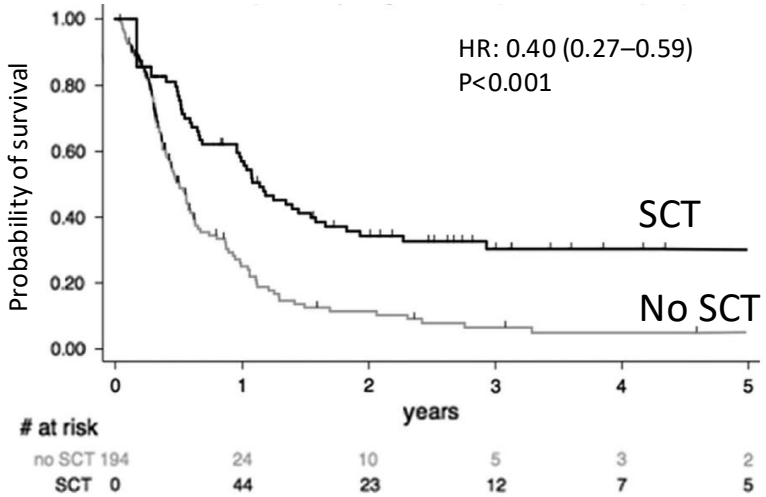
OS by CR1 duration[1]



Post-relapse OS by CR2[2]



Post-relapse OS by allogeneic SCT[1]



No standard of care!

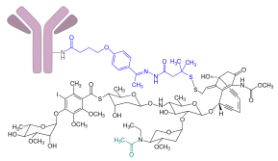
GRAALL[1,2]	n	CR, n (%)
Total	229	121 (53%)
CR1 <18 months	179	87 (49%)
CR1 ≥18 months	50	34 (68%)

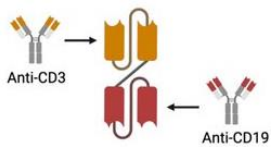
GMALL[3]	n	CR, n (%)
Total	224	95 (42%)
CR1 <18 months	160	58 (36%)
SCT in relapse	18	10 (56%)
CR1 ≥18 months	64	37 (58%)
Standard induction	30	27 (90%)
FLAG-IDA	15	4 (27%)

1. Desjonquères A, et al. Blood Cancer J 2016;6:e504;
2. GRAALL, unpublished data on file;
3. Adapted from Gökbuget N, et al. Blood 2012;120:2032–41.

Approved immunotherapies for R/R B-ALL

	Inotuzumab Ozogamicin	Blinatumomab	Tisa-cel	Brexu-cel
Family	ADC	ICE	CAR-T	CAR-T
Target	**CD22**	**CD19**	**CD19**	**CD19**
Payload/construct	Calicheamycin	xCD3	4-1BB / CD3z	CD28 / CD3z
Pivotal study	INO-VATE (Ph3)	TOWER (Ph3)	ELIANA (Ph2)	ZUMA-3 (Ph2)
Population	• 18y+ • R/R Ph- B-ALL • Refractory • **1st early relapse (< 12 months)** • Untreated second+ relapse • Any relapse after HSCT	• 18y+ • R/R CD22+ B-ALL • Refractory • Due for 1st or 2nd salvage therapy • **Ph-positive ALL if failing 2L TKI**	• R/R BCP-ALL • Refractory • 2nd relapse+ • 1st relapse after HSCT • No prior blinatumomab • **Ph-positive ALL if failing 2L TKI**	• 18y+ • R/R B-ALL • Refractory • **1st early relapse (< 12 months)** • 2nd relapse+ • **Ph-positive ALL allowed**
ORR rate	81% (vs 29%)	44% (vs 25%)	81%	71%
MRD response	78% (vs 28%)	76% (vs 48%)	100%	97%
Toxicity	Cytopenia/VOD	ICANS	CRS/ICANS	CRS/ICANS





Kantarjian, N Engl J Med. 2016 Aug 25;375(8):740-53
Katarjian H, N Engl J Med. 2017 Mar 2;376(9):836-847
Maude SL, N Engl J Med. 2018 Feb 1;378(5):439-448
Shah B, et al. Lancet. 2021 Jun 3;S0140-6736(21)01222-8

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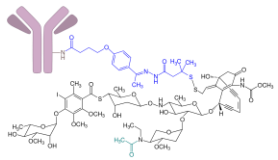
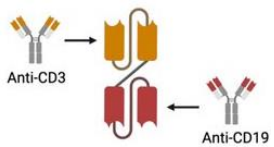
ORR rate	81% (vs 29%)	44% (vs 25%)		
MRD response	78% (vs 28%)	76% (vs 48%)		
Toxicity	Cytopenia/VOD	ICANS		

Access limited
to patients experiencing a 2nd relapse
due to specific marketing authorization indications
or reimbursement constraints





Kantarjian, N Engl J Med. 2016 Aug 25;375(8):740-53
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Maude SL, N Engl J Med. 2018 Feb 1;378(5):439-448
Shah B, et al. Lancet. 2021 Jun 3;S0140-6736(21)01222-8

Blinatumomab / Inotuzumab

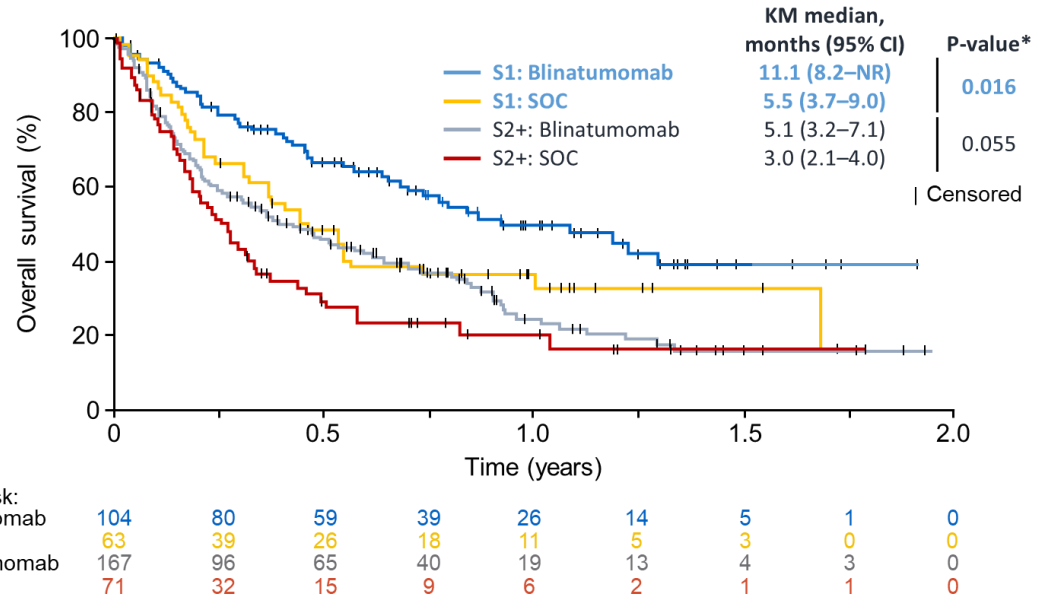
Single agent, first salvage

Blinatumomab / TOWER[1]

S1 : 104 Blina vs 63 SoC (2:1)

CR/CRh/CRi 51.0% vs 36.5% (p=.069)

MRD- 49.1% vs 39.1% (p=.53)

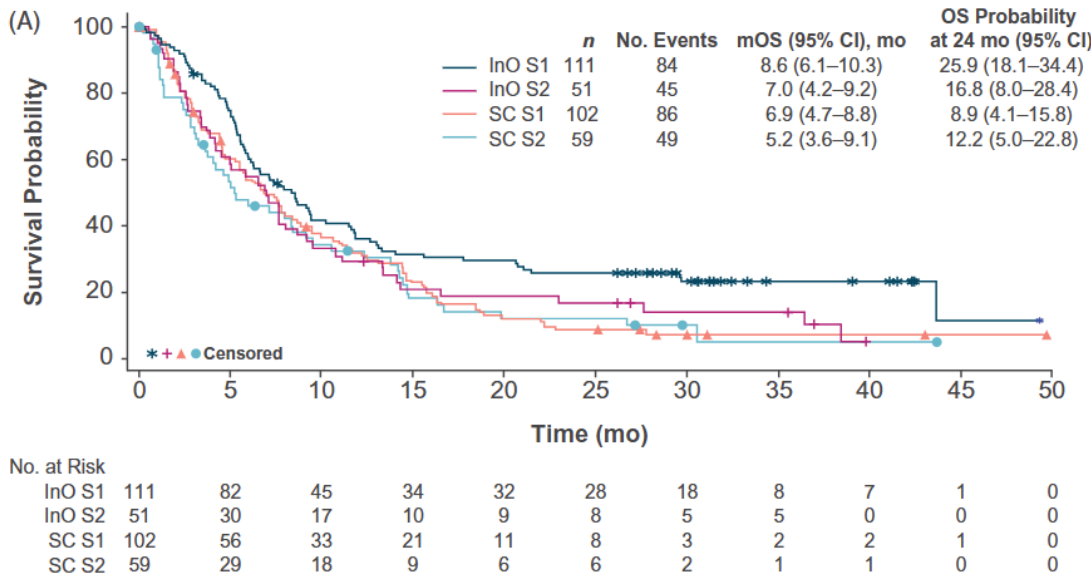


Inotuzumab / INO-VATE[2]

S1 : 111 Ino vs 102 SoC (1:1)

CR/CRi 78.4% vs 28.4% (p<.0001)

MRD- 77.0% vs 34.5% (NA)



- Greater benefit observed in first salvage
- Direct comparison complicated due to differences in eligibility criteria (+/- Ph-positive ALL, early or all 1st relapses…)

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1. Dombret H, et al. Leuk Lymphoma 2019;60:2214–22
2. Jabbour E, et al.Leuk Lymphoma. 2020 Aug;61(8):2012-2015

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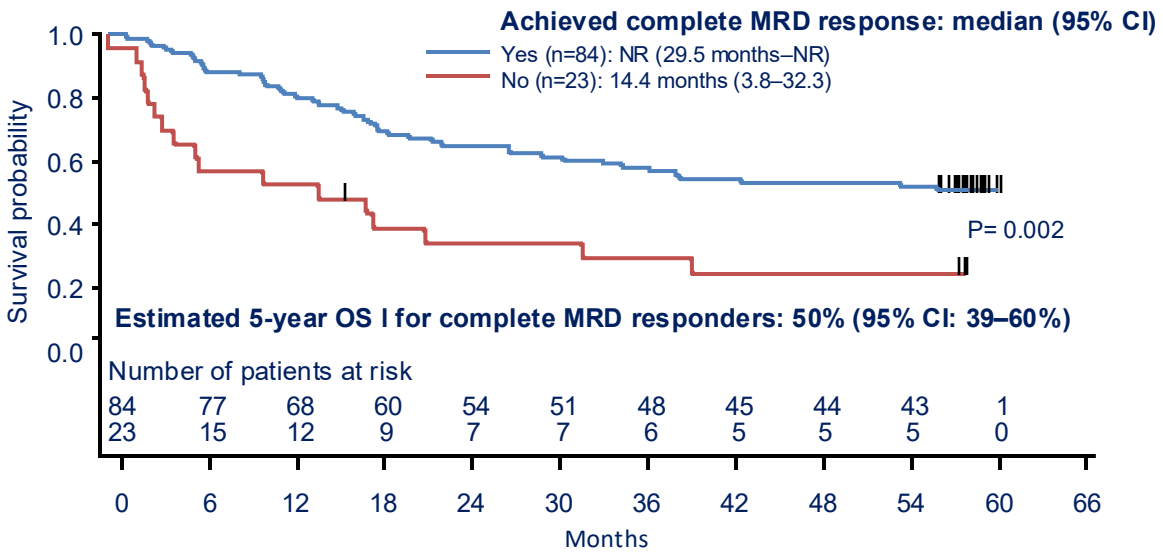
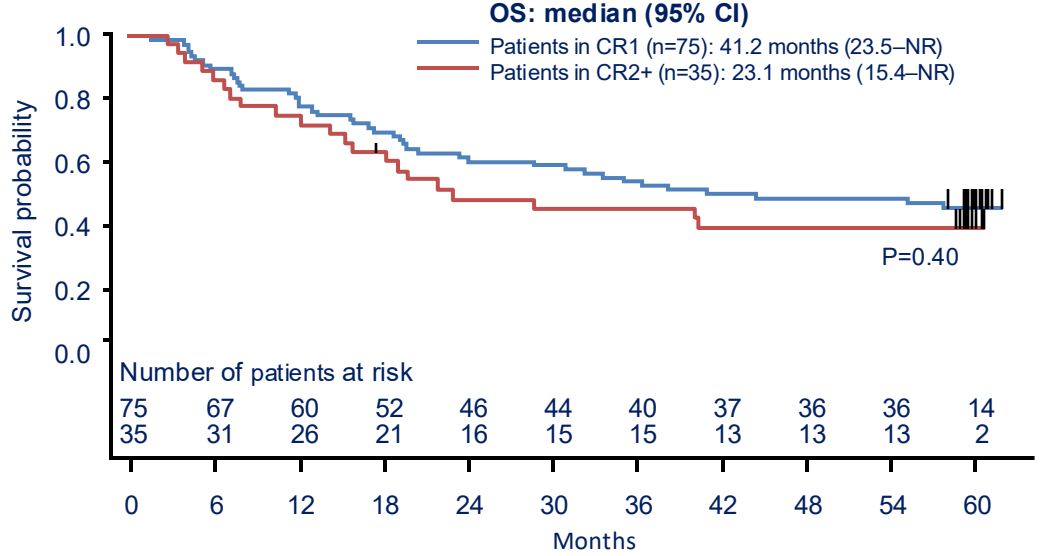
Blinatumomab for MRD+ B-ALL

Efficacy and safety outcomes

Overall Survival by complete MRD response[1]



Overall Survival by remission status at baseline[1]



- Better outcome for patients achieving a complete MRD response (80%, 95%CI[71-87] after cycle 1)
- Similar benefit in terms of OS for patients in CR1 or CR2+

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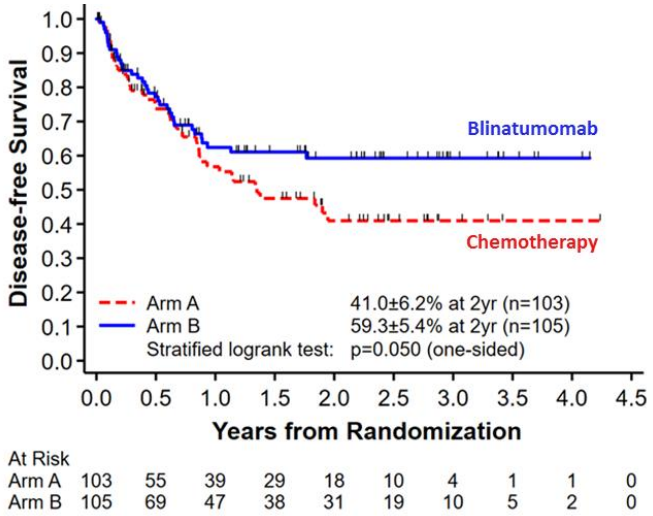
1. Gökbuget N, et al. Leuk Lymphoma 2020;61:2665–73
2. Gökbuget N, et al. Blood 2018;131:1522–31

Phase 3 consolidation in children and AYA

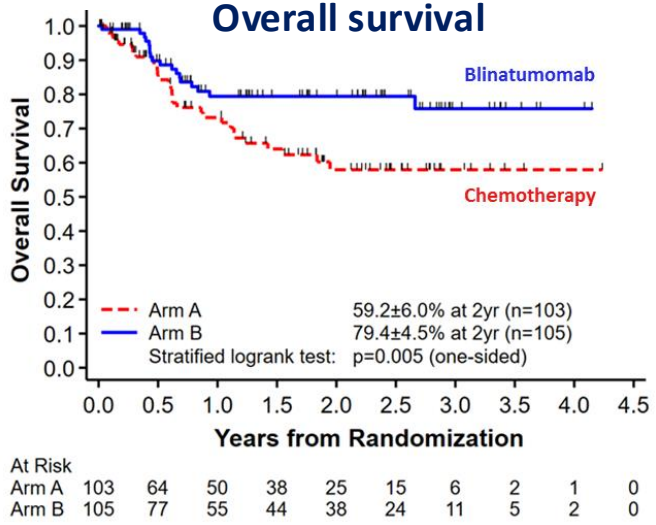
HR/IR Ph-negative B-ALL, 2nd CR

COG study AALL1331
HR/IR B-ALL
Children and AYA

Disease-free survival



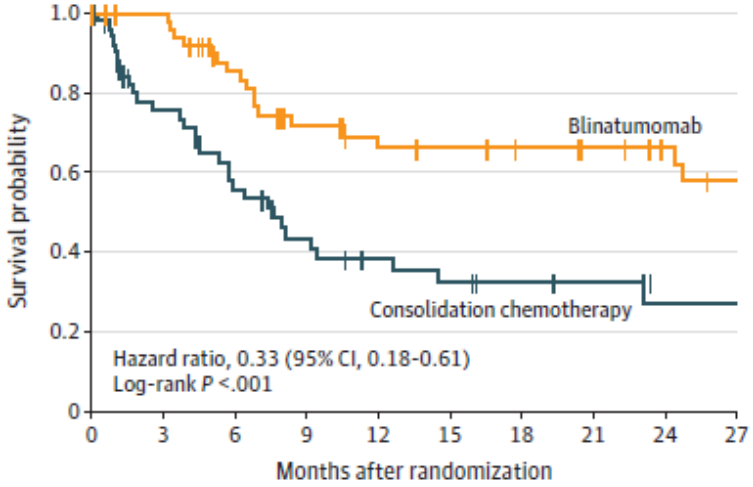
Overall survival



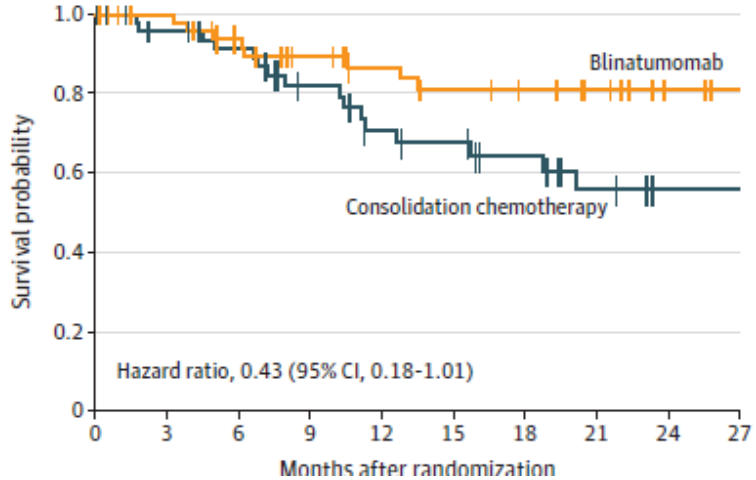
Brown PA, et al. JAMA. 2021;325(9):833-842.

Phase 3 study 20120215
HR B-ALL in first relapse
Children

Event-free survival



Overall survival



Locatelli F, et al. JAMA;325(9):843-854.

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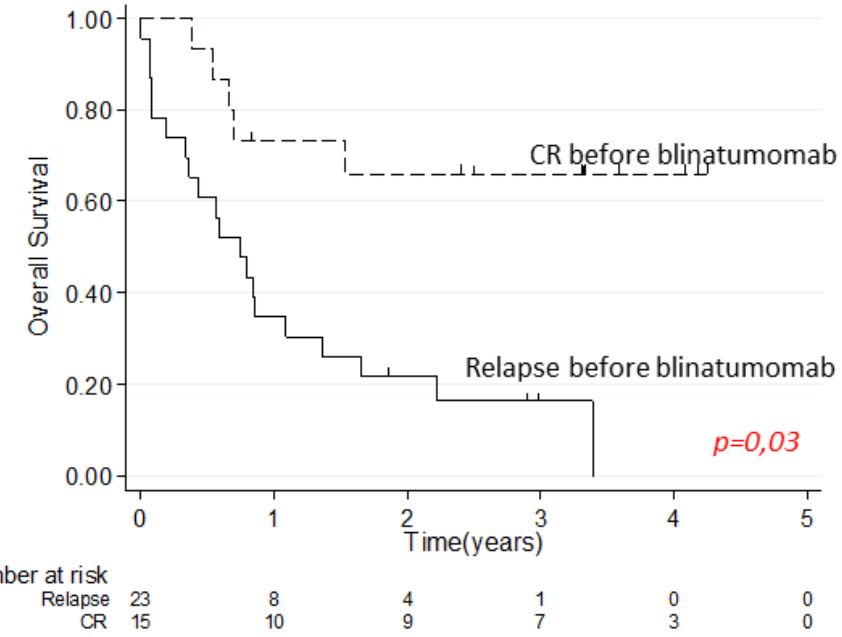
French RWE studies

Blinatumomab for R/R B-ALL

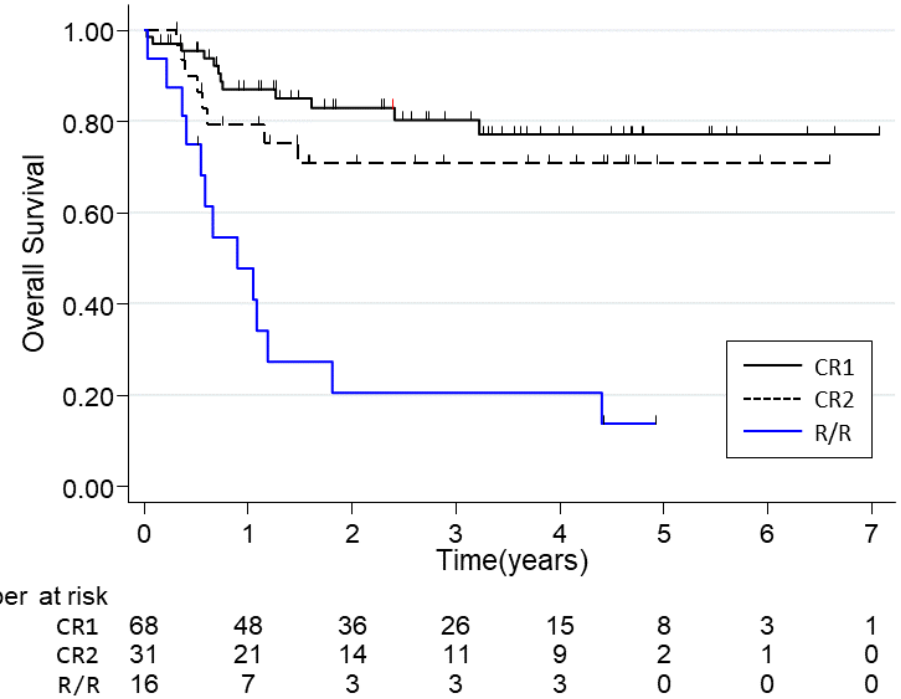
Compassionate use program, RWE[1]

Blinatumomab for salvage or consolidation (CR2+)



Saint-Louis Hospital, RWE[2]

Blinatumomab for CR1/CR2 consolidation



AlloHSCT CR1: 28/68 (41%)
CR2: 17/31 (55%)

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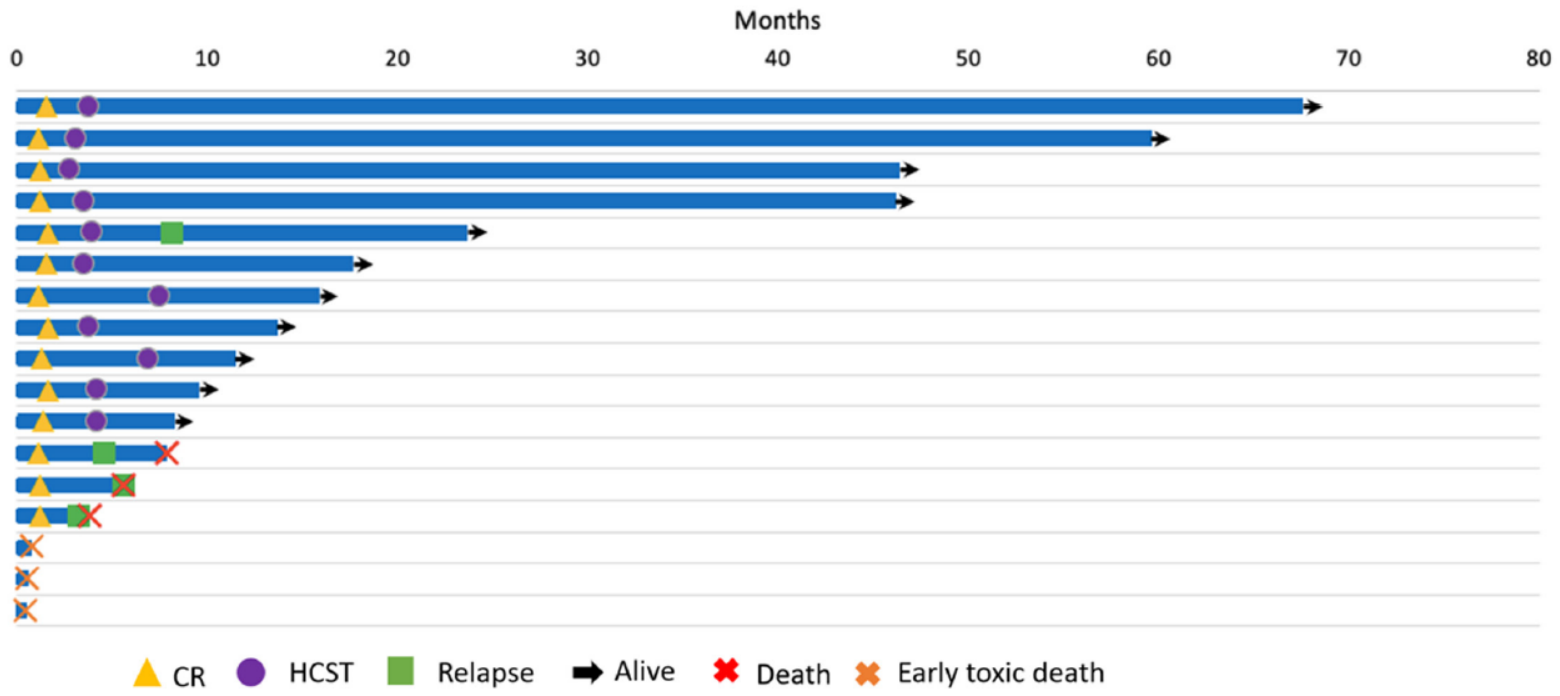
1. Cabannes-Hamy, et al. Haematologica. 2022 Sep 1;107(9):2072-2080
2. Urbino I, et al. Blood Adv. 2024 May 28;8(10):2405-2409

Debulking strategy in 1st relapse

VANDA + Blinatumomab (N=17)

- **Chemotherapy backbone:**
  - Dex D1-D6
  - HD-AraC BID D1-D2
  - VP16 D3-D5
  - Mitox D3-D4
  - PEG-Aspa D6 (age-adapted)
- **Blinatumomab**
  - 9 -> 28 microg/d D7-D28
- **Complete remission**
  - 14/17 (82%)
  - Complete MRD response 64%
- **Bridge to alloHSCT** : 65%



- **1-year OS:** 64.7% [95% CI 37.8–82.3]
- **1-year leukemia-free survival:** 58.8% [95% CI 32.5–77.8]
- Estimated 1-y LFS for transplanted patients= 90.9%

Heraudet L, et al. Br J Haematol. 2022 Aug;198(3):523-527.

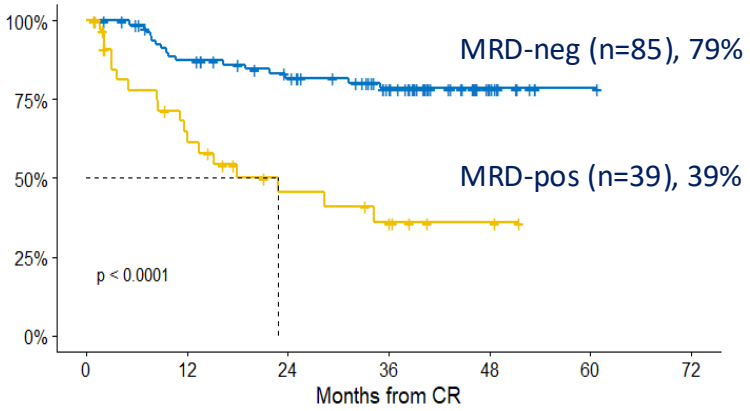
Blinatumomab

Determinants of response/escape

- **Tumor burden**
  - % blasts, MRD[1,2]
  - EM disease[3]
- **Genomic profile**
  - Heterogeneity of response/resistance unclear
  - Increased risk of CD19 loss : *KMT2A*, *ZNF384*, -16 ?
- **MRD response[1,4]**
- **Loss of CD19, lineage switch (10-35%)**
- **Others = Tumor/immune microenvironment**
  - % of T-regs[6]
  - T-cell exhaustion[4], PD1/PDL1 expression[5]
  - % of T-naive T-cells[4]
  - T-cell repertoire diversity[4]

GIMEMA LAL2317

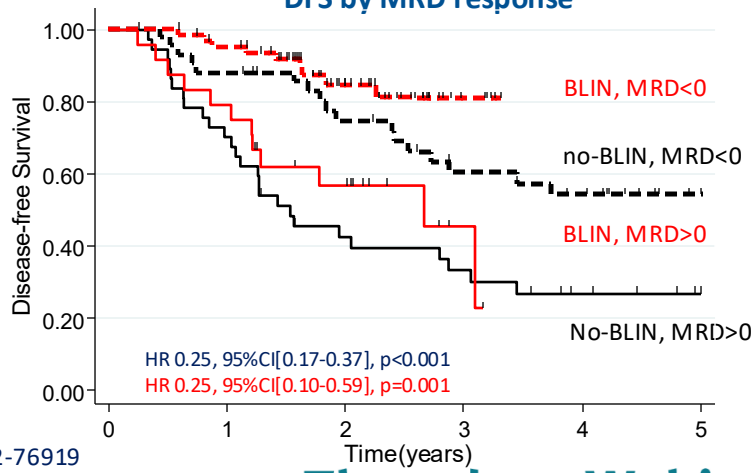
DFS according to pre-BLIN MRD[1]



GRAALL-2014

BLIN vs no-BLIN,

DFS by MRD response



1. Chiaretti S, et al. ASH 2023, #826
2. Queudeville M, et al. Cancer. 2023 May 1;129(9):1384-1393
3. Aldoss I, et al Cancer. 2022 Feb 1;128(3):529-535
4. Boissel N, et al. ASH 2023, #4349
4. Zhao Y. et al. Blood. 2021 Jan 28;137(4):471-484
5. Feucht J, et al. Oncotarget. 2016 Nov 22;7(47):76902-76919
6. Duell J, et al. Leukemia. 2017 Oct;31(10):2181-2190

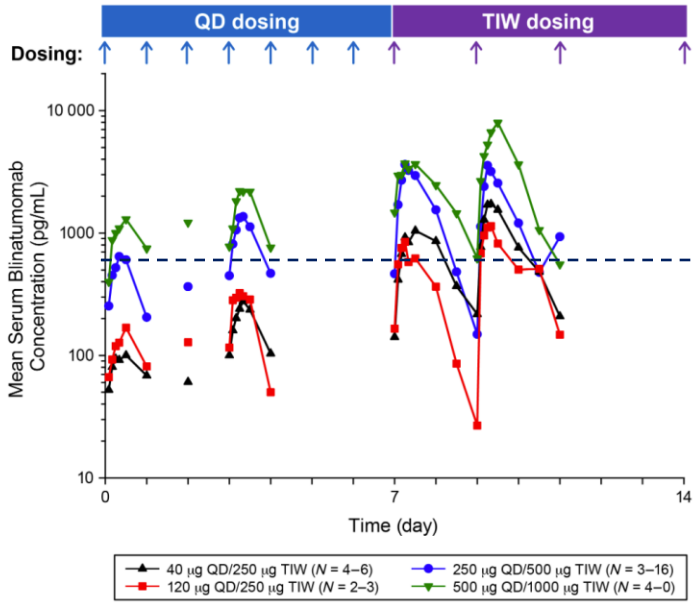
Blinatumomab SC

Expansion phase of phase Ib

- N=14+13 patients with R/R B-ALL
- Week 1 QD, Week 2-4 TIW
- Two dosing schedules 250/500 and 500/1000µg

Pharmacokinetics

½-life: 8-12h vs 2h for cIV



Mean serum steady-state concentration at 28 µg/d cIV 667 pg/mL

Overall response

Response category	250 µg/500 µg dose (*N* = 14)	500 µg/1000 µg dose (*N* = 13)
CR	10 (71.4)	12 (92.3)
CRh	2 (14.3)	0
CR/CRh	12 (85.7)	12 (92.3)
MRD-negative in patients with CR/CRh	9 (75.0)	12 (100.0)
Not evaluated	2 (14.3)	1 (7.7)

Safety profile

Adverse event	250 µg/500 µg (*N* = 14) No. of patients (%)	500 µg/1000 µg (*N* = 13)
Any grade adverse events	14 (100.0)	12 (92.3)
Adverse events related to SC blinatumomab		
Serious adverse event	9 (64.3)	10 (76.9)
Fatal adverse event	0	0
Grade ≥3 adverse events	12 (85.7)	8 (61.5)
Leading to discontinuation of treatment	2 (14.3)	1 (7.7)
Grade ≥3 adverse events of interest		
Cytokine release syndrome	3 (21.4)	3 (23.1)
Neurologic event	6 (42.9)	3 (23.1)

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Jabbour E, et al. Am J Hematol. 2024 Apr;99(4):586-595.

Inotuzumab for MRD+ B-ALL

MDACC Phase 2

Patients characteristics

Characteristics N (%) / median [range]	Full Cohort N = 26
Age (years)	46 [19-70]
Sex	
Males	12 (46)
Females	14 (54)
Remission status	
CR1	19 (73)
≥ CR2	7 (27)
Prior therapy	
Blinatumomab	13 (50)
ASCT	5 (19)
CAR-T cells	1 (4)
Ph-positive ALL	16 (62)
Pre-inotuzumab MRD	
MFC (%)	0.03 [0-1.24]
BCR::ABL1 (%)	0.22 [0-18.97]
CD22 on flow MRD	96.6 (62.9-99.9)

Treatment schedule

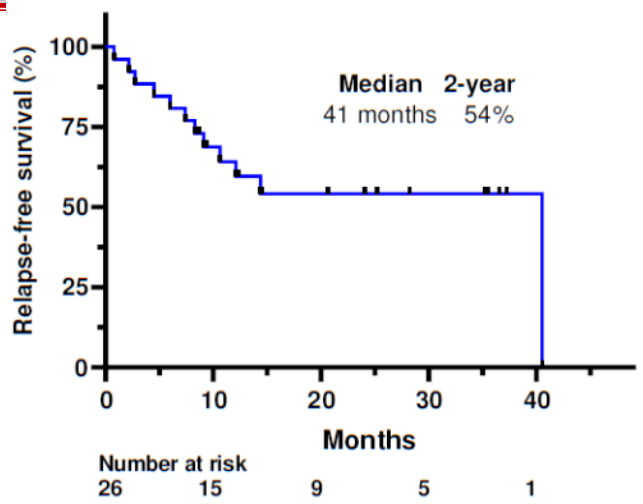
- C1: 0.6mg/m2 D1, 0.3mg/m2 D8
- C2-6: 0.3mg/m2 D1 and 8

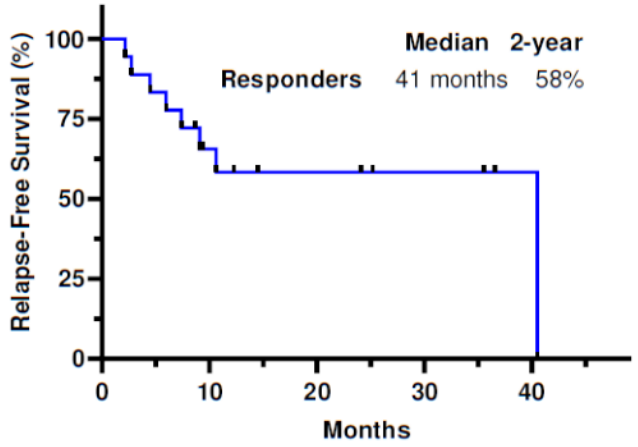
Response

- 18/26 (69%) conversion to MRD- status
- 89% of conversion after C1
- 6/18 (33%) bridge to transplant

Safety

- AST/ALT elevation: 70%, G3+ 8%
- VOD: 8%, G3+ 4%
- Neutropenia: 35%, G3+ 27%
- Thrombocytopenia: 65%, G3+ 35%





Jabbour E, et al. Blood. 2024 Feb 1;143(5):417-421

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Mini-HCVD + Ino ± blinatumomab for R/R B-ALL

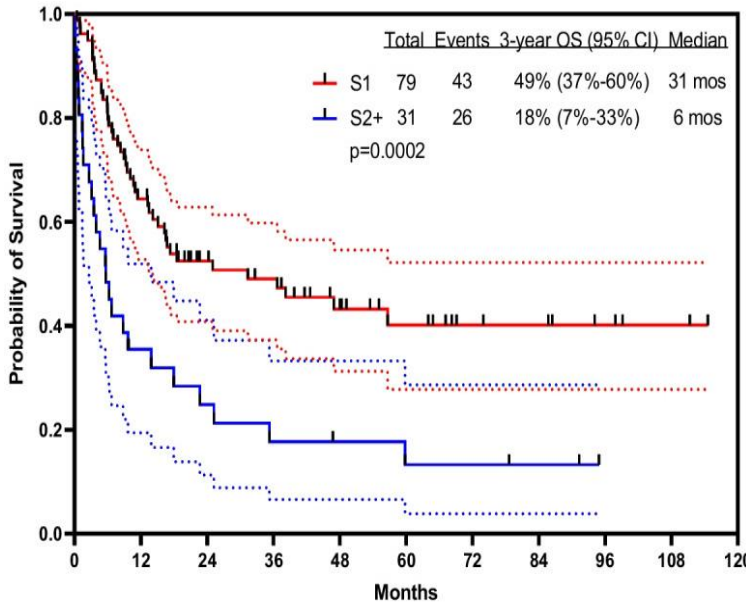
MDACC Phase 2

- **Median age :** 37y (17-87)
- **High risk cytogenetics :** 20%
- **Prior alloHSCT :** 19%
- **Salvage 1 :** 72% (79/110)

Response for S1 :

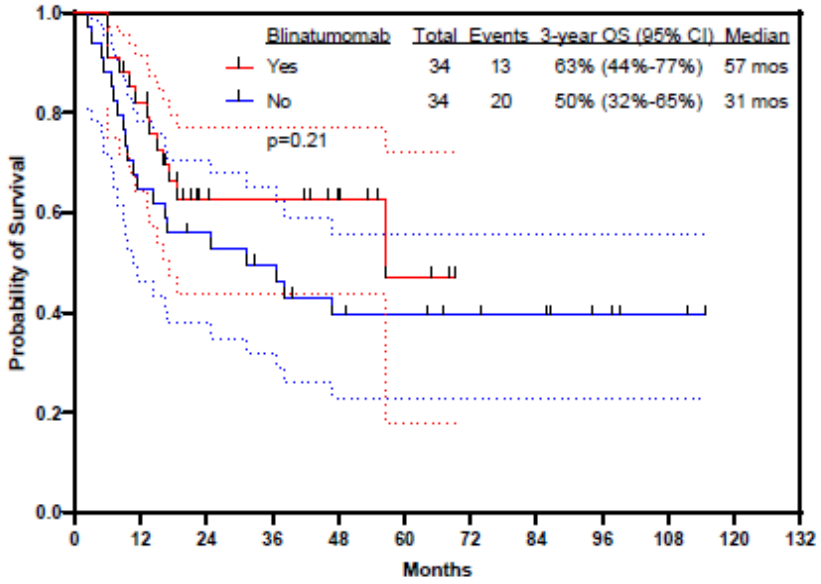
- **ORR (CR/CRi/CRp) :** 92%
- **MRD- response :** 89%

Overall survival according to salvage (S1 vs S2+)



AlloHSCT in S1/S2+ : 48% (53/110)

Overall survival according to blinatumomab In S1



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Kantarjian H, et al. J Hematol Oncol. 2023 May 2;16(1):44

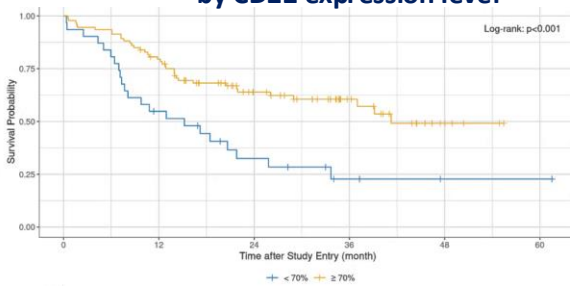
Inotuzumab ozogamicin

Determinants of response/escape

- **Limited impact of tumor burden**
  - R/R, MRD[1,2]
- **CD22 expression level**
  - Lower response rate if low expression[3]
- **Disease genomic profile[3,4]**
  - Similar as chemotherapy (?)
- **MRD response[3]**
- **Others = "payload"-related[5]**
  - Calicheamycin induces DNA double-strand breaks
  - Acquired mutations of *TP53*, *ATM*, *CDKN2A*
  - Hypermutation -> CD22 loss of expression
  - Drug efflux

EWALL-Ino (n=131)
Overall survival

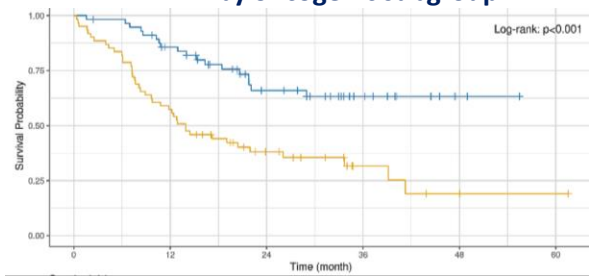
by CD22 expression level



CD22≥70%

CD22<70%

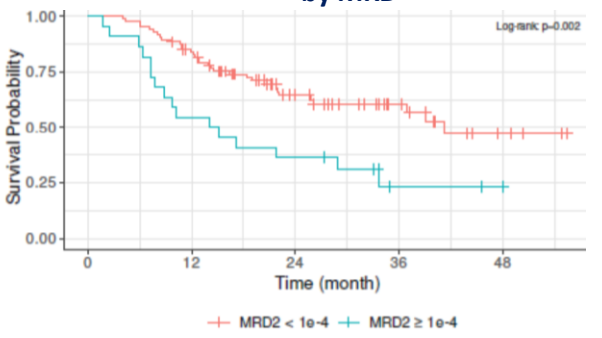
by oncogenic subgroup



Standard-risk

High-risk*

by MRD



MRD<10^{-4}

MRD≥10^{-4}

* low hypodiploidy/near triploidy, complex karyotype (defined as ≥5 abnormalities), 11q23/*KMT2A*-r, *MYC*-r

1. DeAngelo DJ, et al. Blood Cancer J. 2020 Aug 7;10(8):81
2. Jabbour E, et al. Blood. 2024 Feb 1;143(5):417-421
3. Chevallier P, et al. J Clin Oncol 2024 Oct 17:JCO2400490
4. Zhao Y, et al. Blood Adv. 2024 Jun 25;8(12):3226-3236
5. Zhao Y, et al. Blood 2024 Jul 4;144(1):61-73

Approved autologous CD19-CAR-Ts in R/R B-ALL

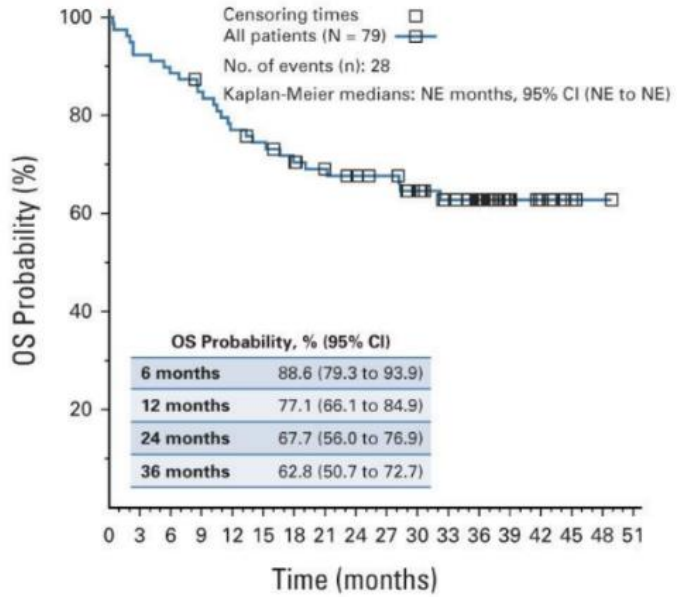
	Tisa-cel	Brexu-cel	Obe-cel
Target	**CD19**	**CD19**	**CD19**
Construct	**4-1BB / CD3z**	**CD28 / CD3z**	**Fast off-rate anti-CD19 / 4-1BB / CD3z**
Indication	<26y 2nd relapse 1st relapse postHSCT	>25y R/R B-ALL (EU)	>17y R/R B-ALL (US only)
Pivotal study	**ELIANA**	**ZUMA-3 (I/II)**	**FELIX**
N, % infused	92 (82%)	99 (79%)	153 (83%)
ORR rate	82%	74%	78%
MRD response	100% (MFC)	97% (MFC)	84% (NGS)
CRS	46%	24%	2.4%
ICANS	13%	25%	7.1%
Ongoing CR w/o further therapy	48%	12%	40%

Maude SL, at al. N Engl J Med. 2018 Feb 1;378(5):439-448
Shah BD, et al. Lancet 2021;398:491–502
Jabbour E, et al. ASCO 2024

Approved CD19-CAR-Ts in ALL

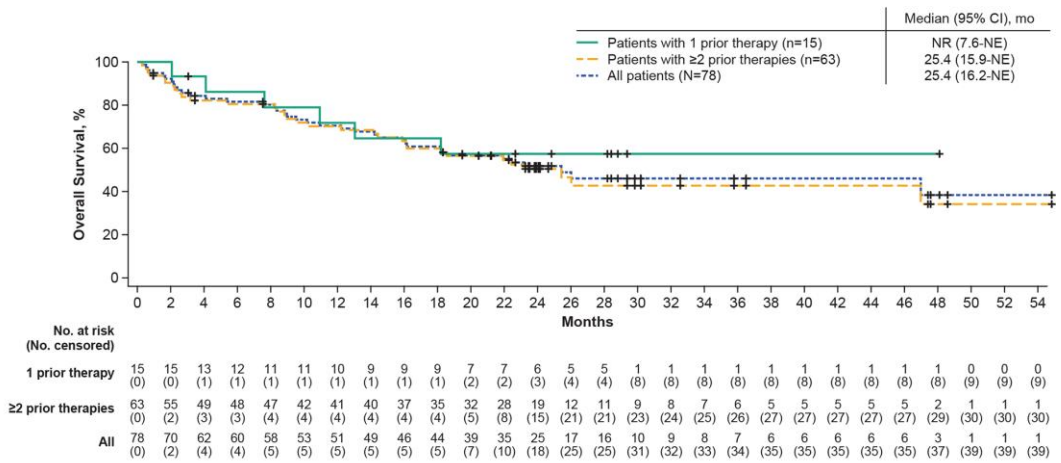
Long-term overall survival

ELIANA study
R/R B-ALL
3–21 years
CD19/4-1BB/CD3z



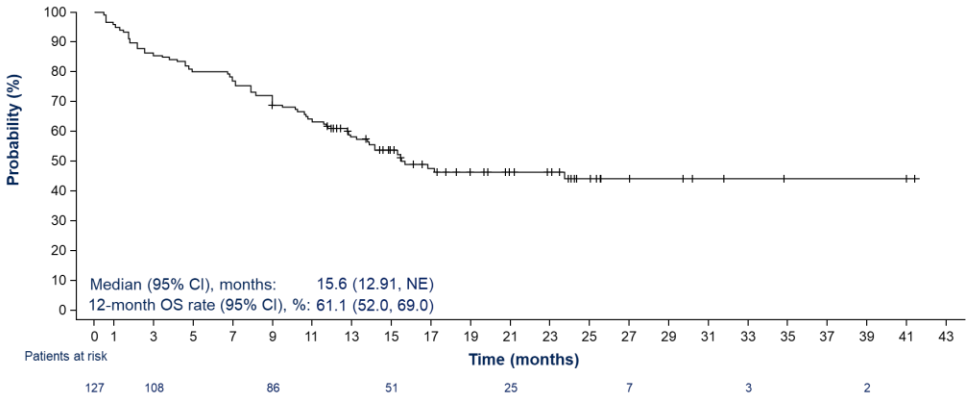
Median follow-up:
21.5 months (range: 8.6–41.4)

ZUMA-3 study
R/R B-ALL
18 years+
CD19/CD28/CD3z



Median follow-up:
29.7 months (range: 20.7–58.3)

FELIX study
R/R B-ALL
18 years+
CD19*/4-1BB/CD3z



Median follow-up:
21.5 months (range: 8.6–41.4)

1. Laetsch TW, et al. J Clin Oncol. 2023 Mar 20;41(9):1664-1669
4. Shah BD, et al. EHA 2023
3. Jabbour E, et al. ASCO 2024

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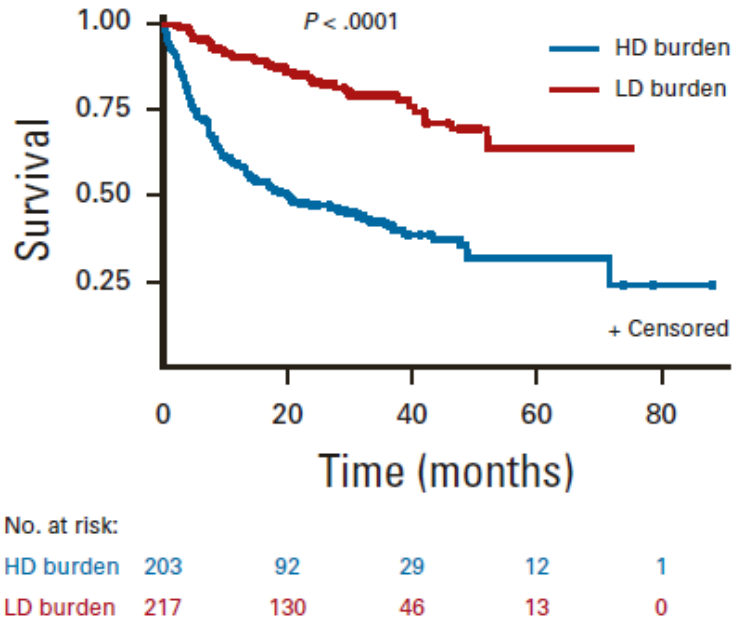
Thursdays Webinars

Prognosis of high tumor burden

US cohort
(N=420, Tisacel & other C19-CAR)[1]

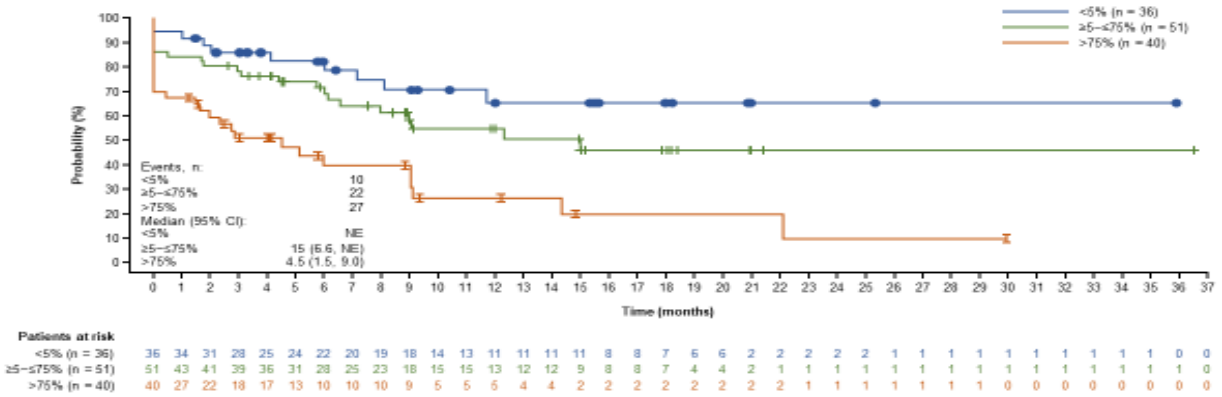


No. at risk:

HD burden	203	92	29	12	1
LD burden	217	130	46	13	0

FELIX study[2]
R/R B-ALL
18 years+
CD19*/4-1BB/CD3z

Event-free survival



BM blasts % prior to lymphodepletion	<5% (n = 36)	≥5–≤75% (n = 51)	>75% (n = 40)
Median EFS (95% CI), months	NE	15.0 (6.6, NE)	4.6 (1.5, 9.0)
6-month EFS (95% CI), %	82 (65, 92)	72 (57, 82)	40 (23, 56)
12-month EFS (95% CI), %	65 (44, 80)	55 (38, 69)	27 (12, 44)

- Safety impact : CRS, ICANS, Infection, ICAHT
- Prognosis :
  - ↓EFS, ↓OS
  - CD19-negative relapses
- Limited data on the impact of debulking & best blast cut-off

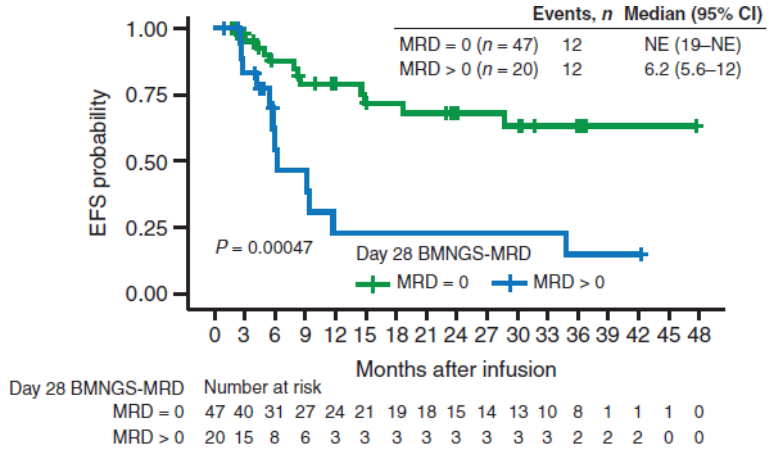
1. Myers RM et al., J Clin Oncol. 2022 Mar 20;40(9):932-944
2. Roddie C. et al, ASH 2023, #222

Prognosis of early MRD response

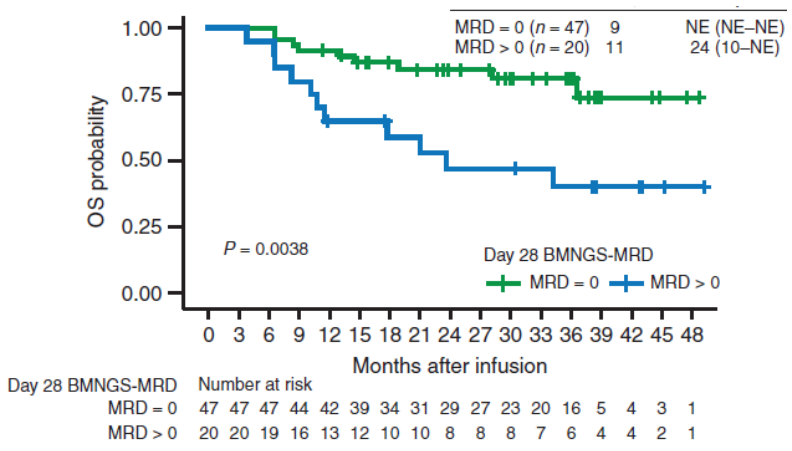
by qPCR or NGS

- **ELIANA + ENSIGN**[1]
  - N=109, Tisacel
  - D28 MRD (NGS) > 0 in 30%

Event-free survival



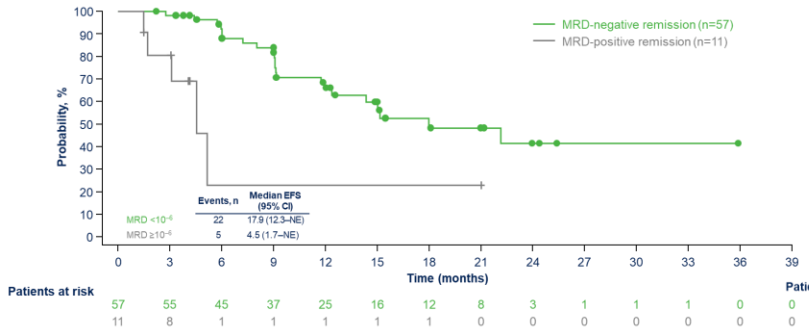
Overall survival



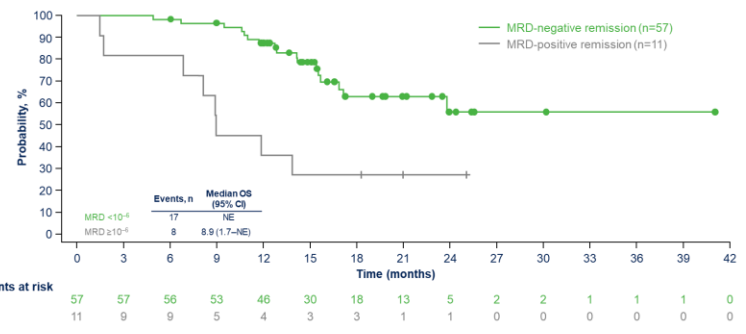
FELIX study[2]
R/R B-ALL
18 years+
CD19*/4-1BB/CD3z

- 1+ post-infusion sample 68/73 (93%)
- MRD (NGS) > 0 in 16%

Event-free survival



Overall survival



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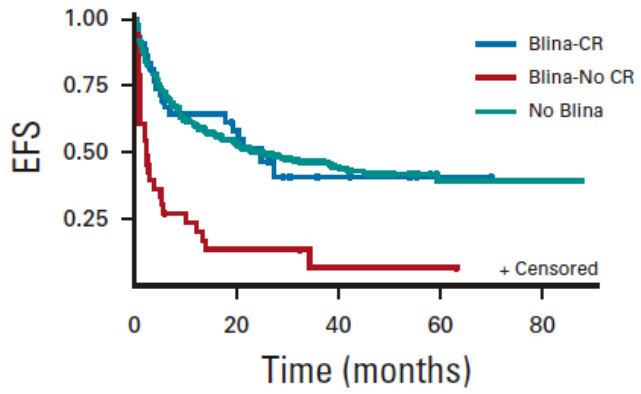
1. Pulsipher M et al., Blood Cancer Discov. 2022 Jan;3(1):66-81
2. Jabbour E et al., ASH 2024, #963

Prognosis of prior exposure to blinatumomab

US cohort
(N=420, Tisacel & other C19-CAR)[1]
Event-free survival



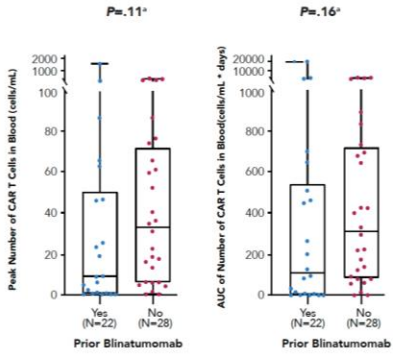
No. at risk:

Blina-CR	43	18	4	1	0
Blina-No CR	34	4	1	1	0
No Blina	343	143	48	16	1

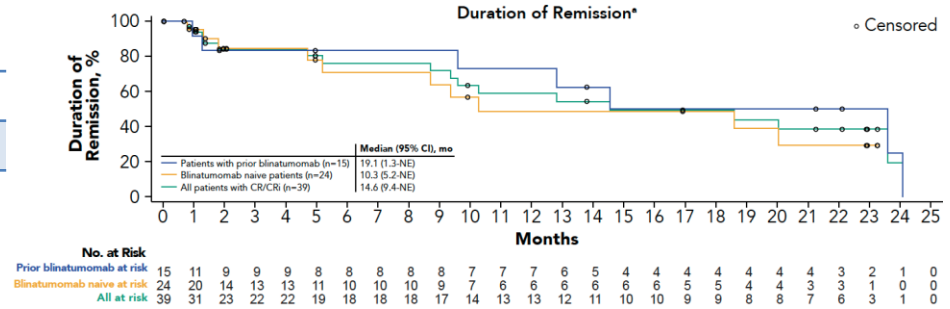
CR/CRi rate

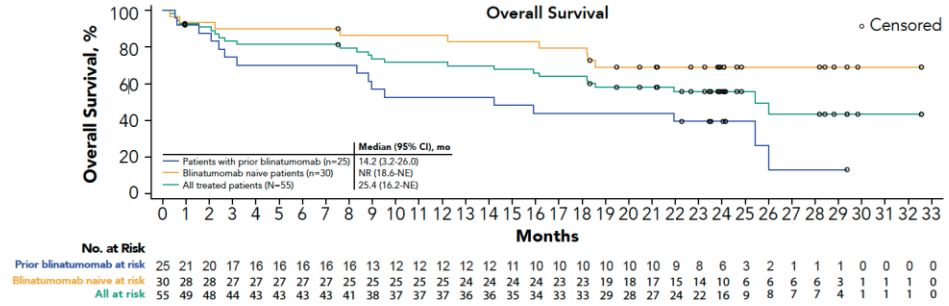
Prior Blin	Blin naive
15/25 (60%)	24/30 (80%)

CAR-T Cmax and AUC



ZUMA-3 study[2,3]
R/R B-ALL
18 years+
CD19/CD28/CD3z





- Blin indication : mostly R/R
- Higher risk of early failure, shorter EFS and OS in patients with prior failure to blinatumomab

1. Myers RM et al., J Clin Oncol. 2022 Mar 20;40(9):932-944
2. Shah et al. J Immunother Cancer. 2023 Aug;11(8):e007118
3. Shah et al. EHA 2022 Abstract #P356

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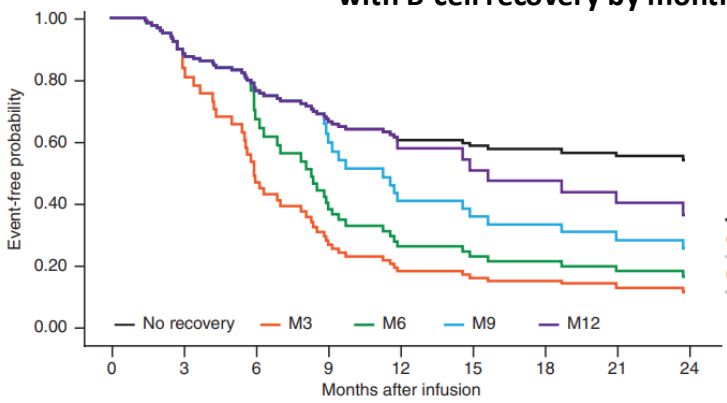
Thursdays Webinars

Prognosis of CAR-T persistence

- B-cell aplasia :
  - a surrogate of CAR-T persistence/function
  - a time-dependent event
- Loss of B-cell aplasia associated with an increased risk of CD19-positive relapse[1,2]
- CD19-negative relapses tend to occur earlier than CD19-positive relapses[1,3]
- **Consequences :**
  - Normal B-cell count is part of patient monitoring
  - Best duration cut-off for intervention = 6 months ?

ELIANA + ENSIGN[1]
(N=109, Tisacel)

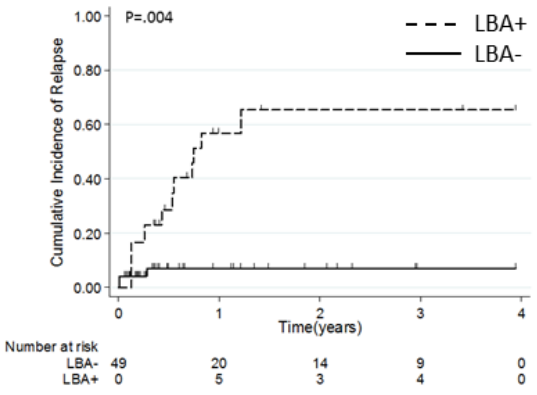
Adjusted EFS curves for patients with B-cell recovery by months 3 to 12



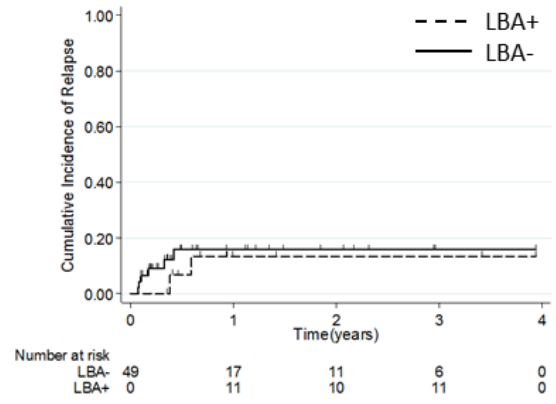
CD19 status at relapse	B-cell status: B-cell recovery	B-cell status: B-cell aplasia
CD19⁻	3 (12%)	22 (88%)
CD19⁺	11 (78%)	3 (22%)

French cohort[2]
(N=51, Tisacel)

CIR, CD19^{pos} relapses



CIR, CD19^{neg} relapses



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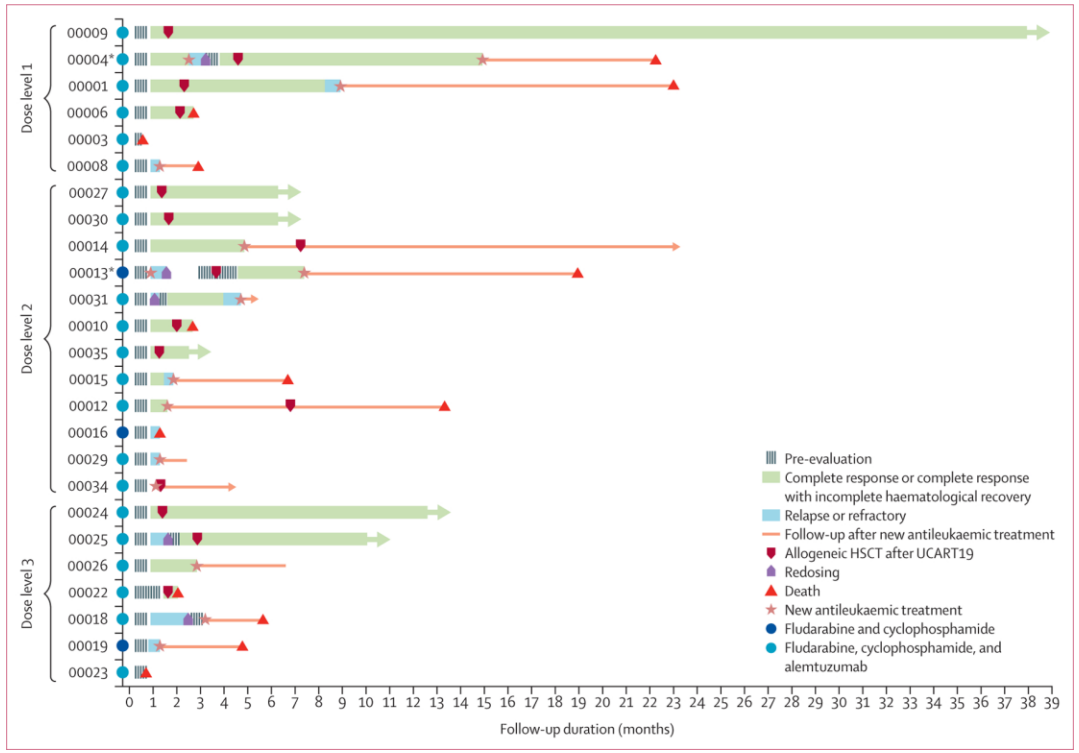
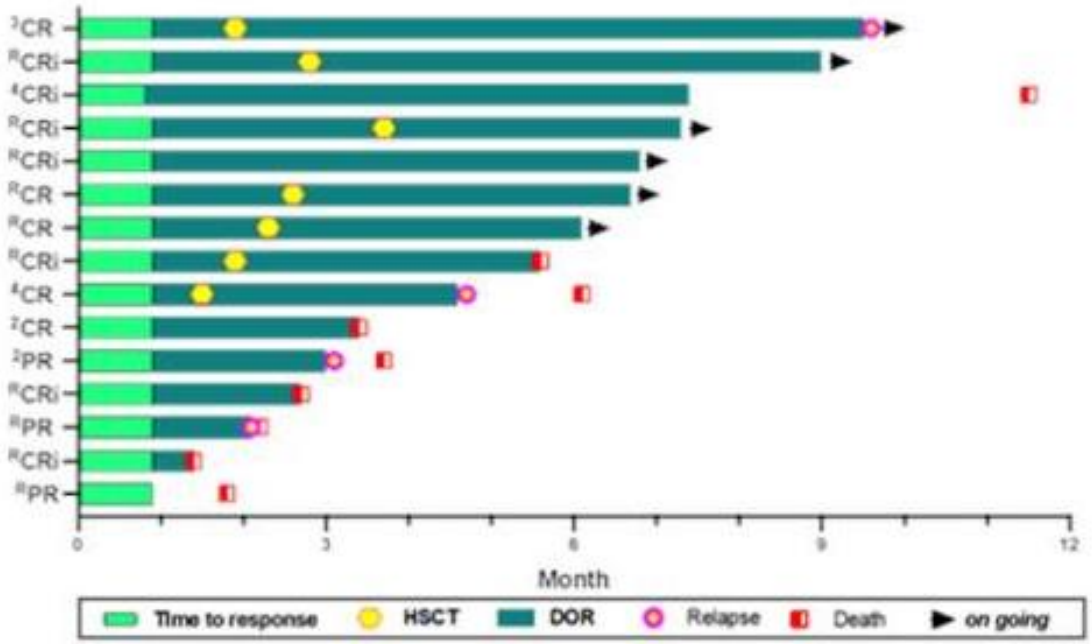
1. Pulsipher M, et al. Blood Cancer Discov. 2022 Jan;3(1):66-81
2. Dourthe ME, et al. Leukemia. 2021 Dec;35(12):3383-3393
3. Hay KA, et al. Blood. 2019 Apr 11;133(15):1652-1663.

Allogeneic CAR-T cells

UCART019[1]



WU-CART-007[2]



- 11 patients alive at the time of database lock,
- 5 with ongoing response after a single UCART19 infusion
- All after allogeneic HSCT

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1. Benjamin R, et al. Lancet Haematol. 2022 Nov;9(11):e833-e843
2. Ghobadi A, et al.. Res Sq [Preprint]. 2024 Aug 5:rs.3.rs-4676375

Determinents of disease progression

	CD19- relapse	CD19+ relapse
Patient age	-	-
Disease characteristics	-*	-
Prior therapy	**Blinatumomab**	-
Tumor burden before LD	**High**	Low ?
CRS (steroids, anti-IL6…)	**+**	-
Response at D28	**MRD+**	-
CAR T expansion	**High**	**Low**
B-cell recovery	**No**	**Yes (<6 months ?)**

- Discuss intervention (**HSCT**, targeted therapy, CAR T…)
- based on patient history and risk of CD19- escape

** Excess of lineage switch reported in specific subgroups*

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1. Dourthe ME, et al. Leukemia. 2021 Dec;35(12):3383-3393
2. Myers RM, et al. J Clin Oncol. 2021 Nov 12
3. Pulsipher M, et al. Blood Cancer Discov. 2022 Jan;3(1):66-81
4. Leahy AB, et al.Blood. 2022 Apr 7;139(14):2173-2185.

Blinatumomab frontline

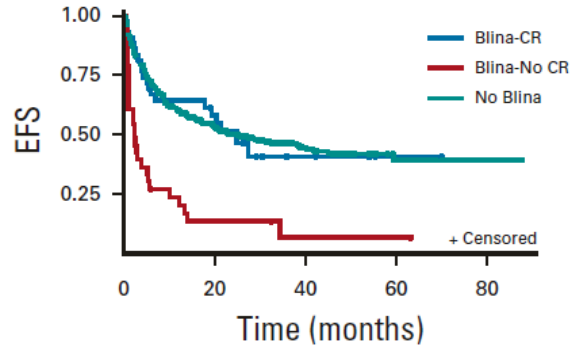
Consequences

- Modification of relapse profile
  - CNS/EM relapses
  - Loss of CD19 target, lineage switch
  - Other immune escape mechanisms ?
    - ➢ **Efficacy for subsequent CD19-targeted therapy ?**
- Decrease alloHSCT indication in CR1
  - ➢ **Opportunity to consolidate with alloHSCT in CR2**
- Modification of TME
  - T-cell repertoire / fitness / exhaustion
    - ➢ **Hypothetical impact on subsequent immunotherapy**

Ph+ ALL
Site of relapse after blinatumomab + TKI[1,2]
***versus* chemotherapy + TKI[3]**

	MDACC Blin+Pona	D-ALBA Blin+Dasa	GRAAPH-2014 Chemo+Nilo
	N=62	N=62	N=264
BM	2 (33%)	4 (44%)	47 (92%)
iCNS	3 (50%)	4 (44%)	3 (6%)
iEM	1 (17%)	1 (11%)	1 (2%)

Impact of prior exposure to BLIN on CD19CAR-T efficacy[4]



No. at risk:

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Blina-No CR	34	4	1	1	0
No Blina	343	143	48	16	1

1. Haddad FG, et al. ASH2023, #2827
2. Foà R, et al. J Clin Oncol. 2024 Mar 10;42(8):881-885
3. Chalandon Y, Blood Blood. 2024 Jun 6;143(23):2363-2372
4. Myers RM et al., J Clin Oncol. 2022 Mar 20;40(9):932-944

Take home messages
R/R B-ALL in adults

- The most important prognostic factor at relapse is **CR1 duration**
- **Combining chemotherapy and immunotherapies** in first relapse shows promising outcomes
- **Blinatumomab** is preferred for patients with debulked disease
- **Inotuzumab** achieves high response rates but bears the safety profile of calicheamycin
- **CAR-T cells** are promising, yet the consequences of prior exposure to blinatumomab (including frontline) remains to be explored

Thank you
for your attention !