Refractory/relapsed B-ALL in children and AYA's CAR T cells first?

Karima YAKOUBEN

University Hospital Robert Debré & Université Paris Cité

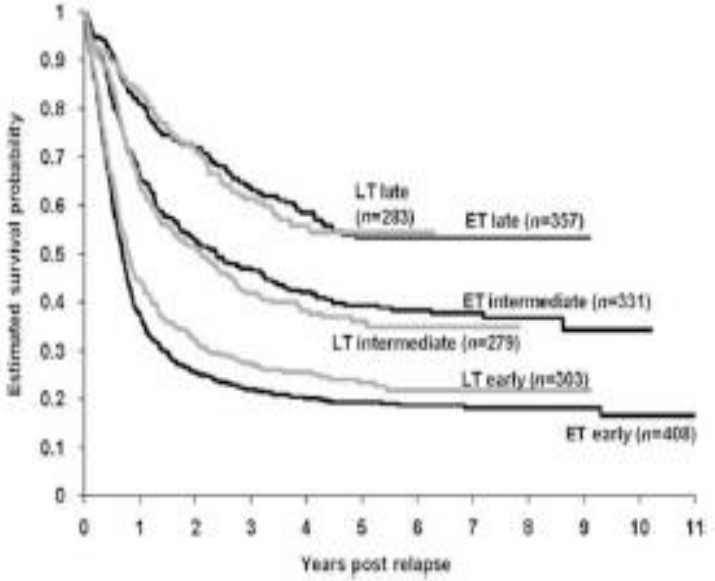
Paris, France

French & German SFGM-TC Day February 02, 2023

No conflict of interest

Outcomes paediatric patients and AYAs with BCP-ALL treated on contemporary protocols

- Long-term survival
  - 90% in children
  - 70% in young adults
- Refractory to primary therapy: 2-3 %
- Relapse
  - 15–20% of paediatric patients , much more in infants (35-40%)
  - 30–40% of AYAs
- Very poor outcomes
  - early bone marrow relapse (<18 mo)
  - ≥2 relapses,
  - relapse after HSCT
  - refractory to induction therapy



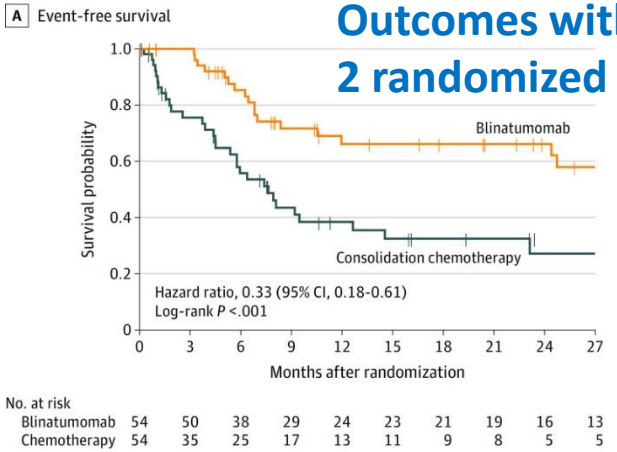
K Nguyen et al, Leukemia (2008) 22, 2142–2150

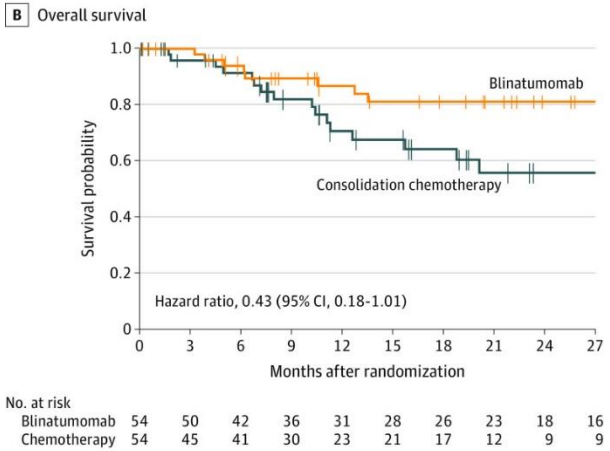
Standard of care for R/R BCP ALL patients

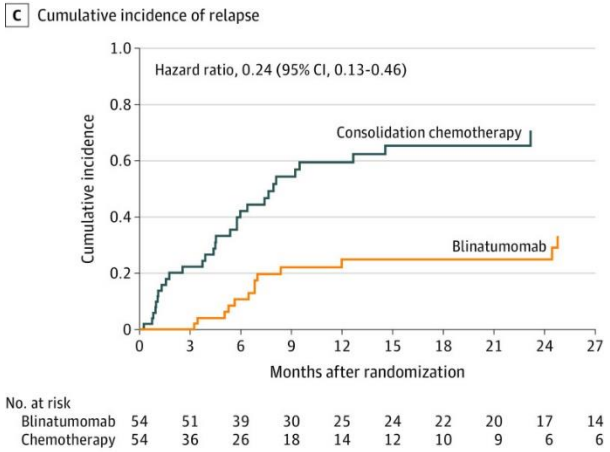
- For SR relapse: HSCT if MRD + after intensive block chemotherapy
- For HR relapse: chemotherapy, Blinatumomab followed by **HSCT if deep remission could be achieved**

- FORUM trial among patients in CR receiving **TBI**+ Etoposide
  - 2-year OS rate 91%
  - cumulative incidence of relapse : 12%
  - TRM: 2%
- But
  - Longer Follow up is necessary in ALL
  - **Toxicities +++(**GVHD, TBI related late effects,,,)
  - **Did not take into account bad responders /refractory patients and death in 1st line therapy**

Outcomes with Blinatumomab in Children, AYA's With First HR Relapse of B ALL
2 randomized Ph III clinical trials



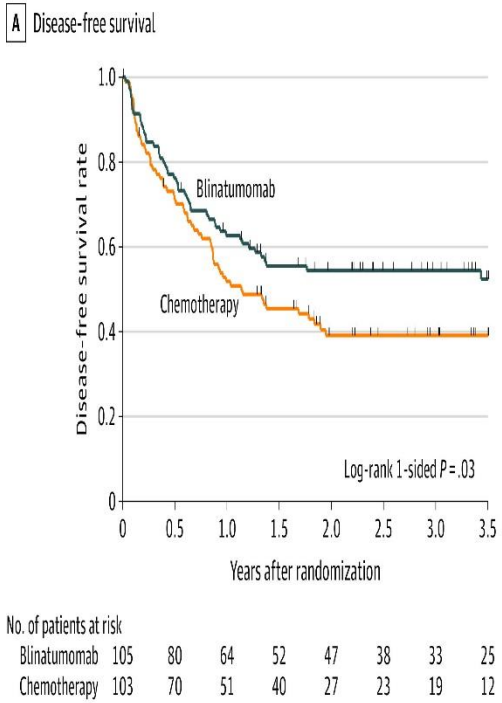


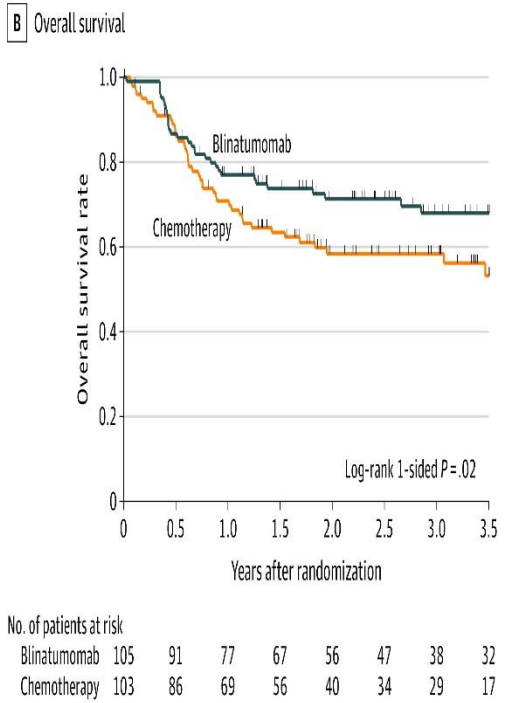


1 Multicentric, 13 countries
Nov 2015 - July 2019
Median F.up: 22,4 mo
Enrollment : N=120
Randomised : 108
Blina: N=54
Chemo: N=54

2 **COG Study**
Dec 2014 to Sept 2019

Enrollment: 669
Randomised 216
Blina N=107
Chemo: N=109
Median F. up 2,9 years

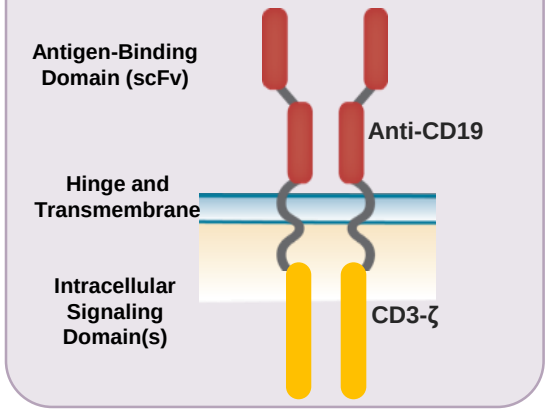




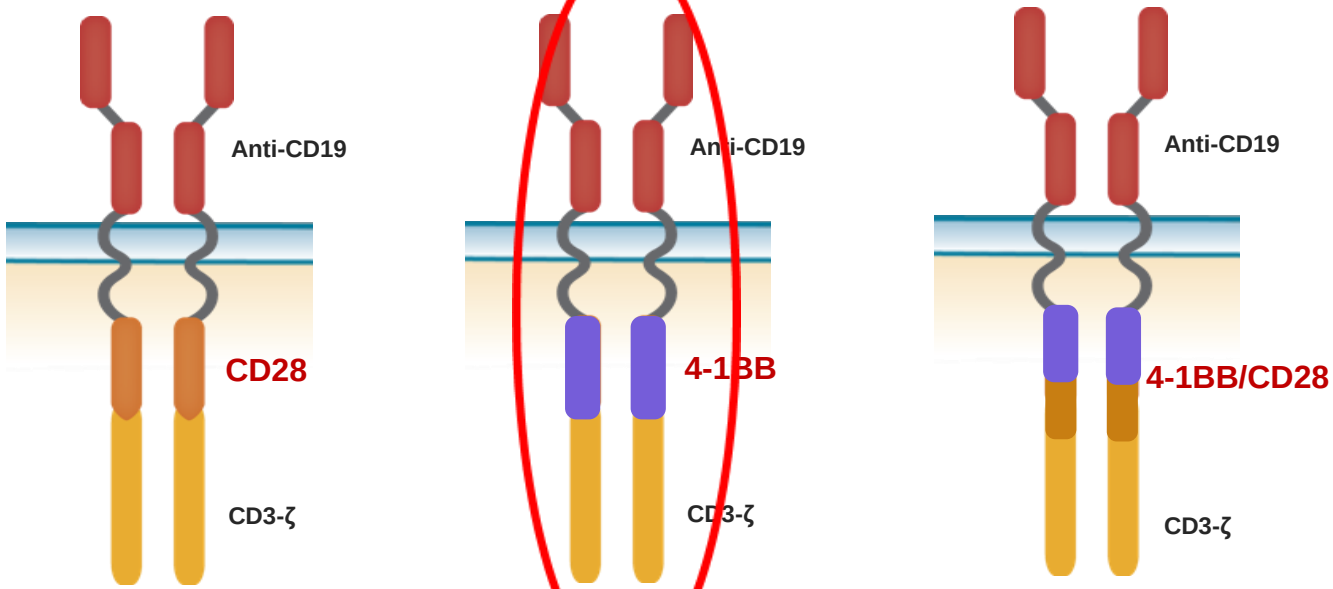
1-Locatelli F, JAMA. 2021 Mar 2;325(9):843-854
2-Brown PA, JAMA. 2021 Mar 2;325(9):833-842

Chimeric antigen Receptor (CAR) Constructs

First-generation CARs lacked a costimulatory domain and often did not elicit antitumor effects[1]



Second- and third-generation CARs incorporate costimulatory domains either individually or in combination[1]



CD28:

- Involved in **early and rapid expansion** with limited long-term persistence in vitro[2]
- Correlated with effector memory T-cell differentiation known to provide **immediate protection** in vitro[1]
- Metabolic profile **supports rapid expansion (glycolytic metabolism)**

4-1BB:

- Enhances early expansion **and long-term persistence** in vitro[1,2]
- Induces central memory T-cell differentiation for **enduring protection** and immunosurveillance in vitro[1]
- Metabolic profile **supports gradual sustained expansion (oxidative metabolism)**

CD28/4-1BB:

- The impact of 4-1BB/CD28 combined costimulatory domains on **expansion, persistence, and central memory** is being investigated[1]

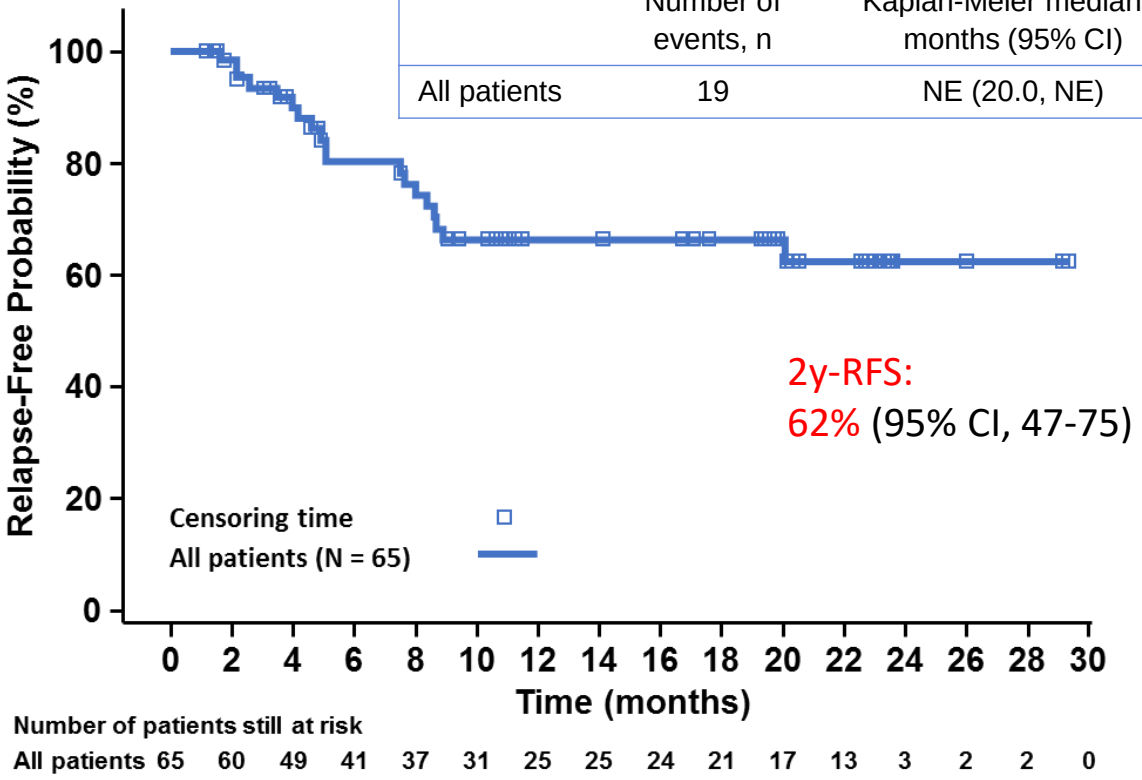
This information is based on animal model data. No head-to-head comparisons of the clinical efficacy of these costimulatory domains have been conducted.

1. Kawalekar OU et al. *Immunity*. 2016;44(2):380-390. 2. Milone MC et al. *Mol Ther*. 2009;17(8):1453-1464.

ELIANA trial (Tisagenlecleucel/CTL019): ASH 2018 update

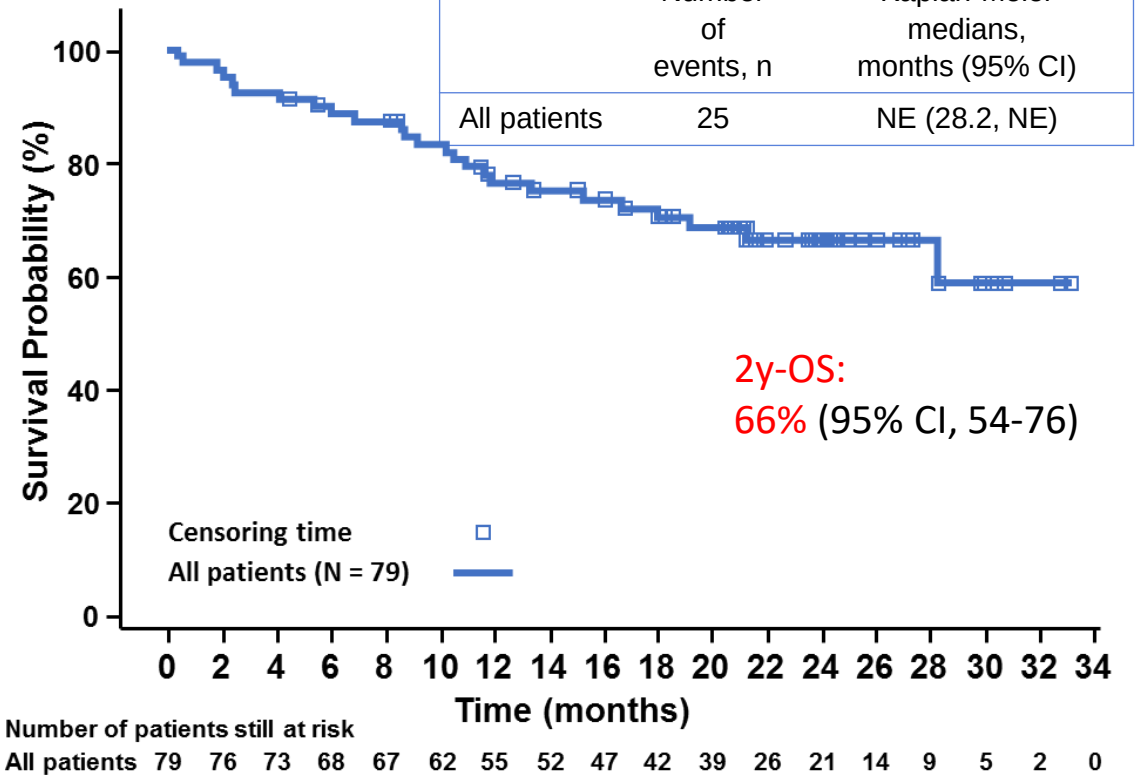
N=79 patients, median follow-up, 24 months

All patients (N = 65)		
	Number of events, n	Kaplan-Meier medians, months (95% CI)
All patients	19	NE (20.0, NE)



2y-RFS:
62% (95% CI, 47-75)

All patients (N = 79)		
	Number of events, n	Kaplan-Meier medians, months (95% CI)
All patients	25	NE (28.2, NE)



2y-OS:
66% (95% CI, 54-76)

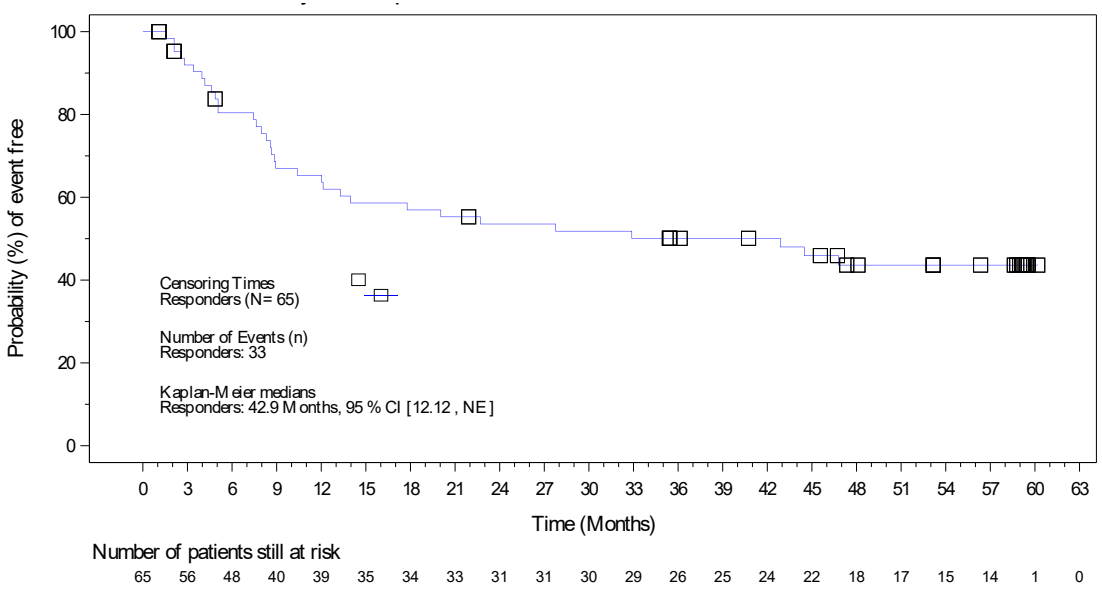
CD19-Negative	CD19-Positive	Unknown CD19 Status
14/19 (73.7% of relapses)	3/19 (15.8% of relapses)	2/19 (10.5% of relapses)

Maude S et al, NEJM 2018
Grupp SA, et al. ASH 2018, abstract 895

ELIANA trial update 2022 (EHA 2022)

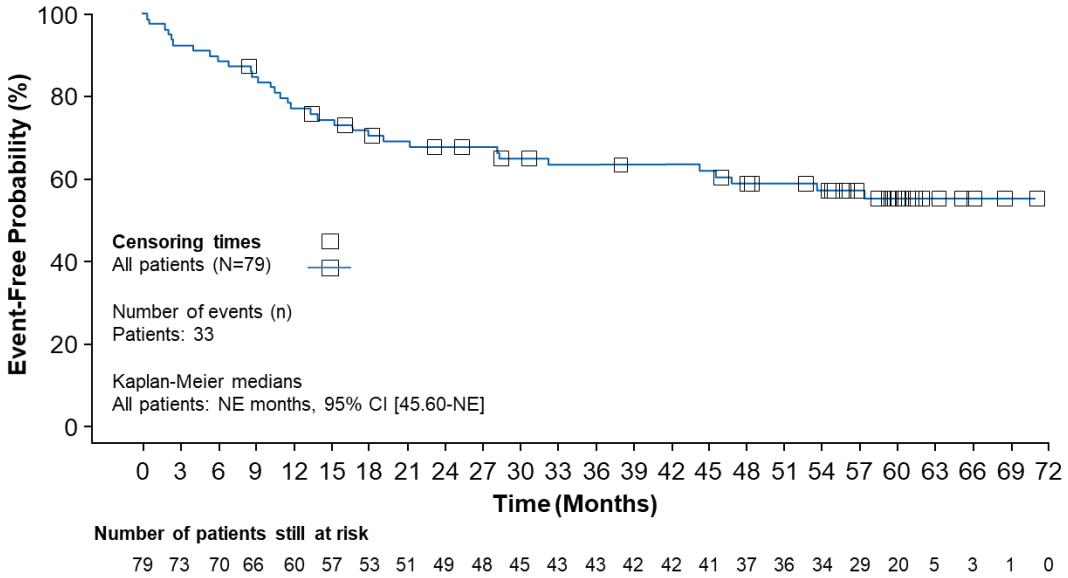
RFS for Patients With a CR/CRi within 3 months

5-year RFS: 43.6% (95% CI, 31%-56%)



Overall Survival

5-year OS: 55% (95% CI, 46%-66%)



Median time from infusion to data cutoff: 5.5 years

17

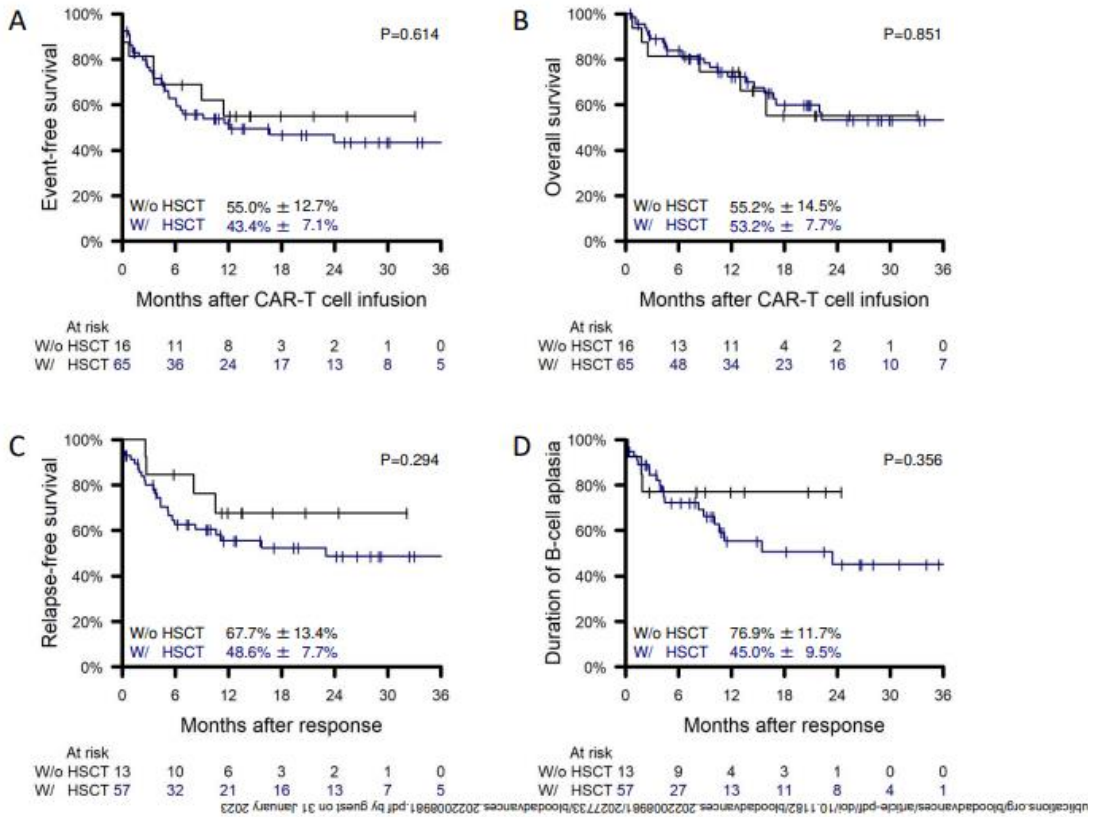
Note: OS is without censoring for alloSCT.
alloSCT, allogeneic stem cell transplant; NE, not estimable; OS, overall survival.

Favorable long-term safety and efficacy [2]

A curative treatment option for heavily pretreated pediatric and AYA's with R/R B-ALL

Rives S et al, EHA 2022
2- Laetsch TW, JCO 2022 Nov

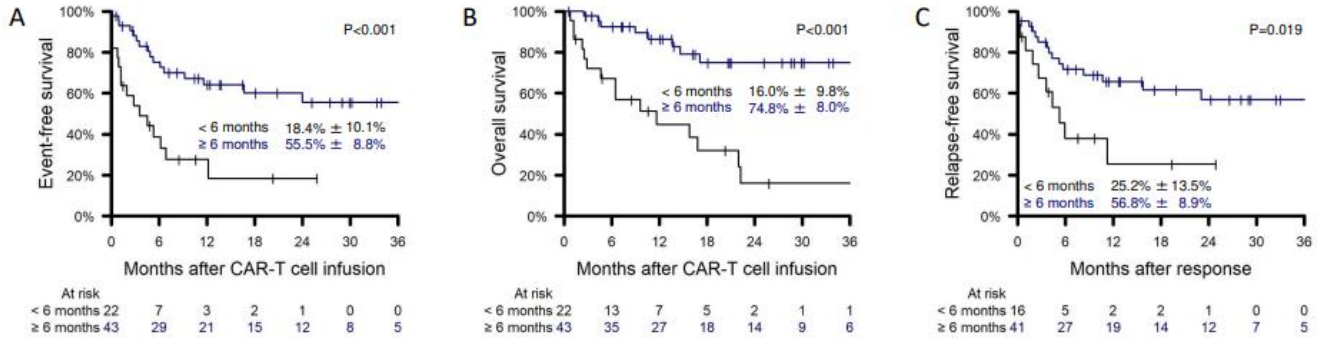
CD19-CAR-T cells are an effective therapy of post-transplant relapse in B- ALL patients: Real-World Data from Germany



A retrospective study
N= 81
80% in post-HSCT relapse
Follow up : 3 years

The time to relapse after HSCT is a strong predictor of outcome.

< 6 mo : pEFS 18,4% , pOS 16.0%
> 6 Mo : pEFS 55.5%, pOS 74.8%

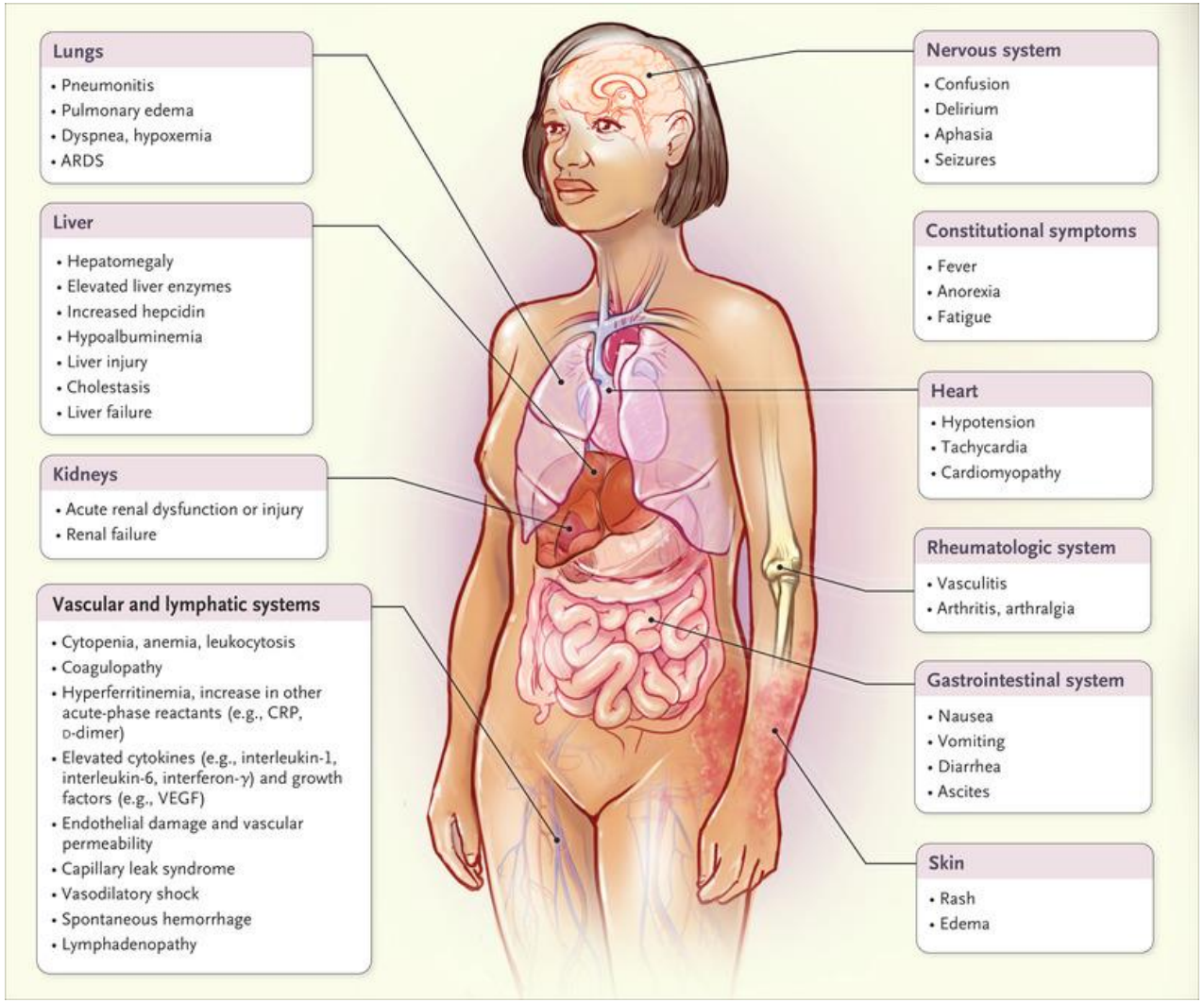


ALL patients post-HSCT had a better pEFS if relapse occurred beyond 6 months

Bader P and al, Blood Adv. 2023 Jan

A significant set of AEs

- CRS +++
- Neurotoxicity +++
- Macrophage Activation Syndrome
- Prolonged cytopenias
- Infections
- « B-cell aplasia»



Fajgenbaum & June NEJM 2020

No new or unexpected long-term AE were reported[1]
Grade 3/4 AE were reported in 29% of patients > 1 year after infusion
(infections (20.4%) and skin disorders (6.1%; all grade 3);
Gr 3/4 infection rate did not increase > 1 year after infusion.
Improvements in quality of life up to 36 months after infusion

1- Laetsch TW, JCO 2022 Nov 18

Using Tisagenlecleucel, are Real World Data really reproducing those of Eliana in terms of type of relapse?

	ELIANA (NEJM 2018 , ASH2018)	Pediatric Real World CAR Consortium (18 US centers) (JCO 2022)	UK (ASH2020)	Paris Robert Debré -Saint-Louis (Leukemia 2021)
N Infused	79	185	49	51
EFS at 12 months (from infusion)	50%	51%	68%	44% (at 18m)
CD19+ relapse (%)	3 **(15.8%)**	30 **(59%)**	? **(60%)**	12 **(55%)**
CD19- relapse	14* (73,7%)	22 (41%)	? (40%)	8** (36%)
Further therapy (including HSCT)	8 pts	NA	28% (12%)	NA

*2 CD19 status at relapse unknown

**2 CD19 status at relapse unknown

Early 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[1,3]

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

First Line B-ALL NCI HR: to replace HSCT ?

CASSIOPEIA trial* (NOVARTIS) : *Tisagenlecleucel for B-ALL NCI HR with FCM detectable MRD after induction (4 drugs) & consolidation (A-BFM IB)

- Opened in 12 countries in «Kymriah» authorized centers
  - COG sites
  - European sites
  - Other groups
- **Monoarm** study with 5y DFS as initial endpoint: ≥ 55% (**vs** 39% **historical comparison)**
- Initial Target: 140 infused pts within 4 years
- Age 1-25, incl.Down syndrome pts, excl. Hypodiploid /Ph+ ALL
- Induction result: M1/M2. Consolidation result : M1 but MRD+ ≥0,01%
  - Centralized FCM MRD (USA and Norway)
- Feb19 –Sept 22:

Screened	Enrolled	Infused
103	96	**92**

- Currently on hold (PIP modification, amendments)

So where to position CAR-T Cells vs HSCT now in the field of B-ALL?

MANY PARAMETERS

Availability of clinical trials for first relapse of ALL

- 1st relapse trials (INTREALL HR only in EU as INTREALL SR closed)
  - final destination : HSCT after 3 courses of chemotherapy & one course of Blinatumomab
- **Future INTREALL : a VHR group going to CAR-T Cells after Inotuzumab**

CAR T cells are indicated for

- Any relapse after HSCT [1]
- Primary refractory or refractory relapse
- More advanced disease **(**Relapse ≥2)

Under investigation

- 1 st line ALL NCI -HR (Cassiopeia)
- Very early relapse (<18 Mo)

Higher risk of failure if Blinatumomab preexposure to be taken into account

1- BADER P, and al, Blood Advance 2023, January

Of note more and more parents and children/AYA refuse HSCT and look for CAR-T cells with the option of a secondary HSCT if failure

Emily infused in April 2012

Elora infused in June 2016

Acknowledgments (1)

Children & AYAs and their parents

OUR NURSING STAFF

Pediatric Hematology
André Baruchel
Marie Emilie Dourthe
Audrey Grain
Mony Fahd
……..
Jean-Hugues Dalle

Apheresis Unit
Emmanuelle Lesprit
Anne Arnould

Pharmacy
Julie Roupret
Cléa Tardy
Clin. Invest. Center
François Luc,
Evelyne Jacqz-Aigrain

CAR-T coordination
Delphine Chaillou

ICU
Jérôme Naudin
Maryline Chomton
Stéphane Dauger

Hematology Lab
Odile Fenneteau
Elodie Lainey

Genetics Lab
Aurélie Caye
Hélène Cavé

Immunology Lab
Valérie Guérin
Ghislaine Carcelain

Cellular Therapy
Miryam Mebarki
Jérôme Larghero

Thanks to U PENN colleagues
Steve Grupp
Shannon Maude

NOVARTIS
Annabelle Merlat
Pat Wood †
L Eldjerou

AYA Unit

Florian Chevillon
Florence Rabian
Nathalie Dhédin
Nicolas Boissel

Apheresis Unit
Nathalie Parquet
Anne Brignier
Delphine Rea

Pharmacy
François Cartier
Isabelle Madelaine

CAR-T coordination
Maxime Berquier

ICU
Virginie Lemiale
Michael Darmon
Lara Zafrani
Elie Azoulay

Hematology Lab
Stéphanie Mathis
Emmanuelle Clappier
Jean Soulier

Immunology Lab
Florence Morin
Vincent Allain
Sophie Caillat-Zucman

Relapse prevention

To prevent CD19(+) relapse:

- Improve persistence
  - Construct (humanized?)
  - Manufacturing
  - Not too low CD19+ burden ?
  - Exposure to fludarabine
- If early loss of CAR-T cells/BCA
  - 2nd infusion :
    - Humanized
    - + Check-point inhibitors?
  - ***HSCT***
    - ++ if no previous one

To prevent CD19(-) relapse:

- No previous anti-CD19 therapy
  - or w/o response or CD19 dim
- Reduced disease burden/less aggressive disease (treat earlier ?)
- Double targeting (e.g. CD19/CD22)?