The Role of Immunotherapy in the Treatment of Acute Lymphoblastic Leukemia: **First Line**

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Tercera edición

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Relapse/Refractory Acute Lymphoblastic Leukemia (r/r ALL)

Prognosis of r/r ALL is poor

- Immunotherapy in chemo-resistant disease has proven clinical benefit
  - Redirecting T-cells against leukemia antigen surface molecules (e.g.CD19)
  - **Approved indications in r/r BCP-ALL:**

BITEs (CD19-CD3)

-Blinatumomab

CD19 CAR T-cells

→ **Tisa-cel:** children and YA (<26 yr):

→ **ARI-0001-cells** (Barcelona academic CAR19 T-cell): adults >25 yr (under hospital exemption)*

→ **Brexu-cel** (KTE-X19): adults ≥18 yr:

*Approved by the Spanish Medical Agency AEMPS, under hospital exemption at Hospital Clínic Barcelona

EMA Approved indications of BITEs and CAR T-cells in ALL

Blinatumomab

- Adults
  - CD19+ Ph neg r/r ALL or MRD ≥0.1%
  - CD19+ Ph pos r/r ALL after failure ≥2 TKI
- Children >1 yr of age
  - CD19+ Ph neg r/r ALL after ≥2 lines of therapy
  - CD19+ Ph neg high risk relapse as consolidation treatment
  - NOT yet approved in MRD+ (FDA approved)

Tisagenlecleucel

- Pediatric and young adults (<26 yr) CD19+ ALL
  - 2nd or greater relapse
  - Relapse after HSCT
  - Refractory/relapse after ≥2 lines of therapy

Activity of Blinatumomab in ALL. The present

Type of ALL	Ph-pos R/R adults	Ph-pos 1st line adults	Ph-neg R/R adults		MRD + adults	Ph-neg R/R children	Ph-neg R/R children	Ph-neg 1st relapse children
Study	**Pivotal Phase II ALCANTARA**	**Plase II D-ALBA[1]**	**Confirm Phase II**	**Phase III TOWER**	**Phase II BLAST**	**Phase I/II Study 205**	**Phase II Exp. access RIALTO**	**Phase III AALL1331 COG**
Patients (N)	45	63	189	271[2]	116	70	98	105[2]
CR/CRh/CRi (%)	36	92	43	45	NA	39	60	-
MRD level <0.01%	88	58	82	76	78	54	76	66
OS, median, mo	7.1	NA (94%, 1y)	6.1	7.7	36	7.5	13	NA (79%, 2y)

Slide Courtesy of Prof. Ribera

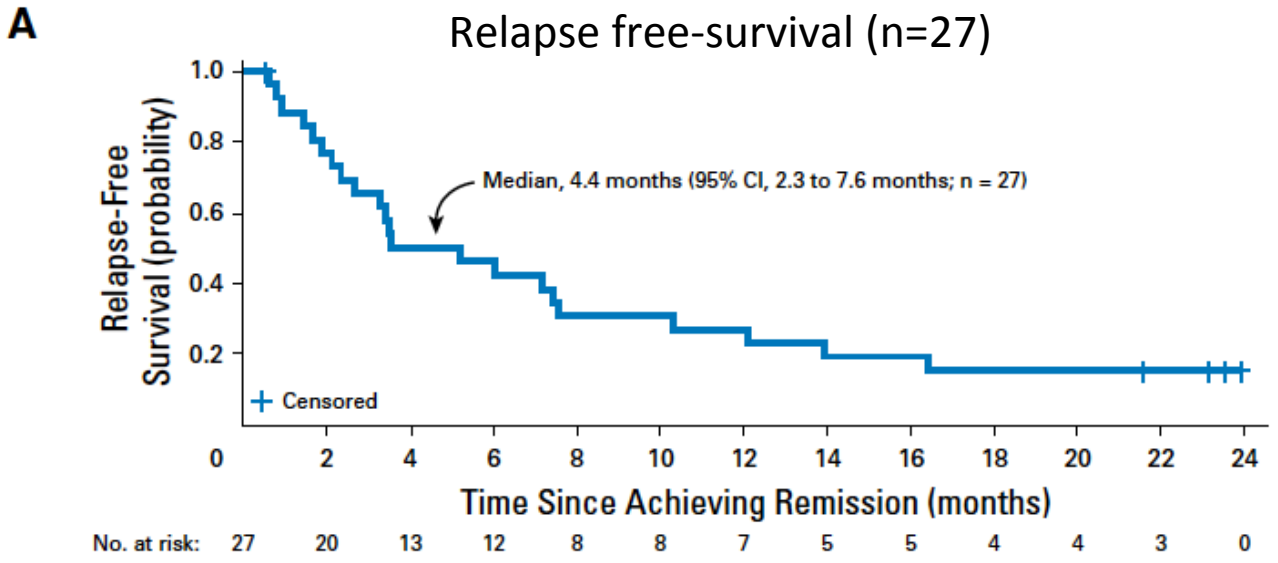
[1] Dasatinib and blinatumomab; [2] Patients randomized to blinatumomab

Blinatumomab in pediatric advanced r/r ALL (monotherapy)

n= 70 patients

Advanced r/r ALL*, >25% blasts in BM

- **CR rate: 39%** (52% MRD neg)
- Median RFS: 4.4 months
- Median RFS patients MRD neg: 7.3 months
- RFS at 6 months: 42%



Stackelberg A et al. J Clin Oncol 2016

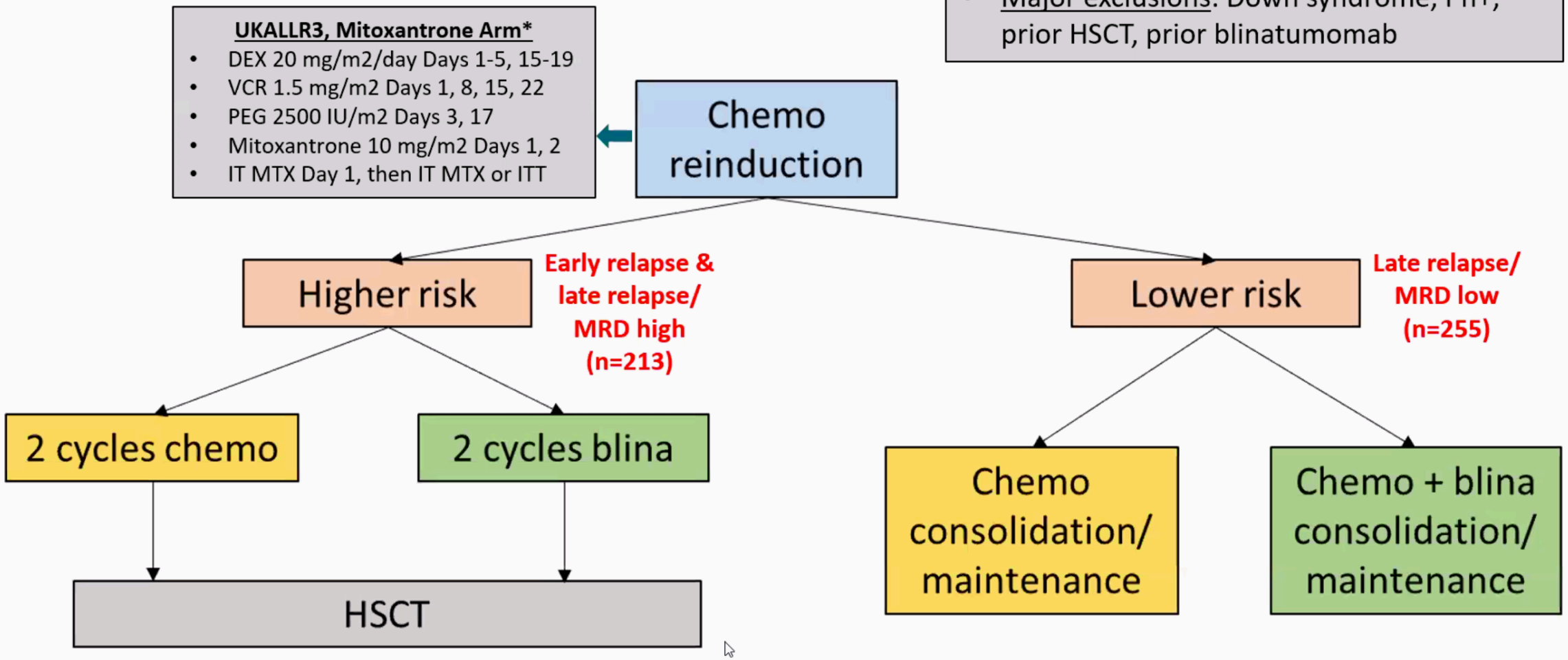
*Refractory ALL, 1st relapse refractory to induction, 2nd or greater relapse, relapse after HSCT

AALL1331: "Big Picture"

- All first relapse (any CR1 duration, any site)
- Ages 1-30
- Major exclusions: Down syndrome, Ph+, prior HSCT, prior blinatumomab

UKALLR3, Mitoxantrone Arm*

- DEX 20 mg/m2/day Days 1-5, 15-19
- VCR 1.5 mg/m2 Days 1, 8, 15, 22
- PEG 2500 IU/m2 Days 3, 17
- Mitoxantrone 10 mg/m2 Days 1, 2
- IT MTX Day 1, then IT MTX or ITT

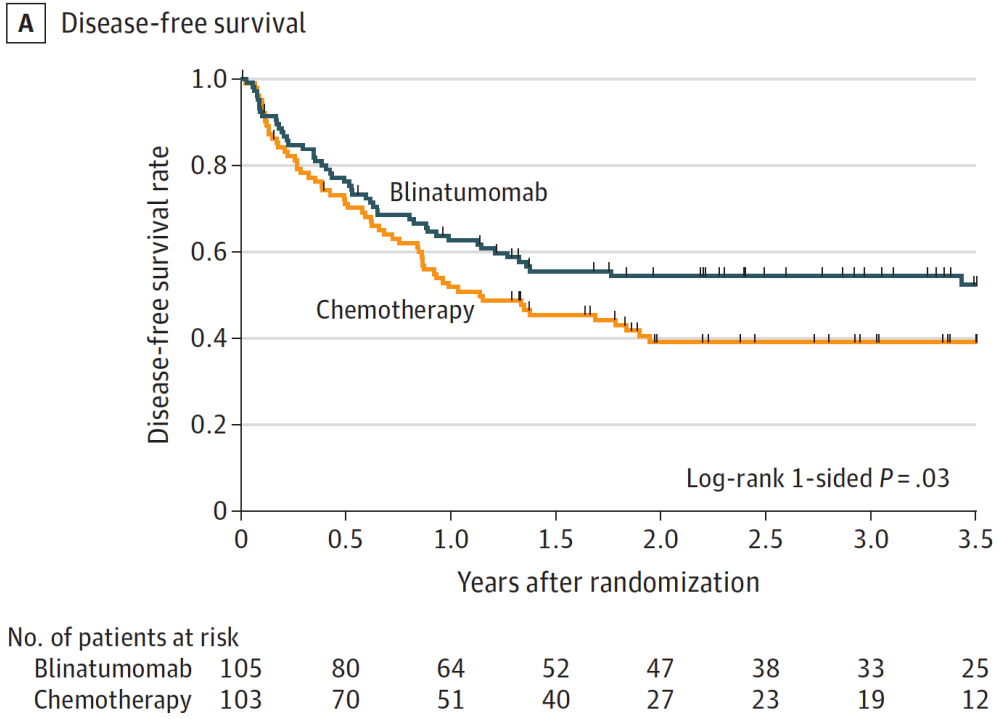


CHILDREN'S ONCOLOGY GROUP

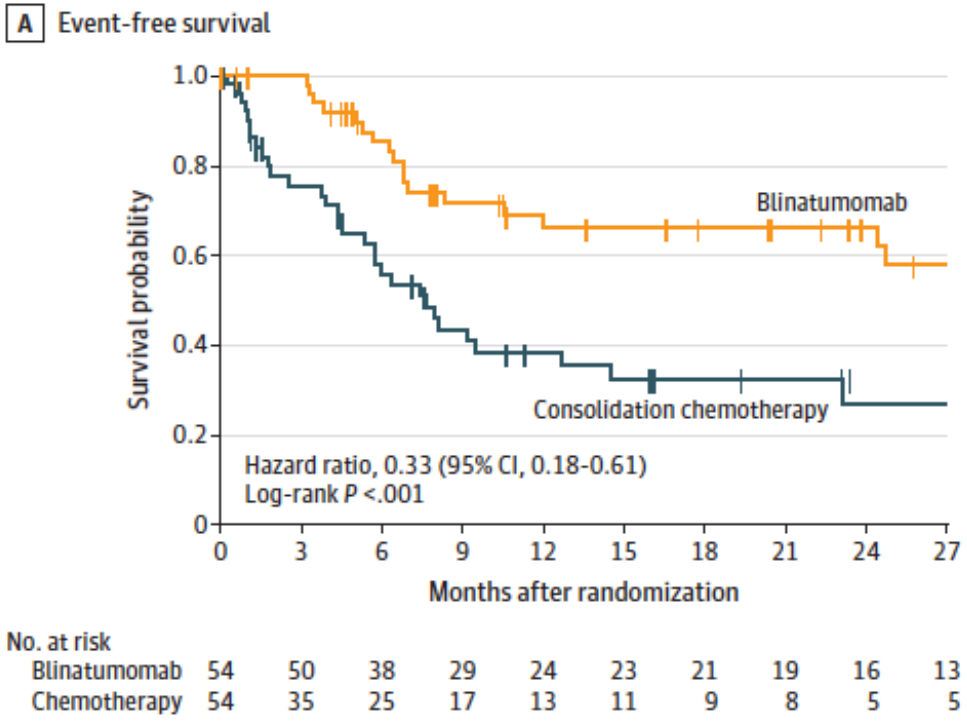
Slide Coutesy of Prof. Brown

Blinatumomab as consolidation in pediatric 1st High Risk Relapse

Caution:BIASS results from randomization: not from the beginng of the trial



Brown P et al JAMA 2021 (COG, Ped + YA <30 yr)



Locatelli F et al. JAMA 2021 (IntReALL)

BLINATUMOMAB in First Line

Blinatumomab in first line in ALL (children & adults)

TABLE 2. Ongoing Clinical Trials With Front-Line Blinatumomab in Pediatric and Adult ALL

Short Title	Primary End Points	Study Design, Sponsor, and NCT Identifier
Blinatumomab added to prephase and consolidation therapy in BCP-ALL	MRD negativity	Phase II, HOVON, NCT03541083
Blinatumomab in consolidation and maintenance in patients with high-risk BCP-ALL	Disease-free survival at 3 years	Phase II, GRAAL, NCT03709719
Combination chemotherapy with or without blinatumomab for newly diagnosed BCR-ABL–negative BCP-ALL	Overall survival	Phase III, ECOG, NCT02003222
Blinatumomab in sequential combination with hyper-CVAD as front-line therapy for BCP-ALL	Relapse-free survival at 2 years	Phase II, MDACC, NCT02877303
Blinatumomab with sequential dose-reduced chemotherapy in older patients with BCR-ABL–negative BCP-ALL	Hematologic and MRD response after induction therapy	Phase II, EWALL, NCT03480438
Blinatumomab during consolidation to reduce mrd in patients with high-risk BCP-ALL	Reduction of MRD determined by MFC	Phase II, PETHEMA, NCT03523429
Front-line sequential treatment with dasatinib and blinatumomab in ph+ BCP-ALL	MRD negativity	Phase II, GIMEMA, NCT02744768
Blinatumomab with sequential chemotherapy to improve MRD response and survival in BCR-ABL negative BCP-ALL	MRD negativity	Phase II, GIMEMA, NCT03367299
Blinatumomab in combination with chemotherapy in pediatric and AYA patients with BCP-ALL	Disease-free survival up to 5 years	Phase III, NCI-COG, NCT03914625
Blinatumomab in adult patients with MRD of BCP-ALL (blast successor trial)	MRD negativity after one cycle	Phase II, GMALL, NCT03109093
Combination of blinatumomab and ponatinib in Ph+ BCP-ALL	MRD negativity	Phase II, MDACC, NCT03263572

Lussana F, Gritti G, Rambaldi A. *J Clin Oncol*. 2021;39(5):444-455

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Blinatumoma BCP-ALL		II, GRAAL, T03709719
Combination BCR-ABL–		III, ECOG, T02003222
Blinatumoma therapy fo		II, MDACC, T02877303
Blinatumoma with BCR-		II, EWALL, T03480438
Blinatumoma BCP-ALL		, PETHEMA, T03523429
Front-line se ALL		I, GIMEMA, T02744768
Blinatumoma survival in		I, GIMEMA, T03367299
Blinatumoma patients with BCP-ALL		II, NCI-COG, NCT03914625
Blinatumomab in adult patients with MRD of BCP-ALL (blast successor trial)	MRD negativity after one cycle	Phase II, GMALL, NCT03109093
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1st line blinatumomab in adult ALL

Randomized trial Chemo vs Chemo + blina (ECOG, NCT02003222)

Chemo + Blina as consolidation /maintenance

Chemo + Blina to reduce MRD (PETHEMA , NCT03523429)

TKI (dasa) + Blina in Ph+ ALL (D-ALBA GIMEMA)

TKI (pona) + Blina in Ph+ ALL (MDACC)

Ino + blina in elderly ALL (Alliance, NCT03739814)

Reduced intensity chemo + blina (+dasa if Ph+) (elderly)

Lussana F, Gritti G, Rambaldi A. *J Clin Oncol*. 2021;39(5):444-455

Ongoing Blinatumomab clinical trials in pediatrics

1st line:
IR/HR: Chemo+ blina (as consolidation or as bridge to HSCT)
Infants (Interfant chemo backbone + blinatumomab)
Down Syndrome (instead of consolidation chemo blocks)

1st relapse
- Blina + chemo (as consolidation or as bridge to HSCT)
- Blina + checkpoint inhibitors in R/R ALL

- After HSCT Blina + DLI (prophylactic or preemptive)

Citation: Queudeville, M.; Ebinger, M. Blinatumomab in Pediatric Acute Lymphoblastic Leukemia—From Salvage to First Line Therapy (A Systematic Review). *J. Clin. Med.* **2021**, *10*, 2544. https://doi.org/10.3390/jcm10122544

Table 2. Table containing all ongoing clinical trials with blinatumomab for pediatric patients.

Clinical Trials Identifier	Other Study ID Numbers	Ref. [1]	Title	Age	Status
NCT01471782	MT103-205 2010-024264-18 (Eudra-CT)	[21]	Clinical Study With Blinatumomab in Pediatric and Adolescent Patients With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia	Up to 17 years (child)	completed
NCT02187354	RIALTO 2014-001700-21 (EudraCT)	[25]	Expanded Access Protocol-Blinatumomab in Pediatric & Adolescent Subjects with Relapsed/Refractory B-precursor ALL (RIALTO)	Up to 17 years (child)	completed
NCT02783651	20150253		A Study of Patients with Ph-Chromosome-negative Relapsed or Refractory Acute Lymphoblastic Leukemia in the US	Child, adult	completed
NCT02879695	NCI-2016-01300 (CTRP)		Blinatumomab and Nivolumab With or Without Ipilimumab in Treating Patients With Poor-Risk Relapsed or Refractory CD19+ Precursor B-Lymphoblastic Leukemia	16 years and older	recruiting
NCT02393859	2014-002476-92 (EudraCT)	[39]	Phase 3 Trial of Blinatumomab vs. Standard Chemotherapy in Pediatric Subjects With High-Risk (HR) First Relapse B-precursor Acute Lymphoblastic Leukemia (ALL)	Up to 17 years (child)	active, not recruiting
NCT04546399	NCI-2020-06813 (CTRP)		A Study to Compare Blinatumomab Alone to Blinatumomab With Nivolumab in Patients Diagnosed With First Relapse B-Cell Acute Lymphoblastic Leukemia (B-ALL)	1 to 31 years (child, adult) Including Down syndrome patients	recruiting
NCT03914625	NCI-2019-02187 (CTRP)		A Study to Investigate Blinatumomab in Combination With Chemotherapy in Patients With Newly Diagnosed B-Lymphoblastic Leukemia	1 to 31 years (child, adult) Including Down syndrome patients	recruiting
NCT02101853	NCI-2014-00631 (CTRP) COG-AALL1331	[38]	Blinatumomab in Treating Younger Patients With Relapsed B-cell Acute Lymphoblastic Leukemia	1 to 31 years (child, adult)	Active, not recruiting
NCT02877303	NCI-2017-00596 (CTRP)		Blinatumomab and Combination Chemotherapy as Frontline Therapy in Treating Patients With B Acute Lymphoblastic Leukemia	14 years and older	recruiting
NCT02790515	REF2HCT NCI-2016-00812 (CTRP)		Provision of TCRγδ T Cells and Memory T Cells Plus Selected Use of Blinatumomab in Naïve T-cell Depleted Haploidentical Donor Hematopoietic Cell Transplantation for Hematologic Malignancies Relapsed or Refractory Despite Prior Transplantation	Up to 21 years	recruiting
NCT03849651	HAP2HCT		TCRαβ-depleted Progenitor Cell Graft With Additional Memory T-cell DLI, Plus Selected Use of Blinatumomab, in Naive T-cell Depleted Haploidentical Donor Hematopoietc Cell Transplantation for Hematologic Malignancies	Up to 21 years	recruiting

INOTUZUMAB

EMA Approved indications of INOTUZUMAB in ALL

ADULTS

AS MONOTHERAPY

- CD22+ Ph neg r/r ALL
- CD22+ Ph+ r/r ALL after failure ≥1 TKI

CHILDREN

Not yet approved

Phase I/II clinical trials in R/R ALL ongoing (results similar to adults)

Phase III clinical trials in 1st line

Activity of inotuzumab in ALL

Study	Phase II, single dose R/R	Phase II, weekly dose R/R	Phase II, weekly dose, multicenter R/R	Phase III INO-VATE R/R	InO + mini HyperCVD, R/R	Phase II R/R Children Compassionate use	InO + mini HyperCVD Frontline elderly
Patients (N)	49	41	35	109	70	51	52
Dose /schedule	1.8 mg/m^2 D1 q 3–4 wks	0.8 mg/m^2 D1 0.5 mg/m^2 D8, 15	0.8 mg/m^2 D1 0.5 mg/m^2 D8, 15	0.8 mg/m^2 D1 0.5 mg/m^2 D8, 15	1.3–1.8 mg/m^2, cycle 1 1.0–1.3 mg/m^2, cycles 2–4		1.3–1.8 mg/m^2, cycle 1 1.0–1.3 mg/m^2, cycles 2–4
ORR, %	57	59	68	88	77	67	87
CR, %	18	20	31	36	59	36	80
MRD negativity*, %	68	71	84	78	81	71	96
OS, median, mo	5	7.3	7.4	7.7	11	6	Not reached

*Among responders.
Adapted from Kantarjian H, Jabbour E. Am Soc Clin Oncol Educ Book 2018;574–78.

Slide Courtesy of Prof. Ribera

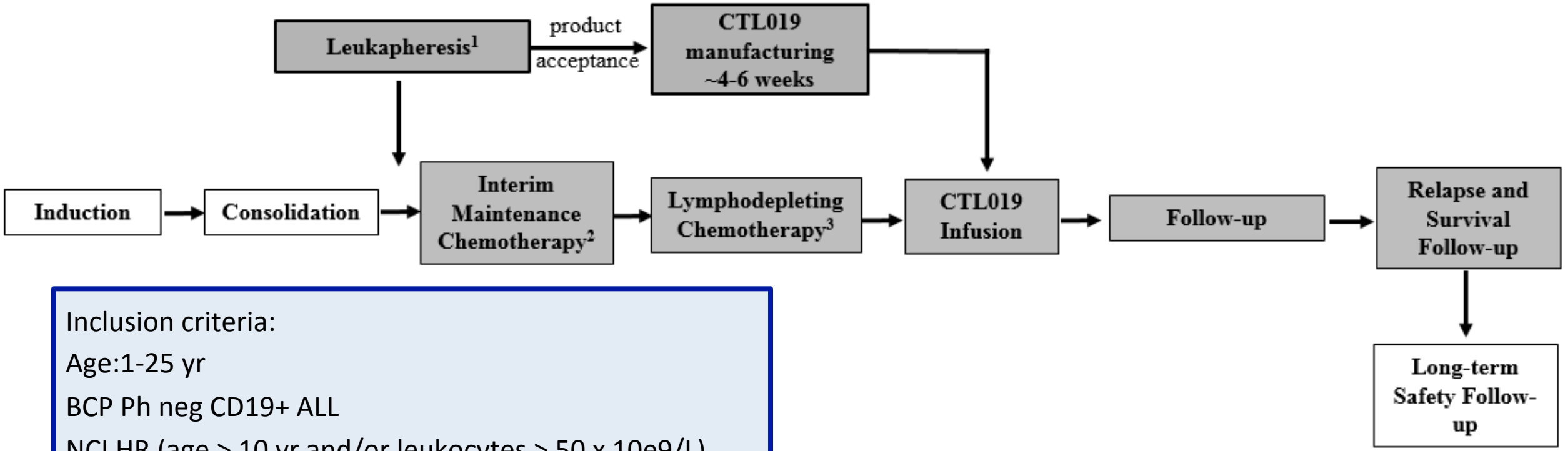
CAR T-CELLS

CAR T-cells FDA approved in ALL

	Brexu-cel		Tisa-cel
FDA Approval	October 2021		2017
Approved indication	Adults R/R BCP ALL (review) BCP children & AYA (≤21 yr) (devel)		BCP children & AYA (≤25 yr)
Clinical Trial	ZUMA-3	ZUMA-4	ELIANA
N Pts (ITT)	71	31	97
N (evaluable)	55	24	79
CR/CRi (%)	71 (evaluable)	67 (evaluable)	82.3 (evaluable)
RFS/PFS/EFS	mRFS 11.6 m (evaluable)	mRFS NR (evaluable)	18m RFS: 66% (evaluable)
OS	mOS 18.2 m (evaluable)	2yr OS 87.5% (evaluable)	18m OS: 70% (evaluable)
G ≥3 AE (%)	95	100	-
G ≥3 CRS, %	24	22	48
G≥ 3 neurol ev.	25	11	13

Slide courtesy of JM Ribera

CAR T-cells in 1st line pediatric & YA ALL Cassiopeia trial (EUDRACT 2017-002116-14)



Inclusion criteria:

Age:1-25 yr

BCP Ph neg CD19+ ALL

NCI HR (age ≥ 10 yr and/or leukocytes ≥ 50 x 10e9/L)

End of induction: M1 or M2 (<25% blasts)

End of consolidation: CR (M1) with flow MRD+ (≥ 0.01%)

HOW TO INTEGRATE IMMUNOTHERAPY APPROACHES IN 1ST LINE ALL

ALL together (A2G)

Molecularly and Immunologically Targeted Therapy in pB ALL

Risk group	Therapeutic question
VLR	Standard chemotherapy RANDOMIZED DE-ESCALATION →Less (or no) anthracyclines →No pulses
IR-low	
IR-high	Inotuzumab
VHR	CAR-T 1st line (instead of transplant)
ABL-class fusions	Imatinib since day +15 induction
Down Syndrome	Blinatumomab (Instead of HR blocks)

CAR-T 1st line: clinical trial CASSIOPEIA (COG AALL1721 + ALL-TOGETHER VHR + SEHOP-PETHEMA 2013 VHR)
Tisagenlecleucel patients NCI-HR (age ≥10 yr and/or leukocytes >50 x 10^9/L & MRD end of consolidation >0,01%)

COG B-ALL : Molecularly and Immunologically Targeted Therapy

Risk group	DFS 5 years	Therapeutic question
SR-favorable	>95%	Standard chemotherapy
HR-favorable	>94%	
SR-average & HR	≈85%	Blinatumomab
HR	≈80%	Inotuzumab
VHR	<50%	CAR-T 1st line (instead of transplant)
Ph and Ph like	60-85%	Molecularly targeted chemotherapy

CAR-T 1st line: clinical trial CASSIOPEIA (COG AALL1721 + ALL-TOGETHER VHR + SEHOP-PETHEMA 2013 VHR + other groups)
Tisagenlecleucel patients NCI-HR (age $\geq$10 yr and/or leukocytes >50 x 10^9/L & MRD end of consolidation >0,01%)

Slide adapted from M. Loh, personal comunication I-BFM Prague, 2019

How to integrate immunotherapy approaches in 1st line ALL?

- Chemotherapy + immunotherapy as consolidation
  - to improve outcomes in HR patients
  - to reduce toxicity (substitution of intensive chemotherapy blocks or even HSCT)
- Reduced intensity chemotherapy + immunotherapy +/- TKI
- Chemotherapy free: eg. blina + TKIs

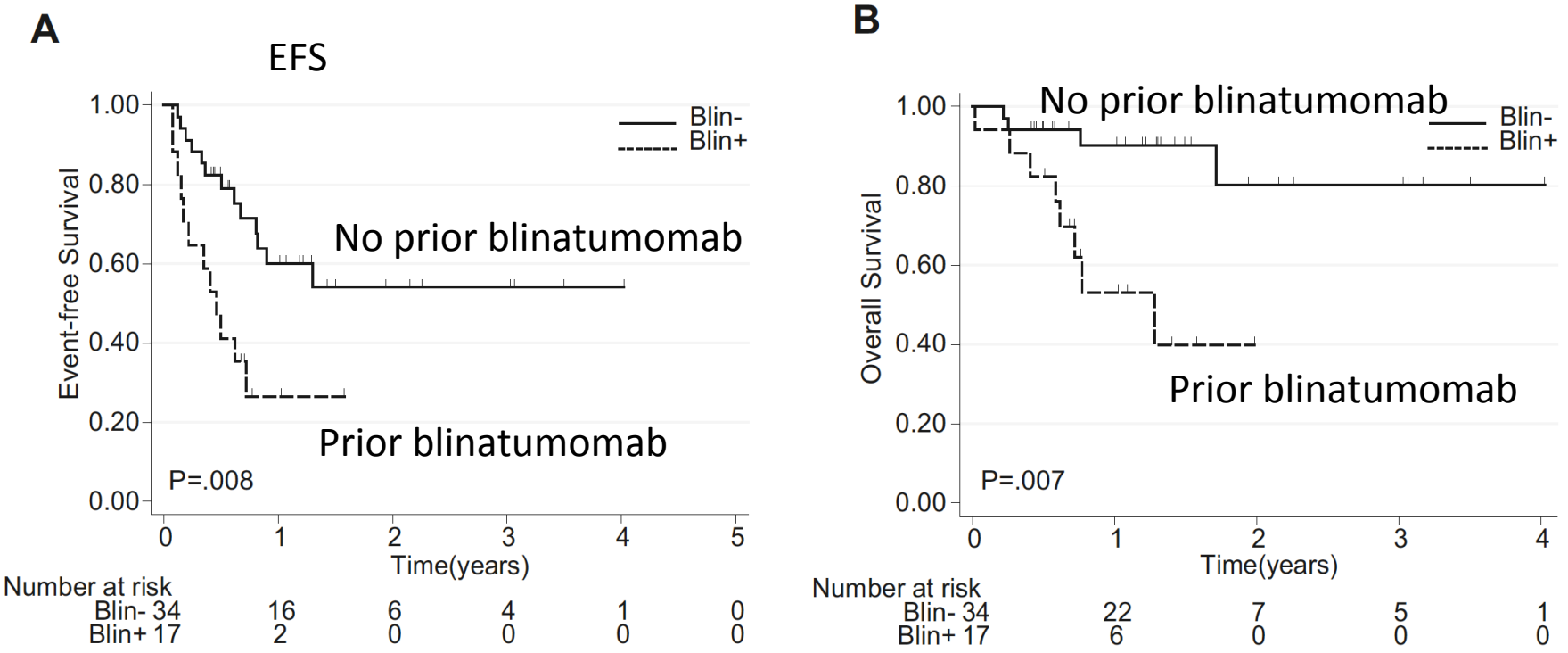
Still many unanswered questions

- How to best use immunotherapy (in front-line and R/R setting)
  - Predictive factors for immunotherapy response
  - Can blinatumomab in MRD+ patients avoid HSCT
  - When to bridge to HSCT after CAR-T?

- How to combine immunotherapy
  - Should we avoid blinatumomab /inotuzumab prior to CAR T-cells
  - Do TKIs after CAR T-cells inhibit CAR T-cell function?

Impact of prior blinatumomab exposure on survival after CAR T-cell

Fig. 2 Outcome according to prior blinatumomab exposure. Kaplan–Meier curves for **A** event-free survival and **B** survival according to prior blinatumomab. Blin blinatumomab.

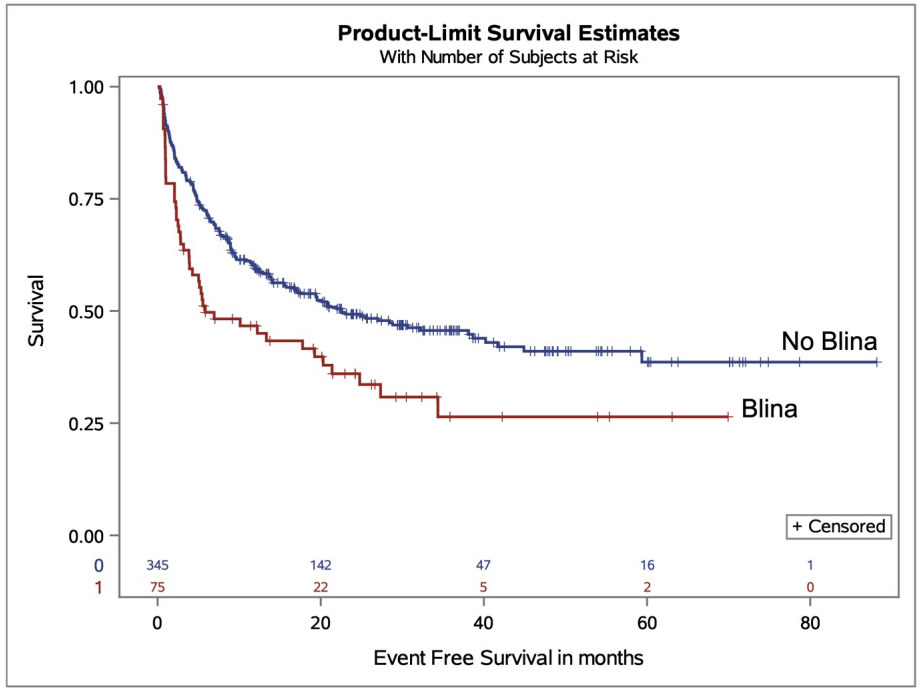


Dourthe ME et al. *Leukemia*. 2021; doi:10.1038/s41375-021-01281-7.

Blinatumomab pre CAR T-cells

n=422 patients (multicentric sutdy)
Different CAR19 constructs
n=75 prior blina

Figure 1B. Event Free Survival



Prior to CAR T	No blina	blina	
Response to CAR T			
MRD neg CR:	90%	80%	
Refractory to CAR T	18%	7%	*p*=0.0052
Survival			
Median EFS	**6 mo**	**23 mo**	*p*=0.0034

Table 1.	All (n=420)	Blina (n=75)	No Blina (n=345)	p
Demographics				
Median age at dx, years (IQR)	7.1 (3.2-13.8)	6.8 (2.0-12.2)	7.6 (3.6-14.0)	0.03
Median age at CAR infusion, years (IQR)	12.4 (7-17.1)	10.0 (5.9-18)	12.8 (7.8-17)	0.12
Median age at blina infusion, years (IQR)	N/A	7.6 (4.0-16.0)	N/A	---
				0.40
				0.03
				0.49
				0.79
				1
				0.25
				0.49
				0.07
				0.07
CD19 negative	0 (0%)	0 (0%)	0 (0%)	---
Unknown	12 (2.9%)	6 (8%)	6 (1.7%)	---
Post-CAR Response^				
Complete Remission, n (%)	375 (91.0%)	58 (81.7%)	317 (92.7%)	0.0052
Non-response, n (%)	37 (10.0%)	13 (18.3%)	24 (7.0%)	
MRD neg CR, n (%)	363 (88.1%)	57 (80.2%)	306 (89.7%)	0.04
Survival				
Median RFS, (95% CI)	40.2 months (24.9-not est)	20.3 months (5.85-34.4 months)	44.9 months (28.4 months-not est.)	0.027
6-month RFS, (95% CI)	78.4% (73.8-82.2%)	63.4% (49.6-74.4%)	81.1% (76.3-85.0%)	---
12-month RFS, (95% CI)	67.7% (62.6-72.3%)	57.5% (43.4-69.2%)	69.2% (63.7-74.1%)	---
Median EFS, (95% CI)	20.2 months (13.9-27.3 months)	5.8 months (3.9-20.3 months)	22.6 months (15.8-38.7 months)	0.0034
6-month EFS, (95% CI)	68.4% (63.8-72.7%)	49.7% (37.8-60.5%)	72.1% (67.1-76.6%)	---
12-month EFS, (95% CI)	57.2% (52.3-61.9%)	46.7% (34.9-57.6%)	59.6% (54.1-64.6%)	---
Median OS, (95% CI)	49.1 months (40.4-not est)	46.3 months (17.9 months-not est)	49.1 months (40.4 months-not est)	0.30
6-month OS, (95% CI)	84.5% (80.7-87.6%)	75.8% (64.4-84.0%)	86.4% (82.3-89.6%)	---
12-month OS, (95% CI)	76.4% (70.1-78.5%)	67.1 (55.0-76.6%)	76.2 (71.7-80.4%)	---

*Only 344 patients evaluated for CNS status; ^Only 412 patients were evaluable for response post-CAR T-cells, this included 341 non-blina patients and 71 blina patients; #CD19 expression captured post-blina, pre-CAR for the blina cohort; **n for Relapse restricted to the number that achieved CR; ^^4-1BB CAR T-cell constructs were comprised of either one of two available constructs, including the construct that eventually was FDA approved; tisagenlecleucel refers to the commercial available construct. IQR: Interquartile range. Not est: not estimable

Taraseviciute A, *Blood* (2020) 136 (Suppl 1): 13–14.
DOI: https://doi.org/10.1182/blood-2020-139260

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  - Predictive factors for immunotherapy response
  - Can blinatumomab in MRD+ patients avoid HSCT
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- How to combine immunotherapy /sequence
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