

# The Optimal Therapy Sequencing of BiTEs and CART Cells

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# Disclosures

## **Research Support**

Amgen, BMS/Celgene, Gilead/Kite, Janssen, Miltenyi, Novartis, Roche, Seattle Genetics, Takeda

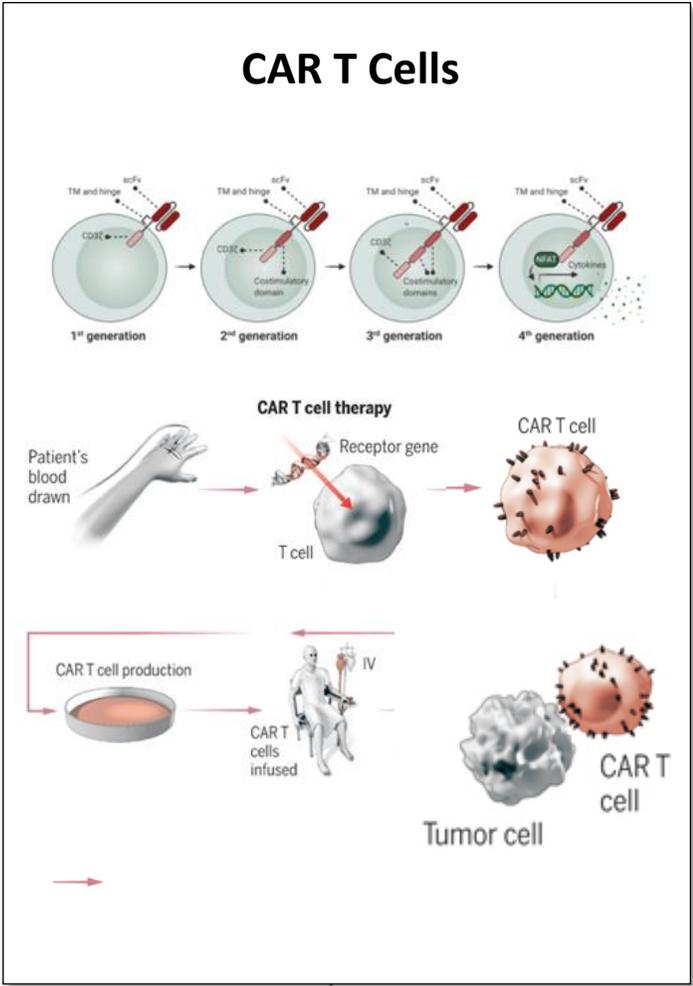
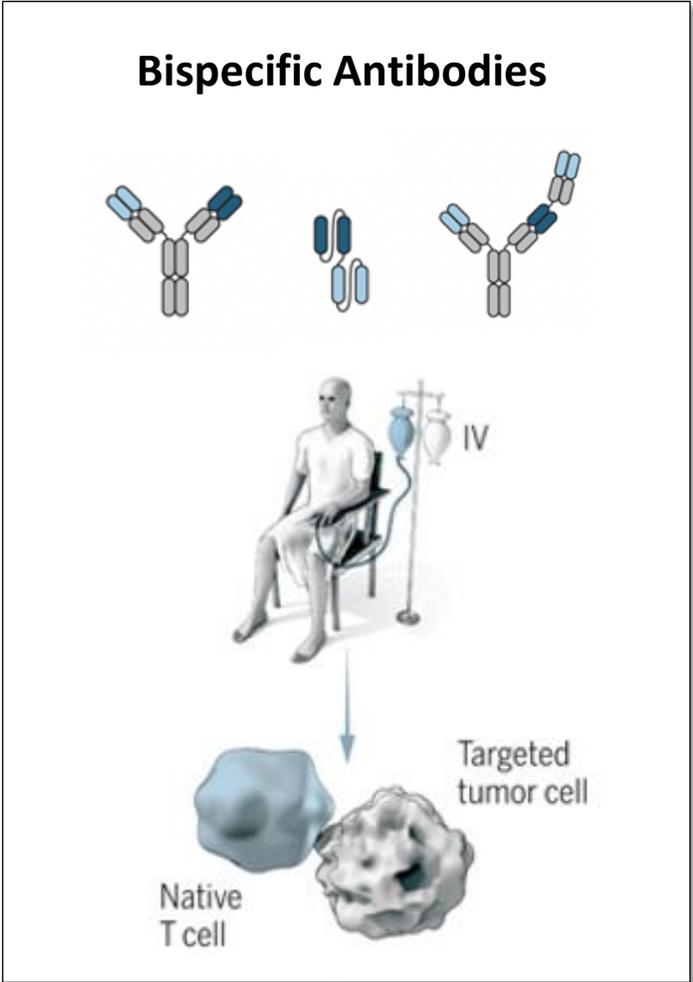
## **Advisory Board**

Astra Zeneca, Avencell, Ichnos, Incyte, Janssen, Molecular Partners, Novartis, Pfizer, Takeda

## **Speaker's Bureau**

Amgen, BMS/Celgene, Gilead/Kite, Novartis

# Forced into Battle



Synthetic Immunity

# EMA Approvals of CART & Bispecifics in BCP-ALL & B-cell lymphoma & MM

Further Approvals expected within the next 12 months

|   | CART             | Disease          | Bispecifics          |   |
|---|------------------|------------------|----------------------|---|
| Relapse after SCT or > 2 Tx Line; < 26 years of age | <b>Tisa-Cel</b>  | <b>BCP - ALL</b> | <b>Blinatumomab</b>  | Ph <sup>-</sup> MRD <sup>+</sup> (0.1%) (1 <sup>st</sup> or 2 <sup>nd</sup> remission); Ped. (>1 year of age) Ph <sup>-</sup> r/r & adults with r/r Ph <sup>-/+</sup> (for Ph <sup>+</sup> after 2 TKI) |
| > 1 Tx Line, <u>≥</u> 26 years of age               | <b>Brexu-Cel</b> |                  |                      |   |
| > 2 Tx Line   | <b>Tisa-Cel</b>  | <b>FL</b>        | <b>Mosunetuzumab</b> | > 2 Tx Line   |
| > 3 Tx Line   | <b>Axi-Cel</b>   |                  |                      |   |
| > 2 Tx Line   | <b>Tisa-Cel</b>  | <b>LBCL</b>      | <b>Glofitamab</b>    | > 2 Tx Line   |
| > 1 Tx Line, early relapse                          | <b>Axi-Cel</b>   |                  |                      |   |
| > 2 Tx Line   | <b>Liso-Cel</b>  |                  | <b>Epcoritamab</b>   | > 2 Tx Line   |
| > 3 Tx Line (after anti-CD38/IMiD/PI)               | <b>Ide-Cel</b>   | <b>MM</b>        | <b>Teclistamab</b>   | > 3 Tx Line (after anti-CD38/IMiD/PI)   |
| > 3 Tx Line (after anti CD38/IMiD/PI)               | <b>Cilta-Cel</b> |                  | <b>Talquetamab</b>   | > 3 Tx Line (after anti-CD38/IMiD/PI)   |

## Upon sequencing of BsAb & CART, questions on the relevance of

- **T cell exhaustion:** continuous bispecific exposure can lead to T cell exhaustion possibly compromising CART efficacy; unclear in what clinical scenario this is taking place, unclear if and how long a treatment free interval will ameliorate these findings (epigenetic scarring ?)
- **Loss of Target Antigen:** Antigen Escape and/or selection of pre-existing Antigen negative / dim cells
  - BCP-ALL: CD19 is the target of both BsAb (Blin) & CART (Tisa-cel, Brexu-cel)
  - DLBCL & FL: CD19 (CART: Axi-cel, Liso-cel, Tisa-cel) and CD20 (BsAb: Glofitamab, Epcoritamab) targeting, however Tafasitamab is also targeting CD19
  - MM: BCMA targeting through BCMA CART (Ide-cel, Cilta-cel) and BCMA bispecifics (Teclistamab), however, Talquetamab is directed against GPRC5D
- **Tumor Biology:** Patients with sequential therapy, with short intervals between therapeutic interventions have a different tumor biology, different immune contexture / immune health; the biology / genetics of the tumor determine response rate, directly and possibly through modulation of the TME & Immune health

## Currently, the Approval Status determines sequence of BsAb & CART

|  | <b>BCP-ALL</b>             | <b>Lymphoma</b> | <b>MM</b> |
|--|----------------------------|-----------------|-----------|
| BsAb                                   | 1st Line, MRD <sup>+</sup> | 3rd Line        | 4th Line  |
| CART                                   | 2nd Line                   | 2nd Line        | 4th Line  |
| <b>Data Availability on Sequencing</b> |                            |                 |           |
| BsAb => CART                           | +++                        | +               | +         |
| CART => BsAb                           | +                          | ++              | +         |

## ChatGPT: What is the optimal therapy sequence of BiTEs and CART ?

The optimal sequencing of BiTEs and CAR-T therapy can vary based on several factors, including the type of cancer, the specific antigen being targeted, the patient's overall health, previous treatments, and the availability of these therapies.

As of my last knowledge update in September 2021, there is no universally agreed-upon optimal sequencing due to the evolving nature of cancer treatment and the limited clinical data available.

However, I can provide some general considerations:

**BiTE Therapy:** BiTEs are typically administered before CAR-T therapy. BiTEs engage the immune system's T cells to directly attack cancer cells by targeting specific antigens. This priming of the immune system can help create a favorable environment for subsequent CAR-T therapy.

**CAR-T Therapy:** CAR-T therapy involves modifying a patient's own T cells to express a receptor specific to a cancer antigen. It is often considered a more potent and targeted treatment than BiTEs, as it involves the genetic modification and infusion of the patient's T cells.

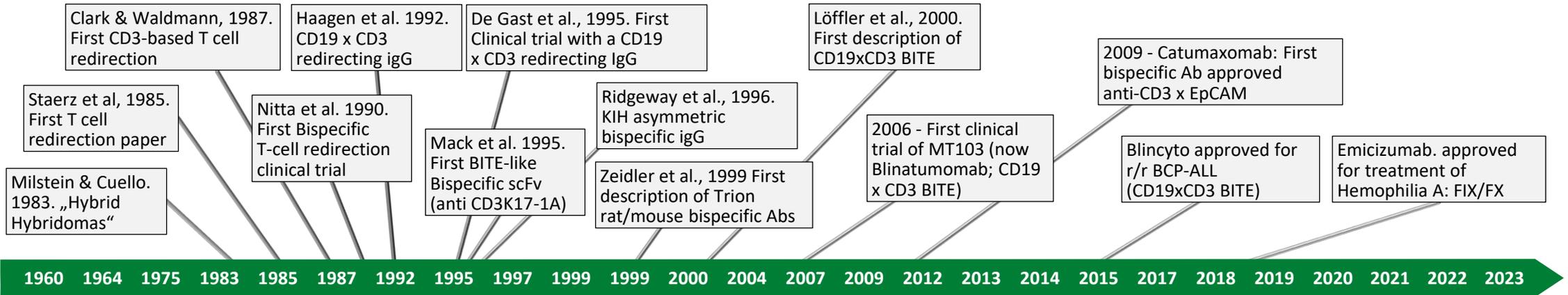
**Consideration of Disease Burden:** CAR-T therapy is often considered when the disease burden is relatively high or after patients have failed other treatments, including BiTEs.

**Assessing Patient Eligibility:** Patient eligibility for CAR-T therapy, including factors like overall health, prior treatments, and disease status, plays a crucial role in determining the timing of CAR-T after or before BiTEs.

**Combination or Sequential Therapy:** Depending on the specific cancer and the patient's condition, there may be cases where BiTE therapy and CAR-T therapy are used in combination or in a sequential manner for maximal efficacy. The decision to use them in combination or sequentially should be made on a case-by-case basis, considering the patient's individual circumstances and treatment goals.

**Clinical Trial Participation:** In some cases, patients may be eligible for clinical trials that explore novel combinations or sequences of these therapies. Clinical trials can provide valuable insights into the optimal sequencing and combination strategies.

# Blinatumomab was the first, and still approved, T cell engaging bispecific antibody



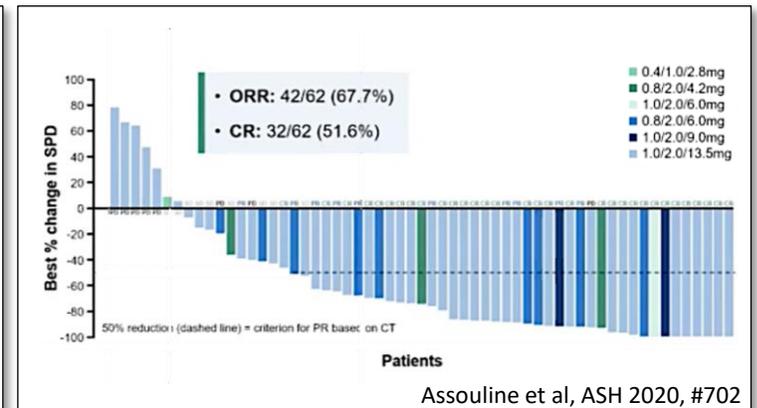
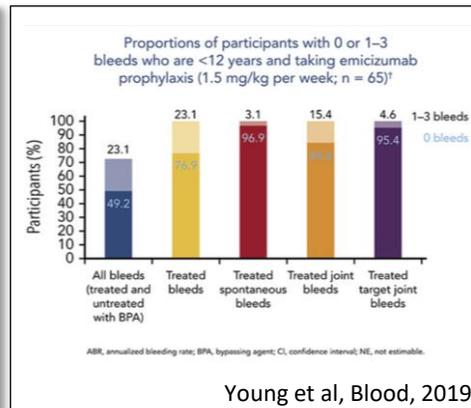
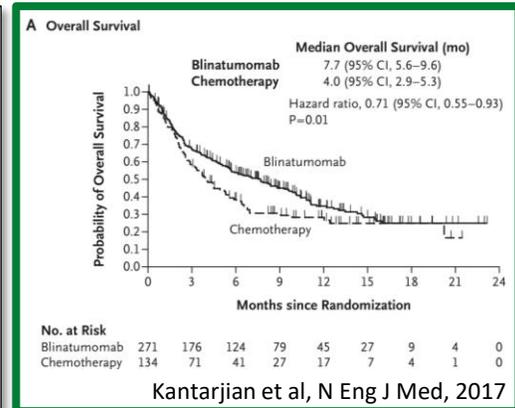
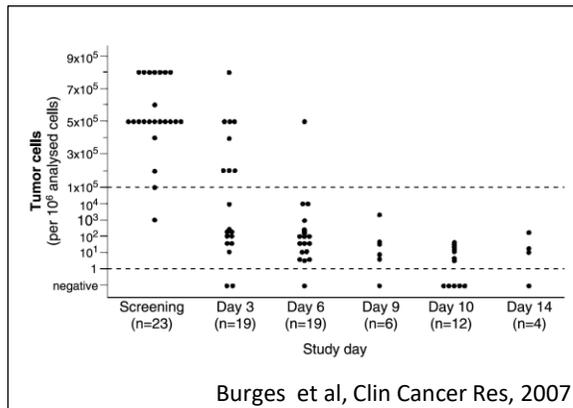
**Catumaxomab (Removab®)**  
2009 by EMA  
(2013 voluntarily withdrawn)

**Blinatumomab (Blincyto®)**  
2014 by FDA  
2015 by EMA

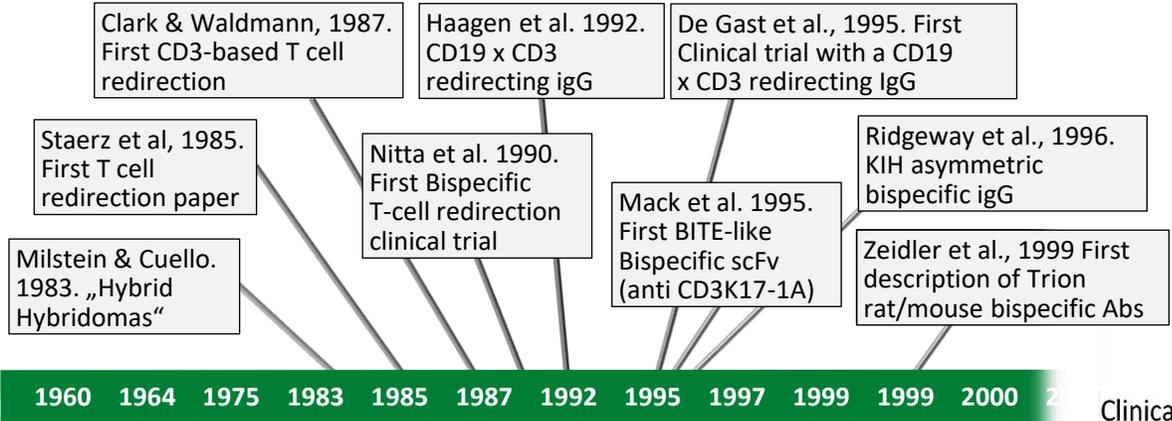
**Emicizumab (Hemlibra®)**  
2017 by FDA  
2018 by EMA

**Mosunetuzumab (Lunsumio)**  
2022 by FDA  
2022 by EMA

**Teclistamab (Tecvayli)**  
2022 by FDA  
2022 by EMA

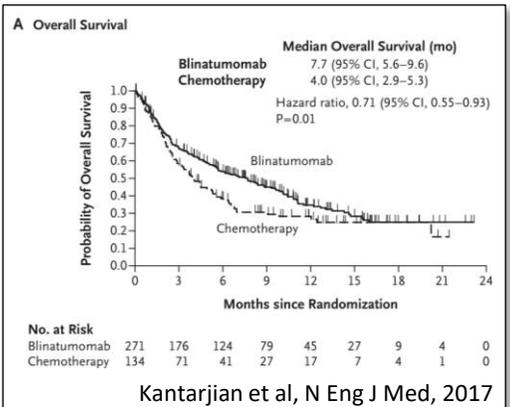
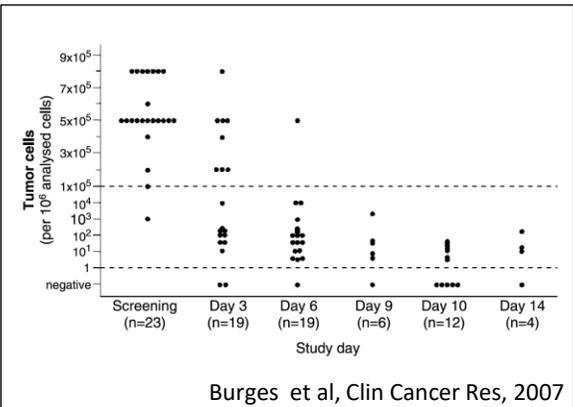


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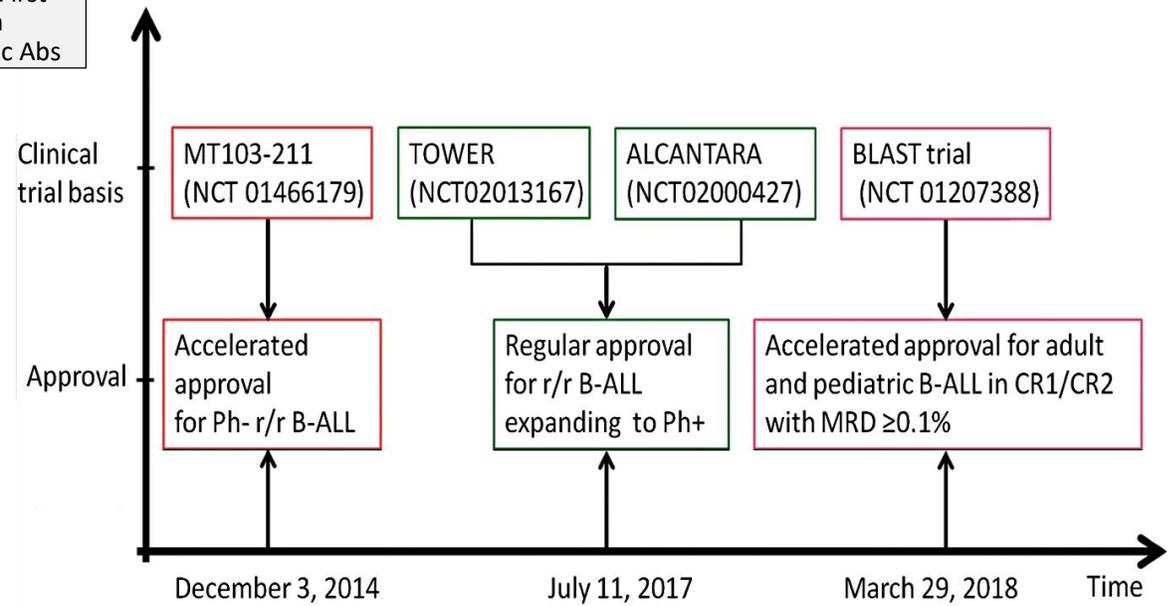


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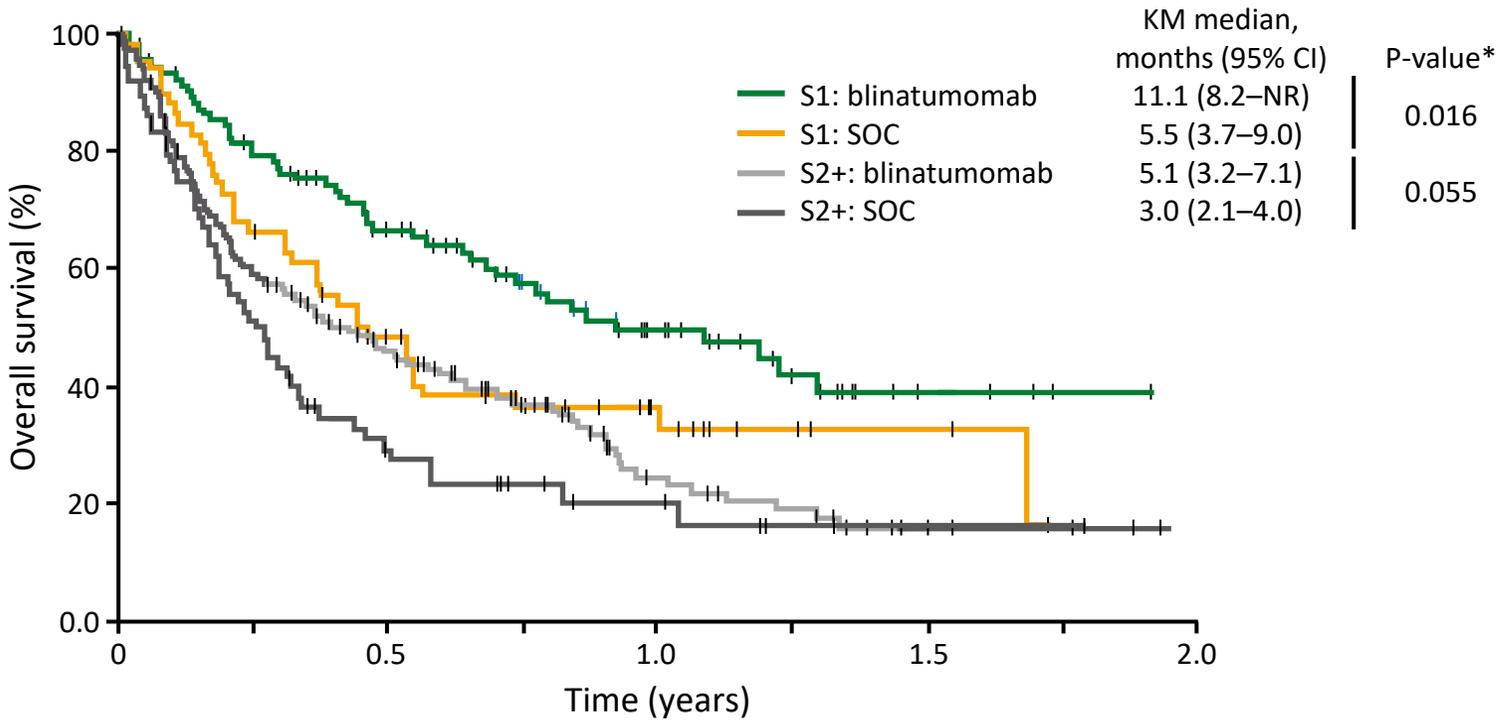


## First Approval in R/R BCP-ALL (MT103-211) Confirmed in a randomized trial (Tower)



# Blinatumumab works best given earlier in treatment lines (S1 > S2)

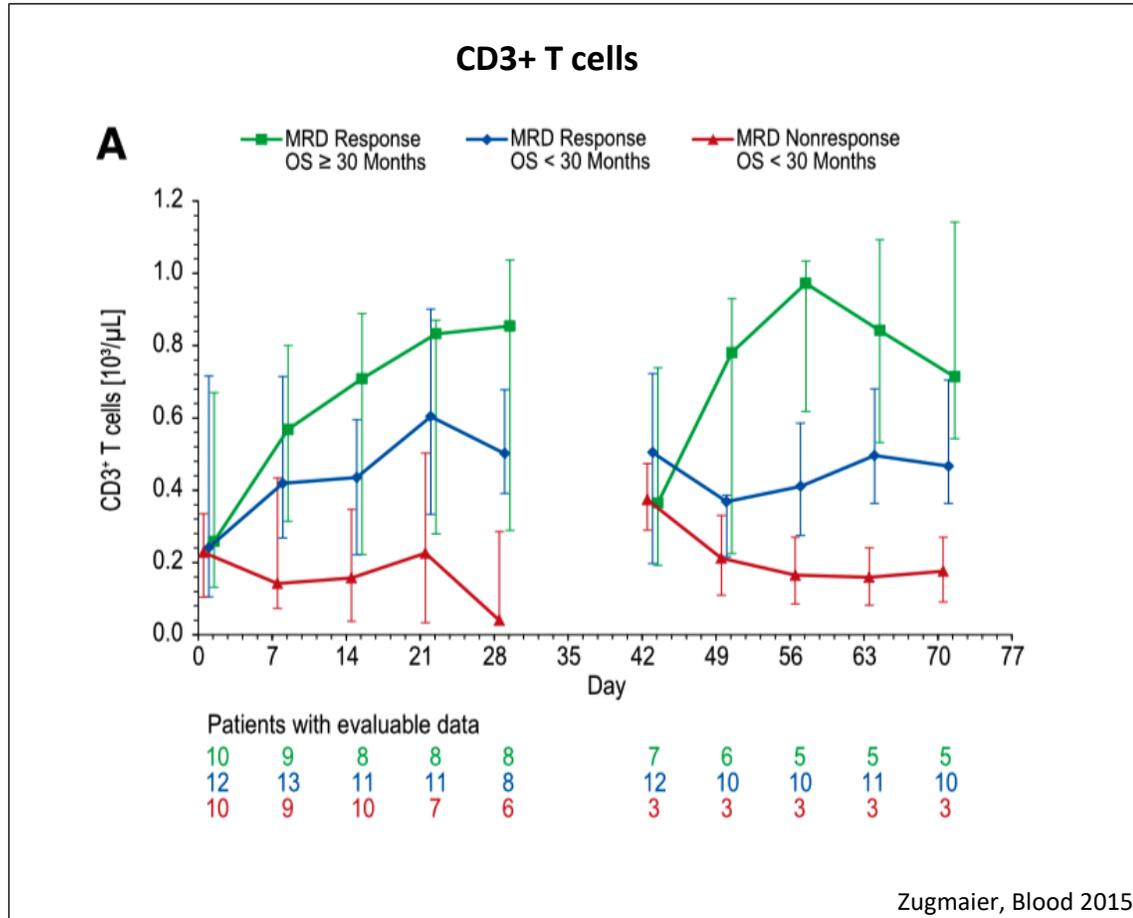
Blina in r/r B-ALL: Best OS in salvage 1 (S1), Median OS 11 months



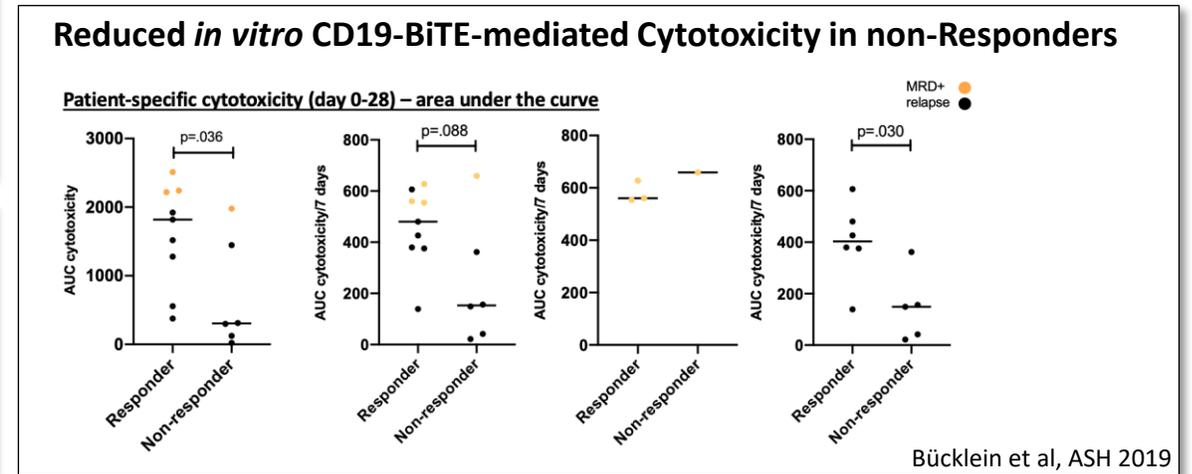
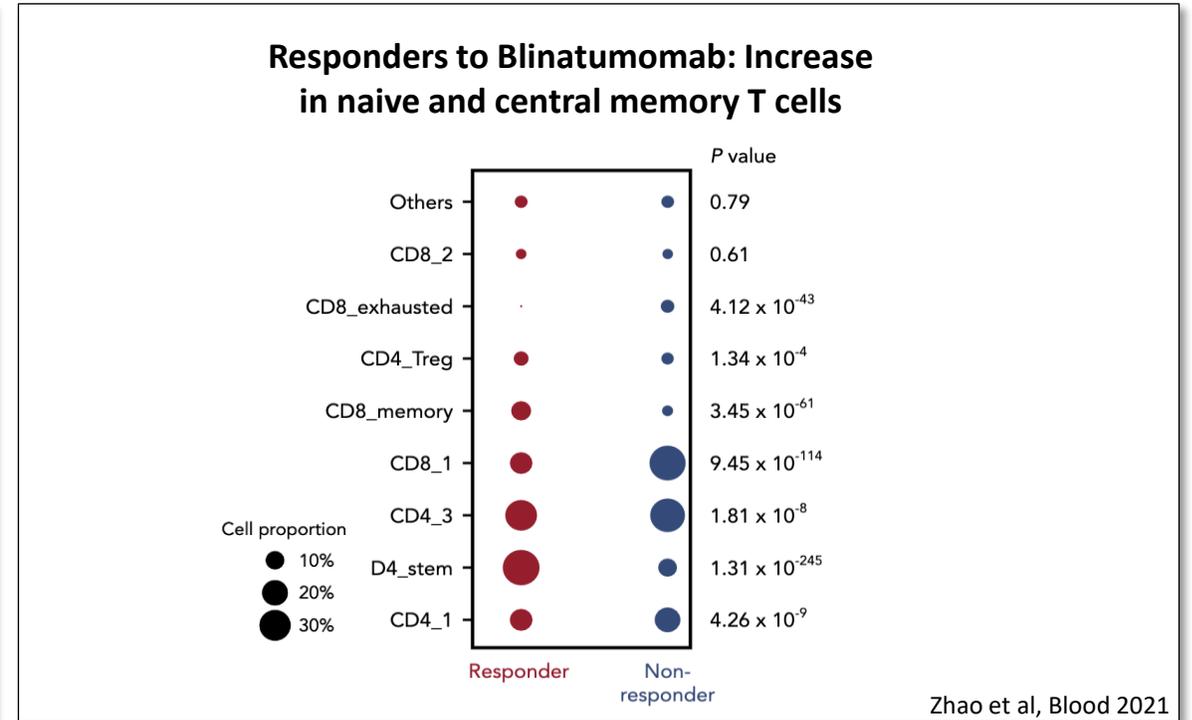
| Patients at risk: | 0   | 0.5 | 1.0 | 1.5 | 2.0 |
|-------------------|-----|-----|-----|-----|-----|
| S1: blinatumomab  | 104 | 80  | 59  | 39  | 26  |
| S1: SOC           | 63  | 39  | 26  | 18  | 11  |
| S2+: blinatumomab | 167 | 96  | 65  | 40  | 19  |
| S2+: SOC          | 71  | 32  | 15  | 9   | 6   |

\*Stratified long-rank P-value.

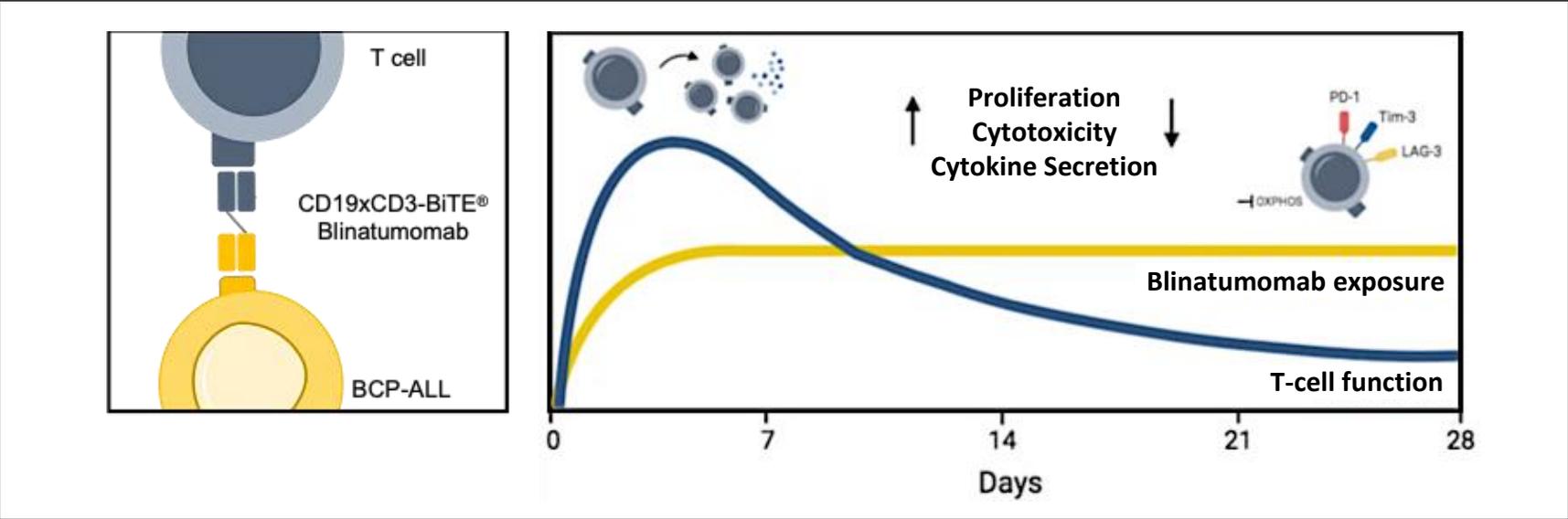
# T cell Fitness & Composition Determines Response Rate



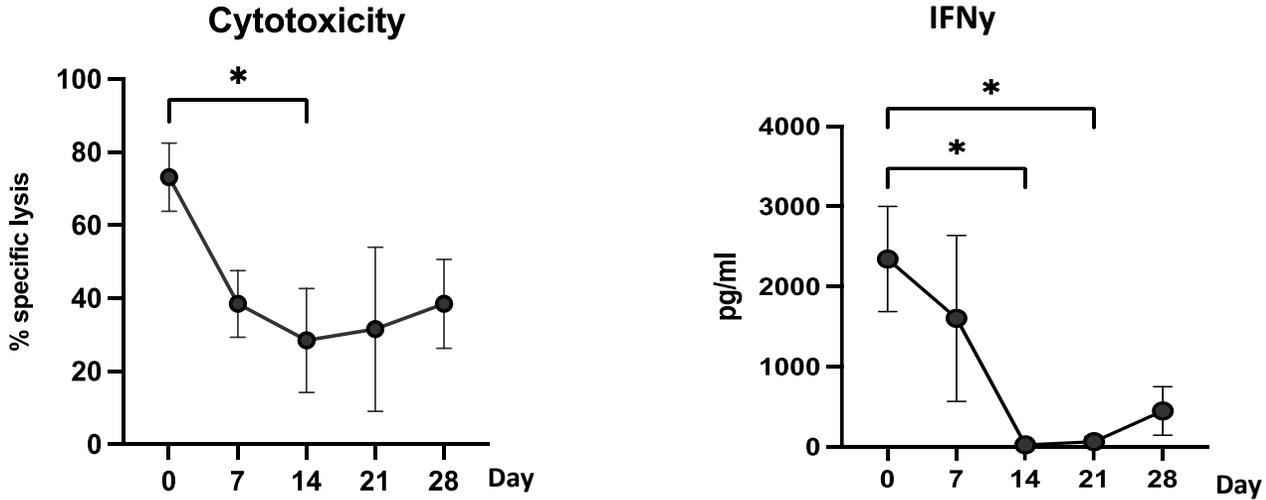
**Long-term survivors (ie, MRD responders with OS >30 months) showed a higher degree of T-cell expansion during treatment cycles 1 and 2**



# Hypothesis: Continuous Exposure to Bispecifics Induces T-cell Exhaustion

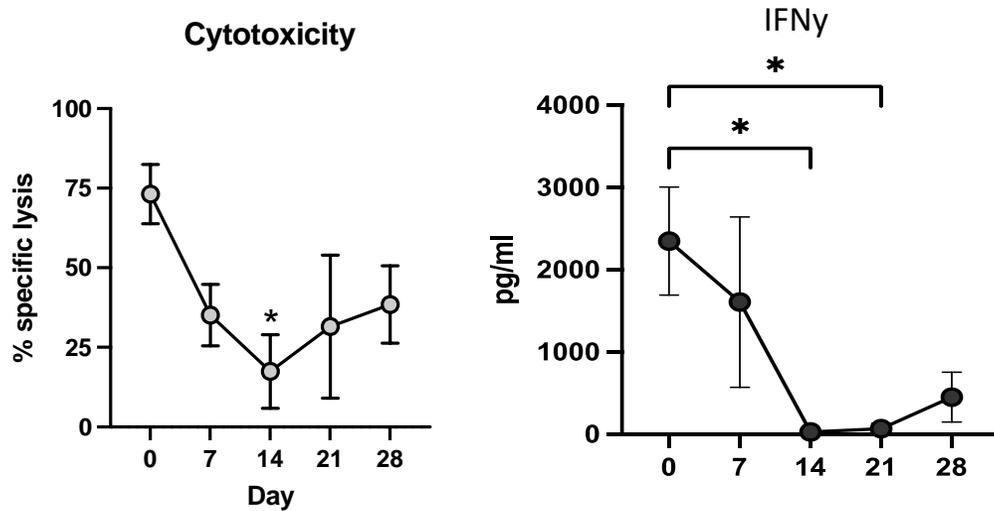
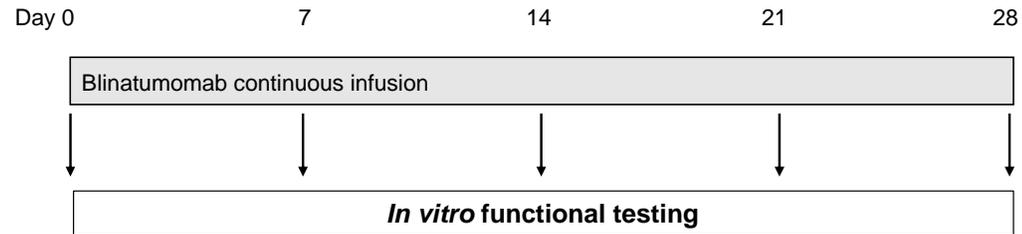


## Immunomonitoring of ALL pt on Blin Tx (CD19 x CD3 BiTE)

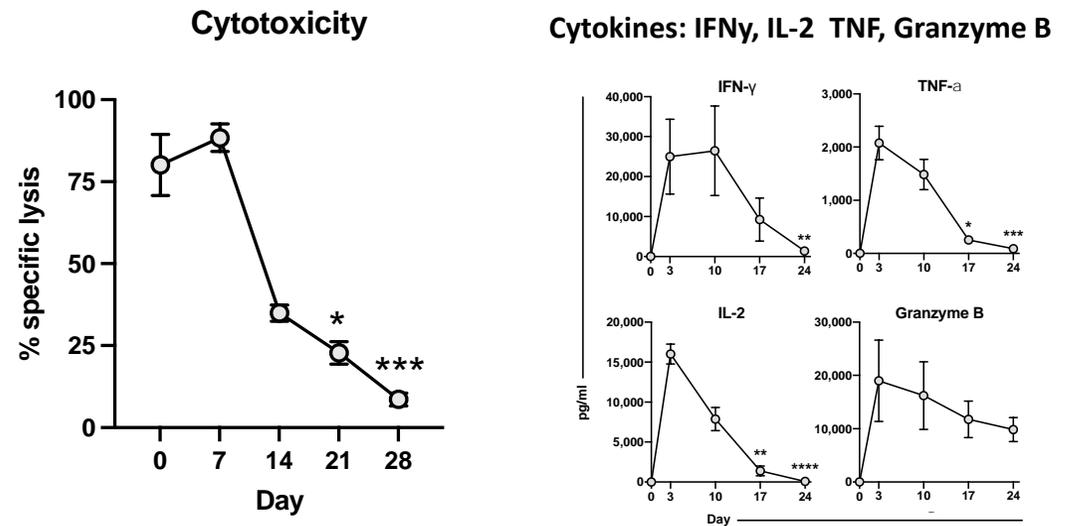
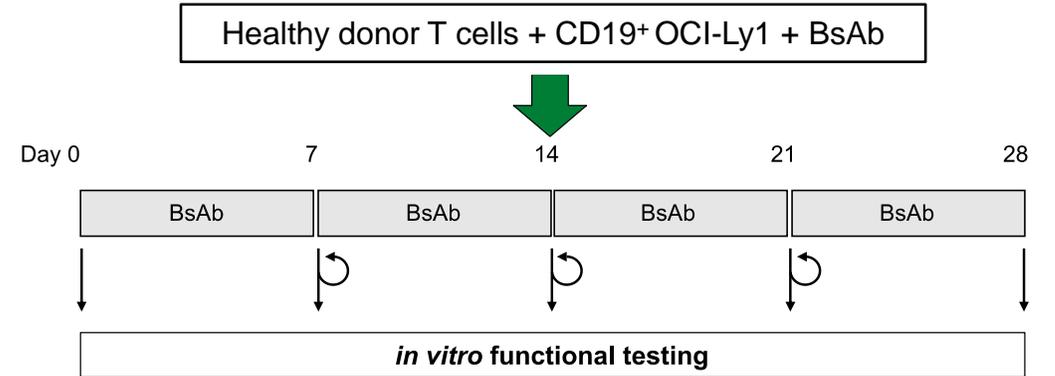


# In Vitro Model System Mimics Continuous BsAb Exposure in Patients

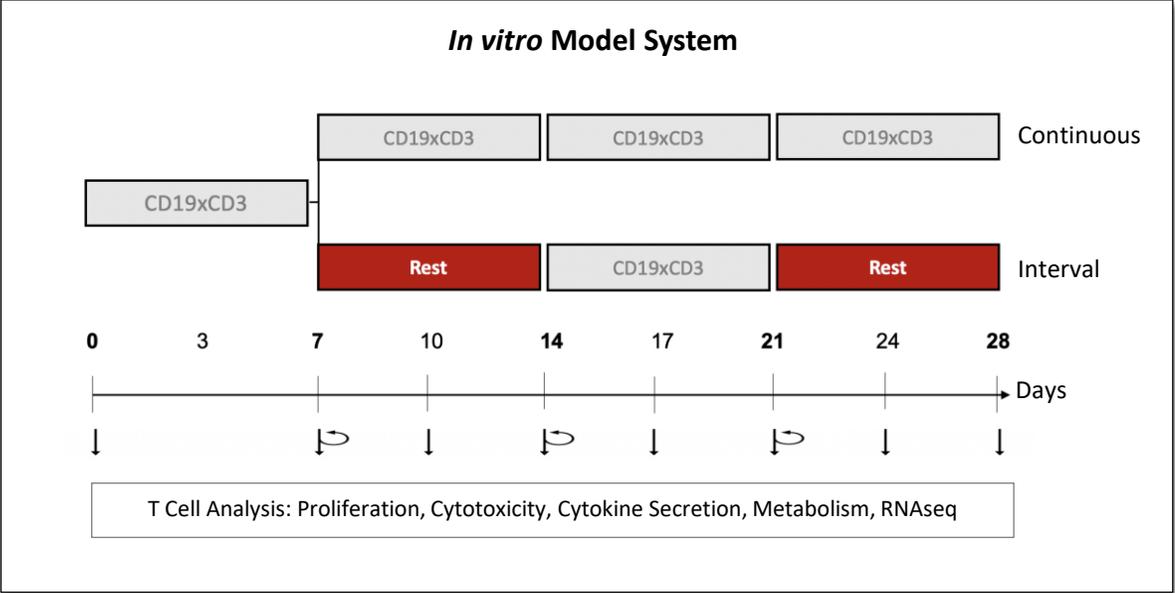
## Patient data: Continuous Blinatumomab Infusion



## *In vitro* Model System of Continuous BsAb Exposure



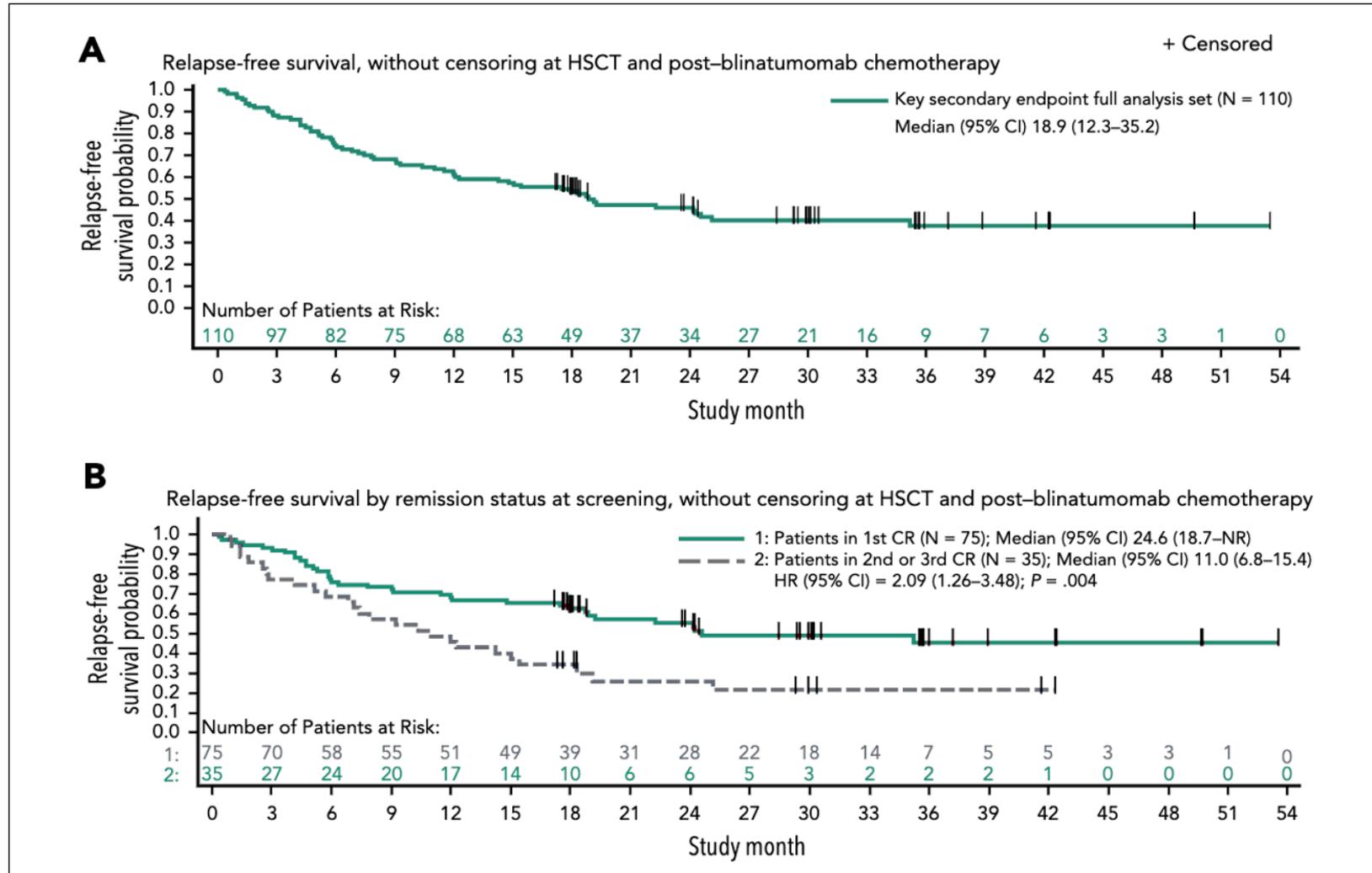
# Continuous CD19 BiTE exposure induced T cell exhaustion Reversed by Resting





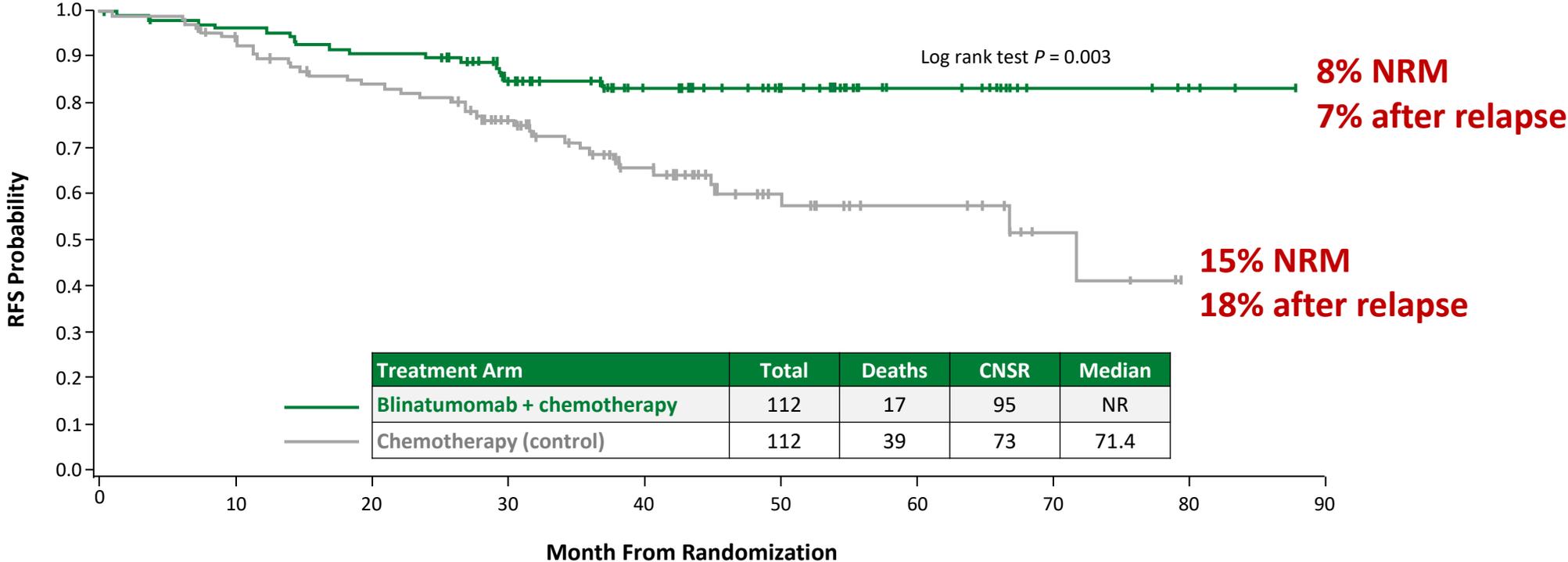
# Relevance of T cell exhaustion in an MRD setting unknown (less target antigens ?)

Blinatumomab in MRD<sup>+</sup> (> 0.1 %): MRD Conversion Rate after 1 Cycle of 78%, the majority received allo SCT



# MRD negative setting (< 0.01%): ECOG-ACRIN (E1910) - Randomized Trial with Blinatumomab consolidation in de-novo BCP-ALL

Deaths on Blin+Chemo Arm = 17 (2° to ALL = 8, NRM = 9), Chemo Arm = 39 (2° to ALL = 20, NRM = 17, Unknown=2)



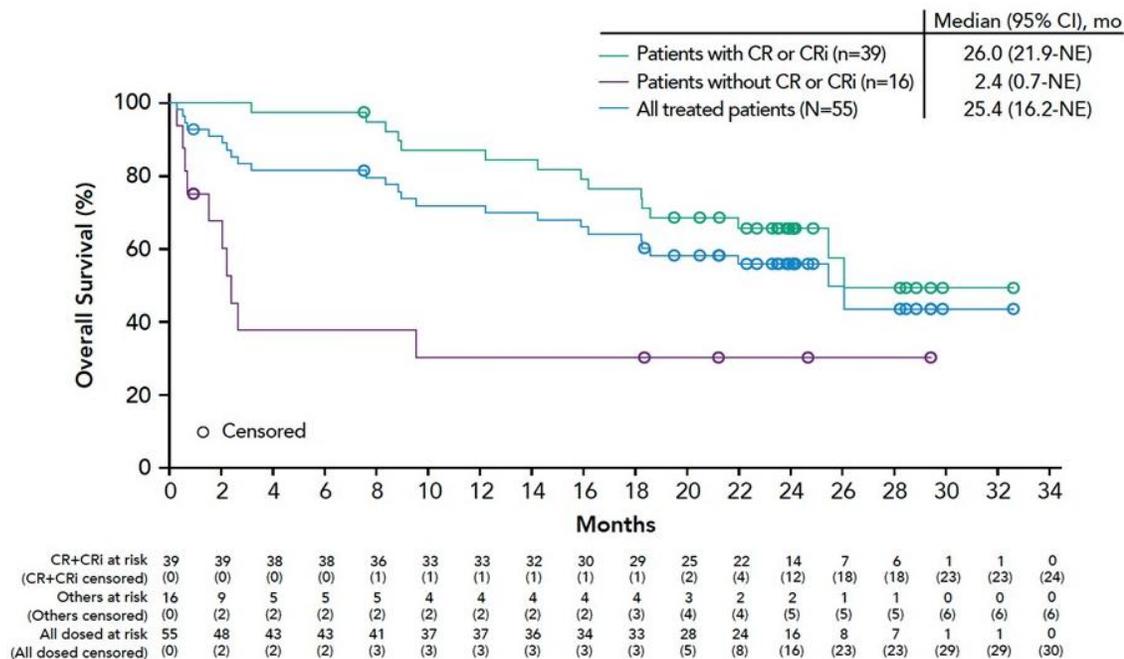
**With a median follow-up of 43 months, median OS in MRD– patients was NR in the Blinatumomab arm vs 71.4 months in the control arm (HR, 0.42; 95% CI, 0.24–0.75; log rank P = 0.003)**



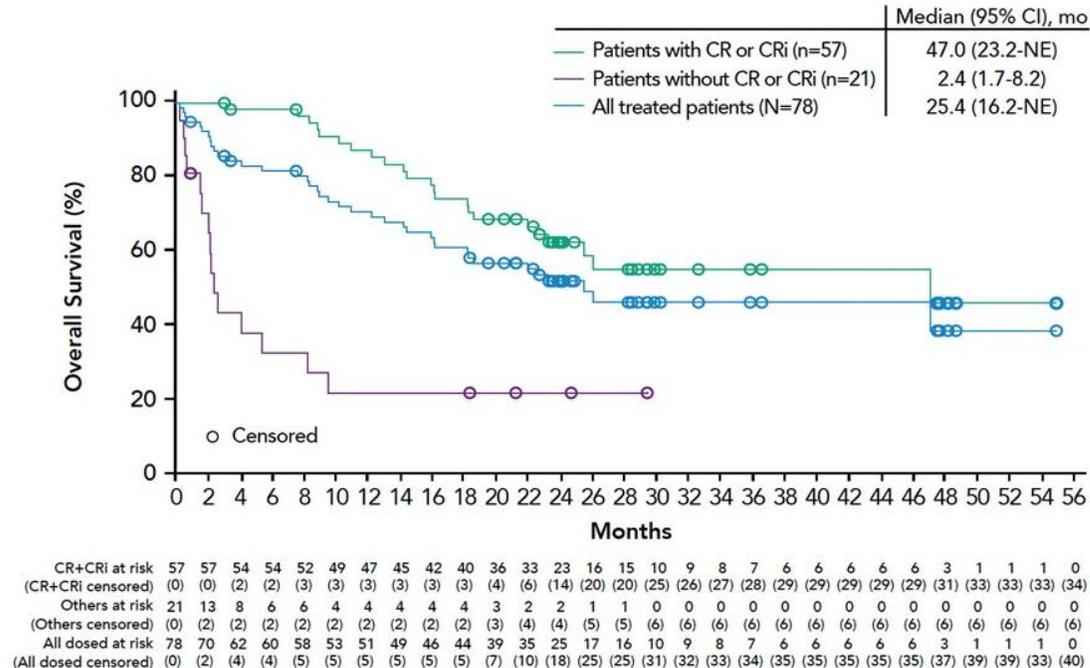
# ZUMA-3 Trial: CD19 CART (Brexu-Cel) in R/R BCP-ALL (Ph 1: n=23; Ph 2 n=55)

Phase 1: 2 × 10<sup>6</sup>, 1 × 10<sup>6</sup>, or 0.5 × 10<sup>6</sup> cells per kg, Phase 2: 1 × 10<sup>6</sup>

## OS in Phase 2 Treated Patients (N=55)



## OS in Pooled Phase 1 and 2 Treated Patients (N=78)



- Median OS was 25.4 months for both Phase 2 treated patients (N=55) and pooled Phase 1 and 2 treated patients (N=78), and was not yet reached in Phase 2 patients who achieved CR
- Efficacy outcomes were similar among the Phase 2 treated patients (N=55) and the pooled analysis of Phase 1 and 2 patients (N=78)

## BsAb => CART: 25/55 prior Blin exposed (all pts were CD19+ at time of ZUMA-3 inclusion)

| Characteristics  | N=55                |
|--|---------------------|
| Age, median (range), years   | 40 (19–84)          |
| Male, n (%)  | 33 (60)             |
| ECOG PS of 1, n (%)  | 39 (71)             |
| Philadelphia chromosome-positive, n (%)  | 15 (27)             |
| CNS-1 disease at baseline, n (%) <sup>a</sup>  | 55 (100)            |
| Number of prior therapies, median (range)  | 2 (1–8)             |
| ≥3 prior lines of therapy, n (%)   | 26 (47)             |
| <b>Prior Blinatumomab, n (%)</b>   | <b>25 (45)</b>      |
| Prior Inotuzumab ozogamicin, n (%)   | 12 (22)             |
| Prior alloSCT, n (%)   | 23 (42)             |
| Relapsed/refractory subgroup, n (%)  |                     |
| Primary refractory   | 18 (33)             |
| Relapsed/refractory to ≥2 prior systemic therapy lines   | 43 (78)             |
| First relapse with remission ≤12 months  | 16 (29)             |
| Relapsed/refractory post-SCT <sup>b</sup>  | 24 (44)             |
| <b>BM blasts at screening, median (range), %</b>   | <b>65.0 (5–100)</b> |
| <b>BM blasts at preconditioning after bridging chemotherapy, median (range), %<sup>c</sup></b> | <b>59.0 (0–98)</b>  |

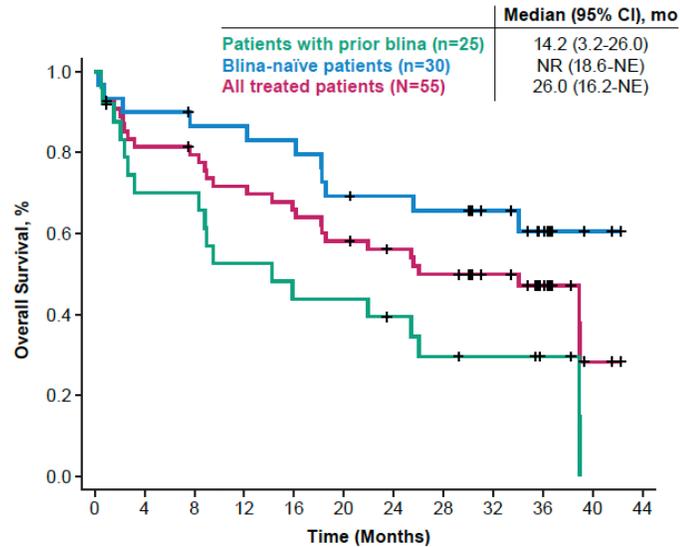
## Efficacy Outcomes in ZUMA-3 by Prior Blinatumomab Exposure: lower CR/CRi rates

The overall CR/CRi rates were numerically lower in patients with prior blinatumomab therapy compared with patients without prior blinatumomab therapy

| Category                     | N  | Overall CR/CRi rate, n (%) | CR, n (%) | CRi, n (%) | BFBM, n (%) | No response, n (%) | Median DOR, mo (95% CI) <sup>b, c</sup> | Median RFS, mo (95% CI) <sup>b</sup> |
|------------------------------|----|----------------------------|-----------|------------|-------------|--------------------|---|--------------------------------------|
| Phase 1 and 2 <sup>a,d</sup> | 78 | 57 (73)                    | 47 (60)   | 10 (13)    | 6 (8)       | 12 (15)            | 18.6 (9.6-24.1)                         | 11.7 (6.1-20.5)                      |
| Age                          |    |                            |           |            |             |                    |   |                                      |
| <26 years                    | 15 | 11 (73)                    | 9 (60)    | 2 (13)     | 1 (7)       | 1 (7)              | 14.6 (0.7-NE)                           | 15.5 (0.0-NE)                        |
| ≥26 years                    | 63 | 46 (73)                    | 38 (60)   | 8 (13)     | 5 (8)       | 11 (17)            | 20.0 (9.4-24.1)                         | 11.6 (5.6-22.1)                      |
| Prior Blinatumomab           |    |                            |           |            |             |                    |   |                                      |
| Yes                          | 38 | 24 (63)                    | 18 (47)   | 6 (16)     | 4 (11)      | 8 (21)             | 14.6 (9.6-24.1)                         | 7.3 (0.0-15.5)                       |
| No                           | 40 | 33 (83)                    | 29 (73)   | 4 (10)     | 2 (5)       | 4 (10)             | 18.6 (5.2-NE)                           | 11.7 (6.1-NE)                        |

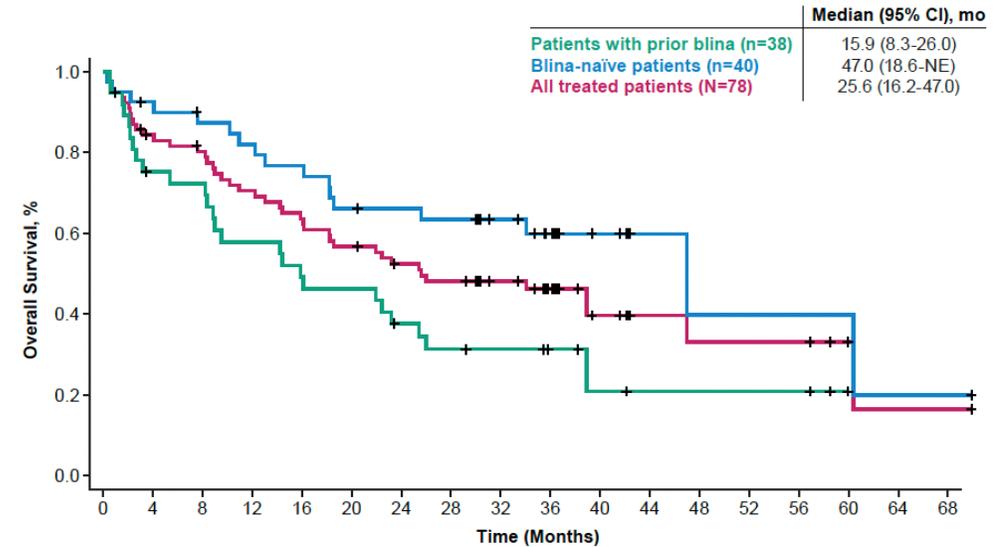
# Overall Survival in ZUMA-3 by Prior Blinatumomab Exposure: pts do worse

## OS in Phase 2 Treated Patients by Prior Blinatumomab



|                               | 0   | 4   | 8   | 12  | 16  | 20  | 24  | 28  | 32   | 36   | 40   | 44   |
|-------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|
| <b>No. at risk (censored)</b> |     |     |     |     |     |     |     |     |      |      |      |      |
| Prior blina                   | 25  | 16  | 16  | 12  | 10  | 10  | 8   | 6   | 5    | 3    | 0    | 0    |
|                               | (0) | (2) | (2) | (2) | (2) | (2) | (3) | (3) | (4)  | (6)  | (7)  | (7)  |
| Blina naïve                   | 30  | 27  | 25  | 25  | 24  | 20  | 19  | 18  | 14   | 8    | 2    | 0    |
|                               | (0) | (0) | (1) | (1) | (1) | (1) | (2) | (2) | (6)  | (11) | (17) | (19) |
| All                           | 55  | 43  | 41  | 37  | 34  | 30  | 27  | 24  | 19   | 11   | 2    | 0    |
|                               | (0) | (2) | (3) | (3) | (3) | (3) | (5) | (5) | (10) | (17) | (24) | (26) |

## OS in Pooled Phase 1 and 2 Treated Patients by Prior Blinatumomab



|                               | 0   | 4   | 8   | 12  | 16  | 20  | 24  | 28  | 32   | 36   | 40   | 44   | 48   | 52   | 56   | 60   | 64   | 68   |
|-------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|------|------|------|------|------|------|
| <b>No. at risk (censored)</b> |     |     |     |     |     |     |     |     |      |      |      |      |      |      |      |      |      |      |
| Prior blina                   | 38  | 26  | 25  | 20  | 17  | 16  | 12  | 10  | 9    | 7    | 4    | 3    | 3    | 3    | 3    | 0    | 0    | 0    |
|                               | (0) | (3) | (3) | (3) | (3) | (3) | (4) | (4) | (5)  | (7)  | (8)  | (9)  | (9)  | (9)  | (9)  | (12) | (12) | (12) |
| Blina naïve                   | 40  | 36  | 33  | 31  | 29  | 25  | 24  | 23  | 19   | 13   | 7    | 3    | 2    | 2    | 2    | 2    | 1    | 1    |
|                               | (0) | (1) | (2) | (2) | (2) | (2) | (3) | (3) | (7)  | (12) | (18) | (22) | (22) | (22) | (22) | (22) | (22) | (22) |
| All                           | 78  | 62  | 58  | 51  | 46  | 41  | 36  | 33  | 28   | 20   | 11   | 6    | 5    | 5    | 5    | 2    | 1    | 1    |
|                               | (0) | (4) | (5) | (5) | (5) | (5) | (7) | (7) | (12) | (19) | (26) | (31) | (31) | (31) | (31) | (34) | (34) | (34) |

**Longer median OS was observed for blinatumomab-naïve patients compared with patients who had prior blinatumomab therapy for both Phase 2 and pooled Phase 1 and 2 patients; however, patients with prior blinatumomab still experienced a median OS of >14 months**

Although most baseline patient and disease characteristics were similar among pooled Phase 1 and 2 patients with and without prior blinatumomab, median BM blast levels at baseline were 70% vs 54%, respectively, and the median number of prior therapies was 3 (range, 1-8) vs 2 (range, 1-5), respectively

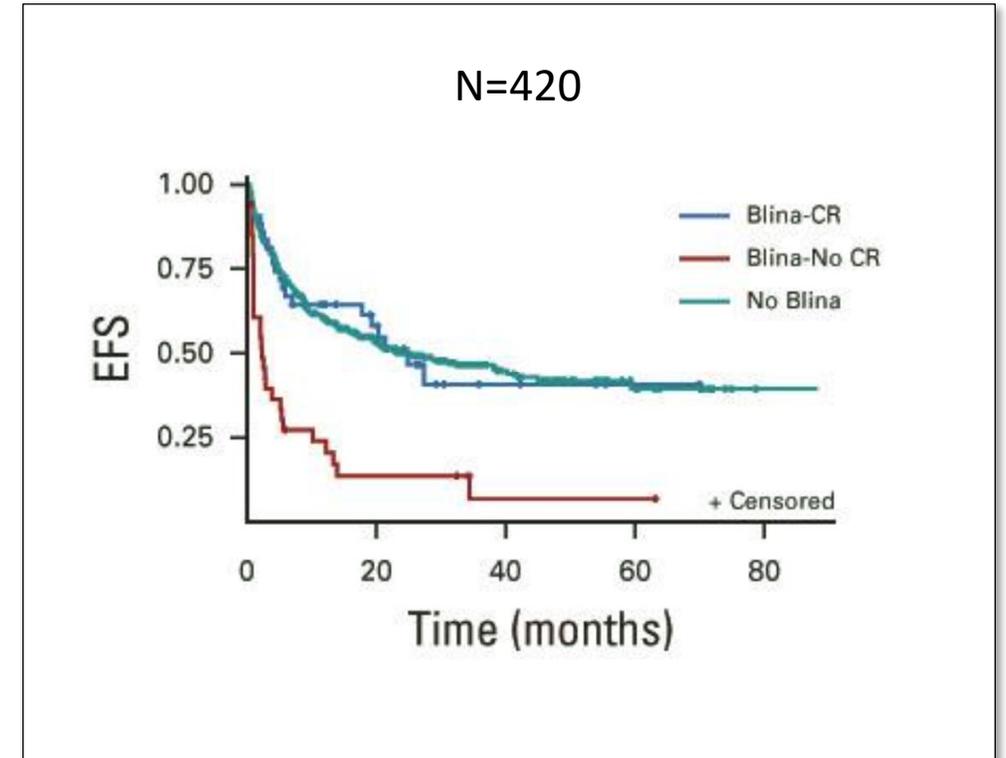
## Summary of Best Overall Responses for Patients with Blinatumomab as Last Prior Therapy in ZUMA-3: 12/17 responded to Brexu-Cel including 8/10 with no blin response

|  |    | Best response to Brexu-cel |           |            |             |           |
|--|----|----------------------------|-----------|------------|-------------|-----------|
|  | N  | Overall CR/CRi rate, n (%) | CR, n (%) | CRi, n (%) | BFBM, n (%) | NR, n (%) |
| <b>Phase 1 and 2 patients with blina as last prior therapy</b> | 17 | 12 (71)                    | 10 (59)   | 2 (12)     | 3 (18)      | 2 (12)    |
| Best response to prior blina                                   |    |                            |           |            |             |           |
| CR   | 6  | 3 (50)                     | 3 (50)    | 0          | 1 (17)      | 2 (33)    |
| PR   | 1  | 1 (100)                    | 0         | 1 (100)    | 0           | 0         |
| NR   | 3  | 3 (100)                    | 2 (67)    | 1 (33)     | 0           | 0         |
| PD   | 7  | 5 (71)                     | 5 (71)    | 0          | 2 (29)      | 0         |

- Of the **38 Phase 1 and 2 patients with prior blinatumomab** therapy, **17 (45%) had blinatumomab as their last prior therapy with a median time from blinatumomab to brexu-cel therapy of 3.4 months** (range, 2.3-45.7)
- **Among patients with blinatumomab as their last prior therapy, 71% (12/17) achieved CR/CRi with brexu-cel therapy including 8/10 patients with no response (NR) or progressive disease (PD) as the best response to prior blinatumomab therapy**

## Blin => CART: Non-response to Blinatumomab is associated with inferior outcomes

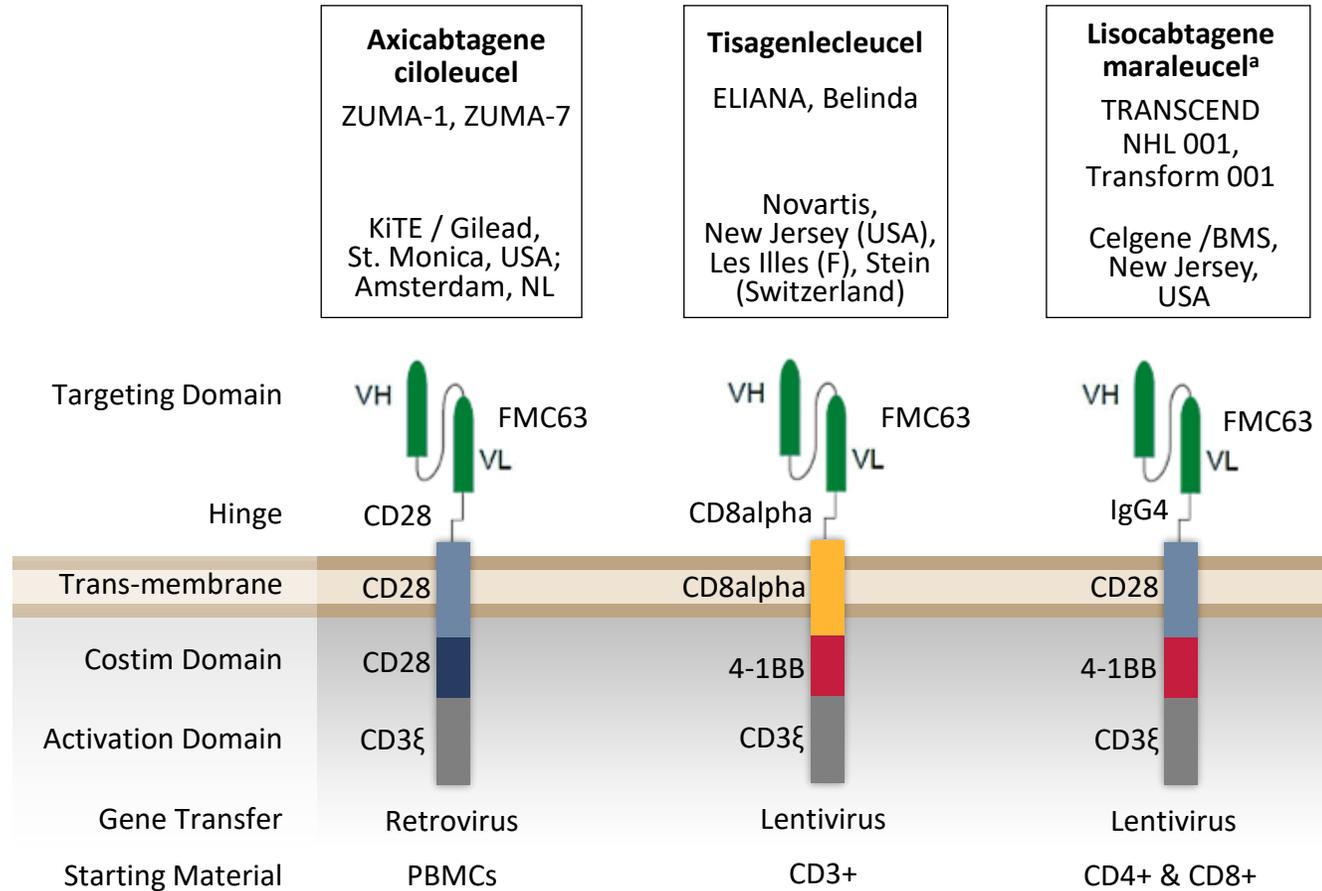
- Single-center analysis: inferior outcomes after CART in patients that had received prior blin
- **CAR-multicenter analyiss (CAR-MA), a retrospective study of 420 patients showed**
  - **NR to prior blina was associated with poor EFS**
  - **Relapse immunophenotype did not differ by blina exposure**
  - **Possible mechanisms: Intrinsic T cell dysfunction? Immunotherapy resistance? Adverse impact of extensive prior therapy?**



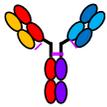
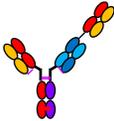
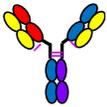
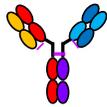
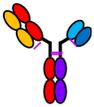
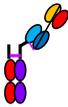
# Starting 2018: CART Products in indolent and aggressive B-cell lymphoma

## Differences in

- Starting material
- Production Sites
- Spacer and Transmembrane Domain
- Co-stimulatory Domains
- Gene Transfer
- Activation & Expansion Protocol

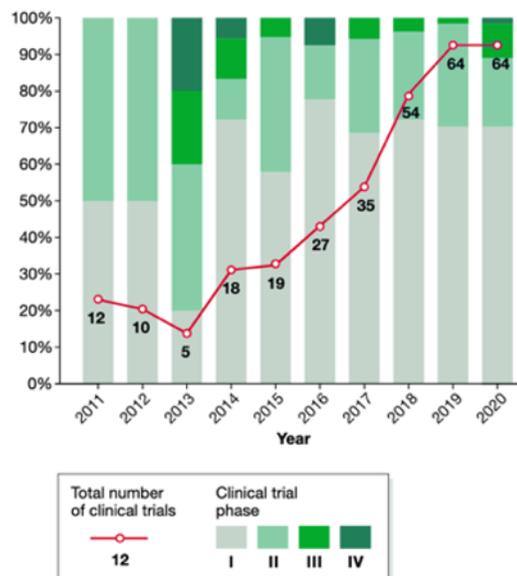


# Starting 2022: Bispecific Antibodies in indolent & aggressive B-cell Lymphoma

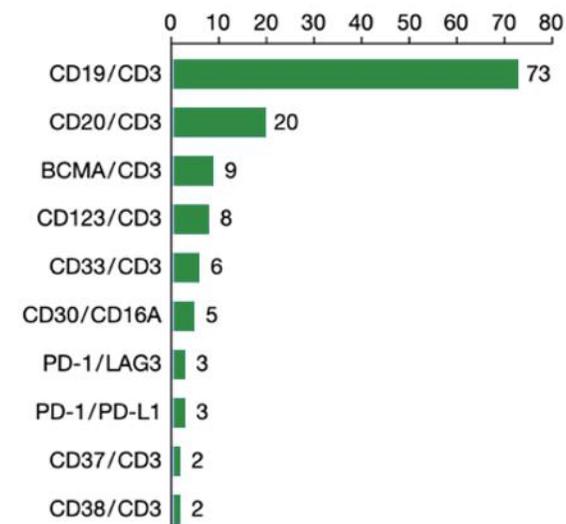
| Ab type      | CD20/CD3  |  |   | CD19/CD3  |   |   |
|--------------|---|--|---|---|---|---|
|              | Mosunetuzumab   | Glofitamab   | Epcoritamab   | REGN1979  | Plamotamab  | Blinatumomab  |
| Structure    |  |  |  |  |  |  |
| Manufacturer | Genentech   | Roche  | GenMab  | Regeneron   | Xencor  | Amgen   |

Hutchings M, et al. ASH 2018. Abstract #226. Lancet 2021, JCO 2021. Budde LE, et al. ASH 2018. Abstract #399. Banerji R, et al. ASH 2018. Abstract #1690. Coyle L, et al. ASH 2018. Abstract #400

## Past 10 Years: Increasing Number of Phase I Trials



## Target Antigens: CD19 >> CD20 > BCMA



# R/R FL: Higher ORR/CR & PFS after Axi-cel & Tisa-Cel compared to Mosunotuzumab

Mosunetuzumab in comparison with CD19CAR T cells

|                 | target | Enrolled /treated | age        | Median prior lines | Prior ASCT | POD24 | ORR/CR   | PFS       |
|-----------------|--------|-------------------|------------|--------------------|------------|-------|----------|-----------|
| <b>Mosun</b>    | CD20   | 90/90             | 60 (29-90) | 3 (2-10)           | 21%        | 52%   | 80%, 60% | 24 mo 48% |
| <b>Axi cel</b>  | CD19   | 124/124           | 60 (53-67) | 3 (2-4)            | 24%        | 55%   | 94%, 79% | 18 mo 65% |
| <b>Tisa cel</b> | CD19   | 98/97             | 57 (29-73) | 4 (2-13)           | 36%        | 63%   | 86%, 69% | 24 mo 57% |

|                 | CRS       |           | NT        |                    | Infection |
|-----------------|-----------|-----------|-----------|--------------------|-----------|
|                 | Any grade | ≥ Grade 3 | Any grade | ≥ Grade 3          | Any grade |
| <b>Mosun</b>    | 44%       | 2.2%      | 4%        | 0                  | 20%       |
| <b>Axi cel</b>  | 78%       | 6%*       | 56%       | 15%                | 18%**     |
| <b>Tisa cel</b> | 49%       | 0         | 37%       | 3%<br>3 gr3, 1 gr4 | 19%       |

1 grade 5 event

\*\* from all pts treated on ZUMA-5 including FL+ MZL

# CART => BsAb: data from Mosunetuzumab post CART

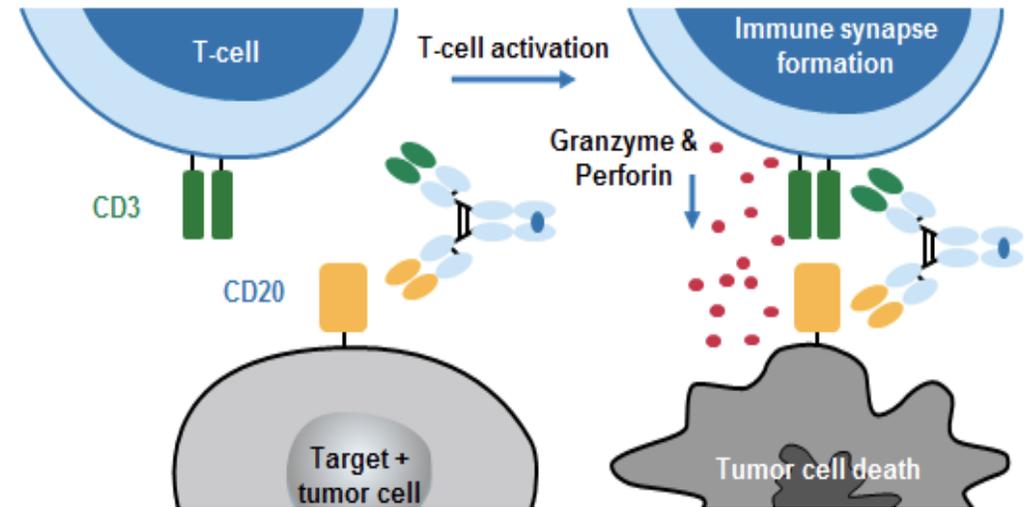
- **Mosunetuzumab (RG7828; BTCT4465A)**

- Full-length, fully humanized IgG1 bispecific antibody<sup>1</sup>
- Redirects T cells to engage and eliminate B cells; T-cell activation, cytokine elevation and increase in TILs observed (Hernandez et al. ASH 2019 P-1585)
- No ex-vivo T cell manipulation required ('off-the-shelf' and no delay in treatment)

- **GO29781**

- We report data for 270 R/R B-cell NHL pts, included Phase I/Ib dose-escalation and expansion study in heavily pre-treated R/R B-cell NHL
- Cycle 1 step-up dosing: mitigates CRS, allowing dose escalation to maximize therapeutic potential<sup>2,3</sup>

- **We report data for 270 R/R B-cell NHL pts, including 30 pts with prior CAR-T**



# Patient population

| n (%)  | N=270*    |                      |
|--|-----------|----------------------|
| Median age, years (range)                          | 62        | (19-96)              |
| Male   | 172       | (63.7%)              |
| ECOG PS 1 at baseline                              | 164       | (61.2%) <sup>†</sup> |
| <b>Aggressive NHL</b>                              | 180       | (66.7%)              |
| DLBCL  | 117       | (43.3%)              |
| trFL   | 32        | (11.9%)              |
| MCL  | 23        | (8.5%)               |
| Other  | 8         | (3.0%)               |
| <b>Indolent NHL</b>                                | 85        | (31.5%)              |
| FL   | 82        | (30.4%)              |
| Other  | 3         | (1.1%)               |
| Median prior systemic therapies, n (range)         | 3         | (1-14) <sup>†</sup>  |
| <b>Prior CAR-T therapy</b>                         | <b>30</b> | <b>(11.1%)</b>       |
| Prior autologous SCT                               | 77        | (28.5%)              |
| Refractory <sup>‡</sup> to last prior therapy      | 194       | (71.9%)              |
| Refractory <sup>‡</sup> to prior anti-CD20 therapy | 233       | (86.3%)              |

## 30 pts with prior CAR-T therapy

- 17 DLBCL, 8 trFL, 5 FL
- Median 5 lines of prior systemic therapies (range 3–14)
- 29 pts (96.7%) refractory to prior anti-CD20 therapy
- 25 pts (83.3%) refractory to last prior therapy
- 22 pts (73.3%) refractory to prior CAR-T therapy

# Patients with prior CAR-T therapy

## Efficacy

|                 | N*       | ORR, n (%)       | CR, n (%)        |
|-----------------|----------|------------------|------------------|
| All histologies | 18       | 7 (38.9%)        | 4 (22.2%)        |
| <b>DLBCL</b>    | <b>9</b> | <b>2 (22.2%)</b> | <b>2 (22.2%)</b> |
| tFL             | 5        | 1 (20.0%)        | 0 (0.0%)         |
| FL              | 4        | 4 (100%)         | 2 (50.0%)        |

\*efficacy-evaluable pts: pts who were enrolled for at least 3 months, or had response data available at any time, or discontinued treatment for any cause; CCOD: Aug 9, 2019

## Case

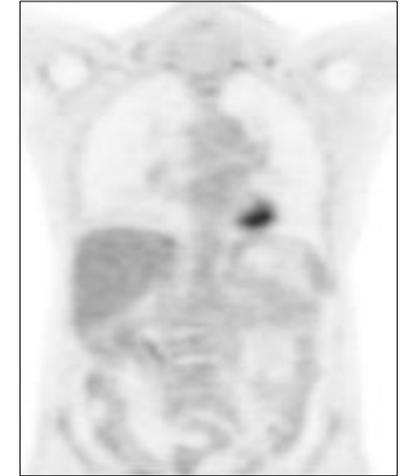
- 58-year old patient with R/R FL
- 8 prior lines of systemic treatment
  - Refractory to prior anti-CD20 and alkylating agents
  - Relapsed after CD19-CAR-T therapy
  - Progressed on checkpoint inhibitor and no response to PI3K inhibitor

Day -12  
(baseline)



CAR-T PCR:  $\leq 50$  copies/ $\mu$ g DNA

After Cycle 3 of  
mosunetuzumab



380 copies/ $\mu$ g DNA

8 months in CR off treatment

## Exploratory biomarkers

- Expansion of lymphocytes (including residual CAR-T cells in 2/8 tested pts)
- CR to mosunetuzumab observed **with** or **without** CAR-T expansion

# bsAb => CART: no data in FL

Sequencing

## Mosenutuzumab after CAR-T Therapy

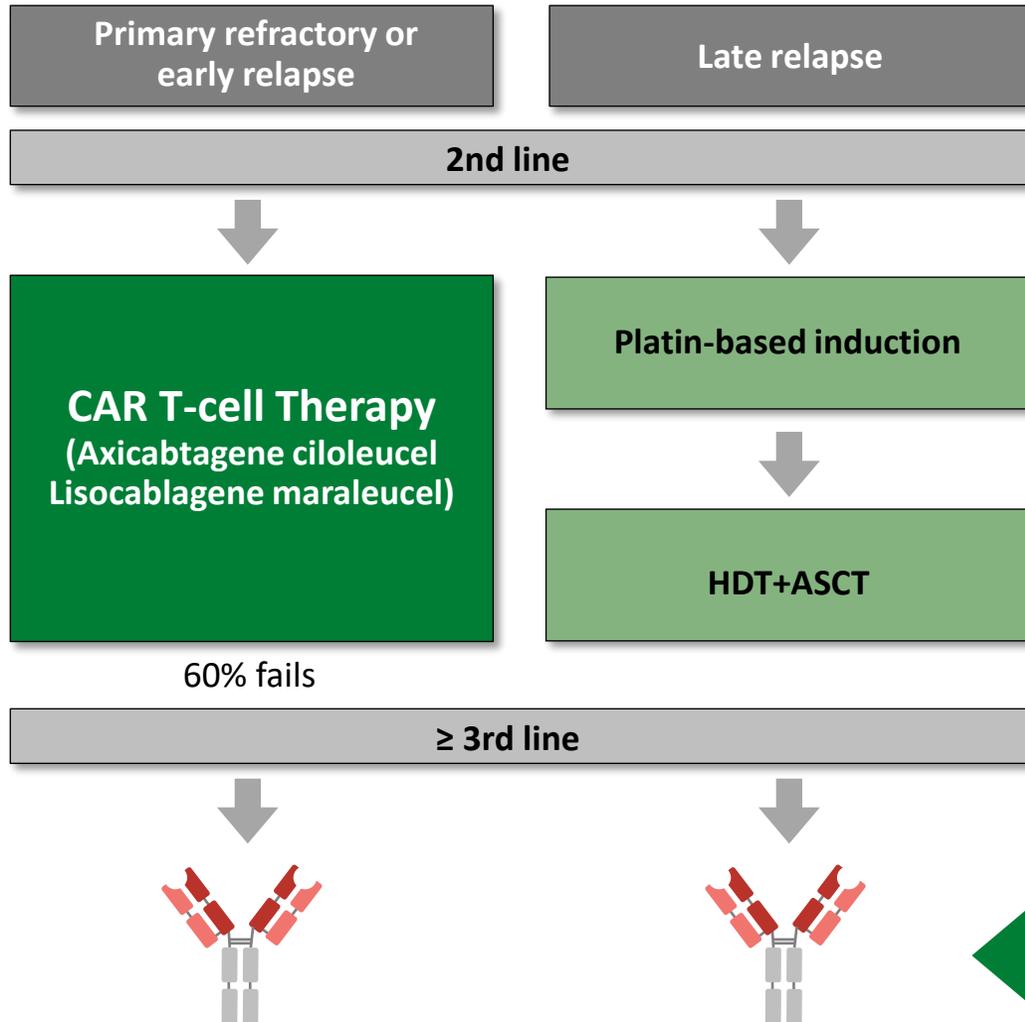
|                        | <b>N*</b> | <b>ORR, n (%)</b> | <b>CR, n (%)</b> |
|------------------------|-----------|-------------------|------------------|
| <b>All histologies</b> | <b>18</b> | <b>7 (38.9%)</b>  | <b>4 (22.2%)</b> |
| DLBCL                  | 9         | 2 (22.2%)         | 2 (22.2%)        |
| trFL                   | 5         | 1 (20.0%)         | 0 (0.0%)         |
| FL                     | 4         | 4 (100%)          | 2 (50.0%)        |

## CAR-T Therapy after Mosenutuzumab

?

# CD20 Bispecific Antibodies & CD19 CART in LBCL, 3rd Line

## CAR-T eligible R/R DLBCL



### CAR-T or bispecific Ab? individual choice based on

- patient characteristics  
(age, co-morbidities, social circumstances)
- disease characteristics  
(high risk, aggressive behavior)
- patient preference

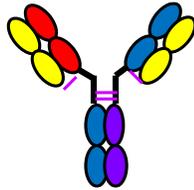


## Summary of Clinical trials for CAR T vs Bispecific antibodies in R/R LBCL, 3rd Line

|                              | Axi-cel   | Tisa-cel    | Lisocel   | Glofitamab | Epcoritamab |
|------------------------------|-----------|-------------|-----------|------------|-------------|
| <b>Median follow-up (mo)</b> | 63        | 49          | 24        | 24         | 20          |
| <b>ORR (%)</b>               | <b>82</b> | <b>52</b>   | <b>73</b> | <b>67</b>  | <b>71</b>   |
| <b>CR (%)</b>                | <b>58</b> | <b>39</b>   | <b>53</b> | <b>39</b>  | <b>39</b>   |
| <b>Median DOR (mo)</b>       | 62        | Not reached | 26        | NR         | 20.8        |
| <b>Ongoing CR</b>            | 30 %      | 26 %        | 26 %      | 31 %       | 27 %        |

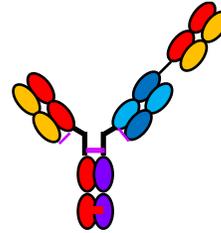
# CD19 CART => BsAb: Slightly decreased CR rates

## Epcoritamab



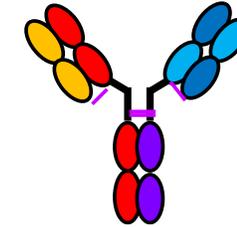
N=157  
mFU 10.7 mos,  
mTTR- 1.4 mos  
1 yr PFS 40%  
ORR 63%, **CR 39%**  
**Post-CART n= 61; CR 35%**  
Grade  $\geq$  3 CRS/NT -6%

## Glofitamab



N=155  
mFU 12.6 mos  
1 yr PFS 37%  
ORR 52%, **CR 39%**  
(78% CR ongoing at 1yr)  
**Post-CART n=52; CR 35%**  
Grade  $\geq$  3 CRS/NT -3%

## Odronestmab



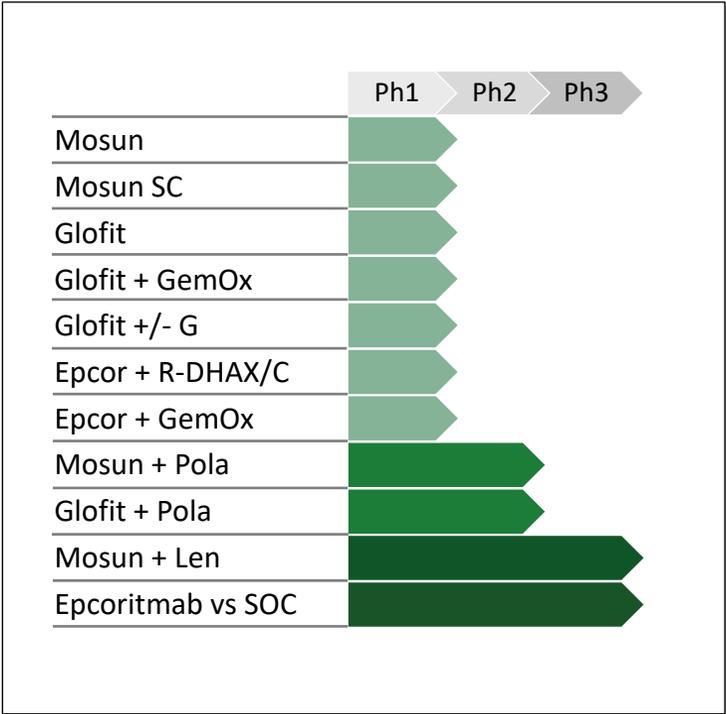
- N=35
- w/o prior CART (n=11): **ORR 55%**  
**Post-CART (n=24): ORR 33%**
- w/o prior CART (n=11): CR 55%
- Post-CART (n=24): CR 21%
- w/o prior CART: 10.3;
- post-CART: 2.8 not yet mature

**BsAb moving up the line...**

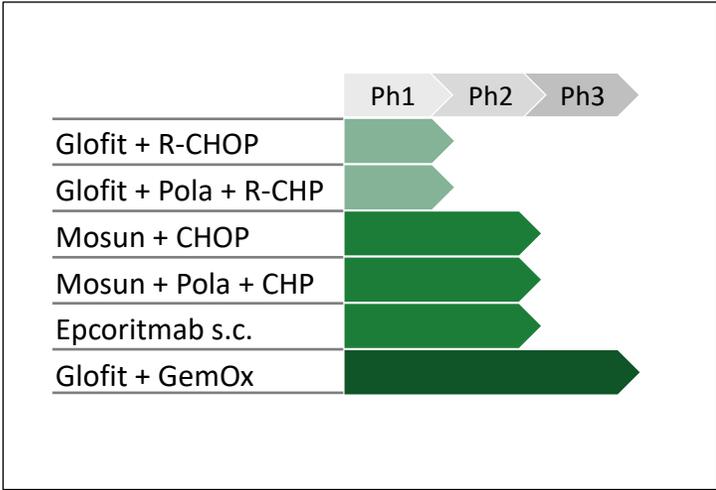


# Bispecifics: > 1000 pts treated so far, Multiple Monotherapy & Combination Studies

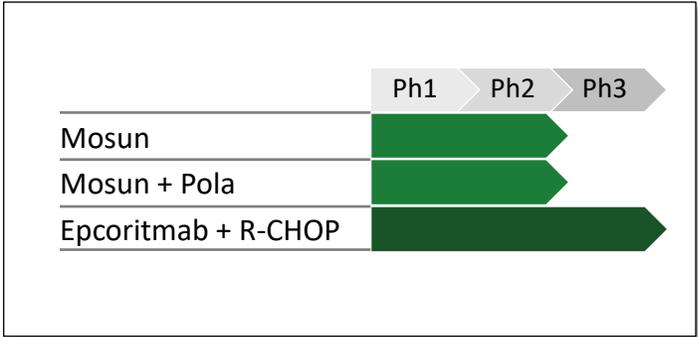
## R/R DLBCL



## 1st LINE DLBCL



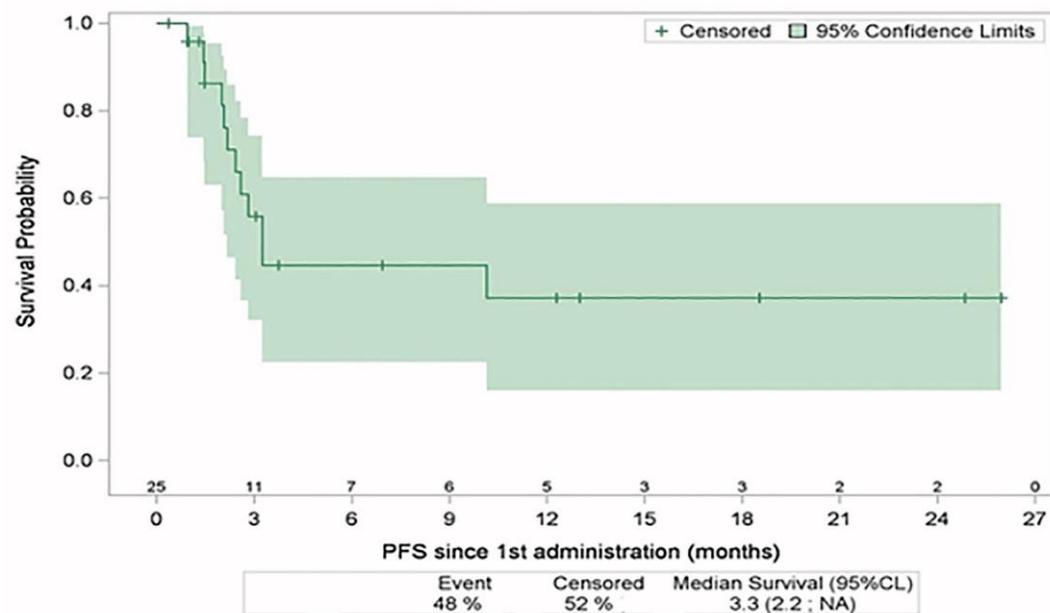
## Elderly/Unfit DLBCL



# BsAb => CART: CAR T cell Therapy remained effective in pts with R/R B-cell lymphoma after bispecifics – results of the Lysa Study based on the Descar T Registry

32 pts, 28 available for analysis, 23/28 LBCL, 1 FL, 3 MCL, 2 FL; prior Tx: 4 (2-9), median time to next treatment: 142 days (range 37–482), ORR: 92 %, CR 46%, median PFS 3.3, median DOR: 2.4

### PFS in LBCL subgroup after CAR T-Cell Therapy



### Outcomes after CAR T-Cells for DLBCL Patients with R/R disease after prior bispecific Antibodies

|                                 | BA therapy          |       | CAR T-cells therapy   |     |
|---------------------------------|---------------------|-------|-----------------------|-----|
| Treatment description           | (CD20xCD3)          | 91.4% | Axi-cel               | 72% |
|                                 | (CD19xCD3)          | 4.3%  |                       |     |
|                                 | (CD22xCD3)          | 4.3%  | Tisa-cel              | 28% |
| <b>Response Rate</b>            |                     |       |                       |     |
| ORR                             | 43.5%               |       | 91.6%                 |     |
| CR                              | 21.7%               |       | 45.8%                 |     |
| PR                              | 21.7%               |       | 45.8%                 |     |
| SD                              | 13.0%               |       | 0%                    |     |
| PD                              | 43.5%               |       | 8.3%                  |     |
| <b>Median PFS [95% CI] (mo)</b> | 3.1 [2.9 ; 4.2]     |       | 3.3 [2.2 ; NR]        |     |
| <b>6 mo PFS [95% CI]</b>        | 17.4% [5.4% ; 35%]  |       | 44.6% [22.4% ; 64.7%] |     |
| <b>1 year PFS [95% CI]</b>      | 4.3% [0.3% ; 18.2%] |       | 37.2% [15.9% ; 58.7%] |     |
| <b>Median DOR [95% CI] (mo)</b> | 2.7 [1.6 ; 4]       |       | 2.4 [1.4 ; NR]        |     |
| <b>1 year DOR [95% CI]</b>      | 10% [0.6% ; 35.8%]  |       | 40.7% [17.4% ; 63.1%] |     |

# Clinical trials for and Bispecific antibodies vs CD19 CARTs

|                                | Axi-cel                 | Tisa-cel                | Mosunetuzumab          | Glofitamab            | Epcoritamab           | Odronextamab           |
|--------------------------------|-------------------------|-------------------------|------------------------|-----------------------|-----------------------|------------------------|
| Trial/NCT                      | ZUMA-1                  | JULIET                  | NCT02500407            | NCT03075696           | NCT03625037           | NCT02290951            |
| N                              | 108                     | 111                     | 270                    | 28                    | 68                    | 136                    |
| All AEs, n (%)<br>Any Grade    | 108<br>100%             | 111<br>100%             | 255<br>94%             | 27<br>96%             | 80<br>100%            | 135<br>99%             |
| All AEs, n (%)<br>Grade ≥ 3    | 106<br>98%              | 99<br>89%               | 170<br>63%             | 11<br>39%             | -                     | 110<br>81%             |
| CRS, n (%)<br>Any Grade        | 100<br>93%              | 64<br>58%               | 78<br>29%              | 19<br>68%             | 40<br>59%             | 83<br>61%              |
| CRS, n (%)<br>Grade ≥ 3        | <b>12</b><br><b>11%</b> | <b>24</b><br><b>22%</b> | <b>3</b><br><b>1%</b>  | <b>2</b><br><b>7%</b> | <b>0</b><br><b>0%</b> | <b>10</b><br><b>7%</b> |
| ICANS. AEs, n (%)<br>Any Grade | 72<br>67%               | 23<br>21%               | 118<br>44%             | 5<br>18%              | 4<br>6%               | -                      |
| ICANS AEs, n (%)<br>Grade ≥ 3  | <b>35</b><br><b>32%</b> | <b>13</b><br><b>12%</b> | <b>10</b><br><b>4%</b> | <b>0</b><br><b>0%</b> | <b>2</b><br><b>3%</b> | -                      |

# Multiple Myeloma: Bispecifics vs CART 10/2023

|   | Bispecific mAbs                              | CAR T-cell Therapy                                  |
|---|--|---|
| <b>FDA Approved Commercial Products</b> | Teclistamab, Talquetamab                     | Idecabtagene vicleucel<br>Ciltacabtagene autoleucel |
| <b>Cost</b>                             | ++<br>~\$400k/year                           | +++<br>>\$400k/dose                                 |
| <b>Availability</b>                     | Off-the-shelf                                | Slots, production times, bridging therapy           |
| <b>Accessibility</b>                    | Beyond academic/major centers<br>REMS        | Academic/major centers<br>REMS                      |
| <b>Administration</b>                   | Weekly or Q2 Weeks, IV or s/c<br>Continuous  | Single cell infusion<br>“one and done”              |
| <b>Responses</b>                        | +++  | ++++  |
| <b>Toxicities</b>                       | CRS (++) , ICANS (+), cytopenias, infections | CRS (+++), ICANS (++) , cytopenias, infections      |

## Currently available FDA approved BCMA Therapies – Late R/R

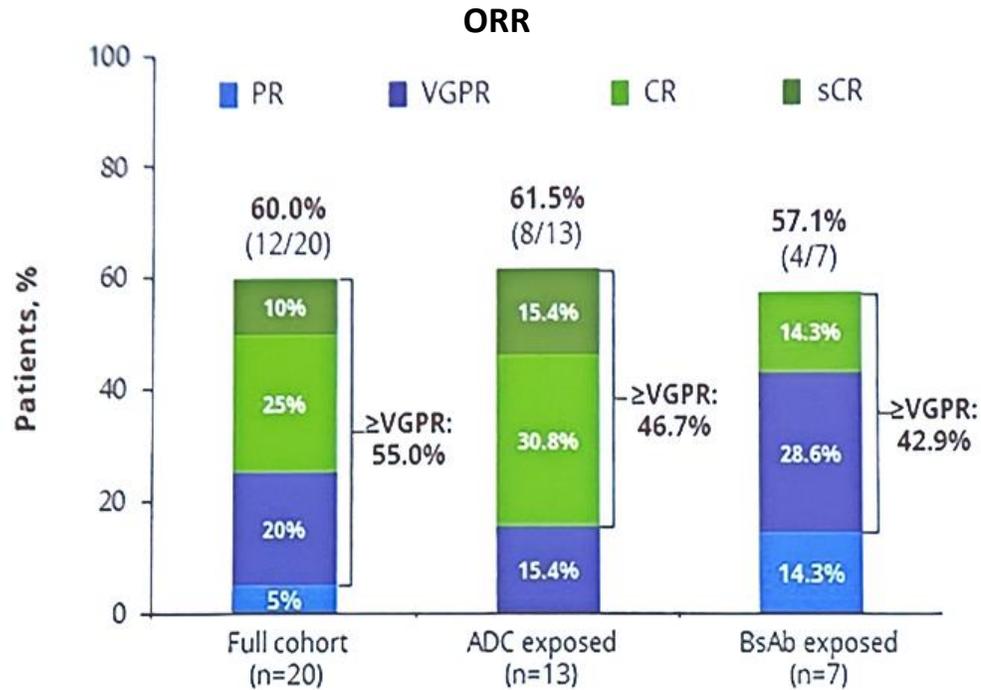
|   | Ide-cel   | Cilta-cel | Teclistamab | Elranatamab                       |
|---|-----------|-----------|-------------|-----------------------------------|
| <b>Efficacy</b>   |           |           |             |                                   |
| Overall Response, %                                       | 73        | 98        | 63          | 61                                |
| Complete Response, %                                      | <b>33</b> | <b>67</b> | <b>59</b>   | <b>35</b>                         |
| Duration of Response, months                              | 10.7      | 33.9      | 18.4        | NR                                |
| Progression free survival, months                         | 8.8       | 34.9      | 11.3        | NR                                |
| <b>Safety</b>   |           |           |             |                                   |
| Cytokine Release Syndrome, any grade ( $\geq$ grade 3), % | 84 (5)    | 95 (5)    | 72 (1)      | 57 (0)                            |
| Hematologic toxicities, any grade ( $\geq$ grade 3), %    | 18 (3)    | 22 (12)   | 15 (1)      | 17(0.8) PN; 14(0) MN; 3.4(0)ICANs |
| Infection Rate, any grade ( $\geq$ grade 3), %            | 69 (22)   | 58 (20)   | 76 (45)     | 69 (40)                           |
| Non-relapse deaths, %                                     | 13        | 16        | 16          | 11                                |

## BsAb => CART: CARTITUDE-2, Cohort C, (n=20): inferior ORR, PFS and DOR

|            | CARTITUDE-1, n=97 | Cohort C<br>CARTITUDE-2, n=20 |
|------------|-------------------|-------------------------------|
| ORR        | 97%               | 60%                           |
| Median PFS | 34.9 mo           | 9.1 mo                        |
| Median DOR | 33.9 mo           | 11.5 mo                       |

- Cohort 2 comprised of 20 patients (13 ADC exposed; 7 BsAb exposed; 1 in the ADC group also had prior BsAb exposure)
- 80% refractory to BCMA
- Median f/up 11.3 months

# BsAb => CART: CARTITUDE-2 Cohort C – Timing



ADC, antibody-drug conjugate; BsAb, bispecific antibody; CR, complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

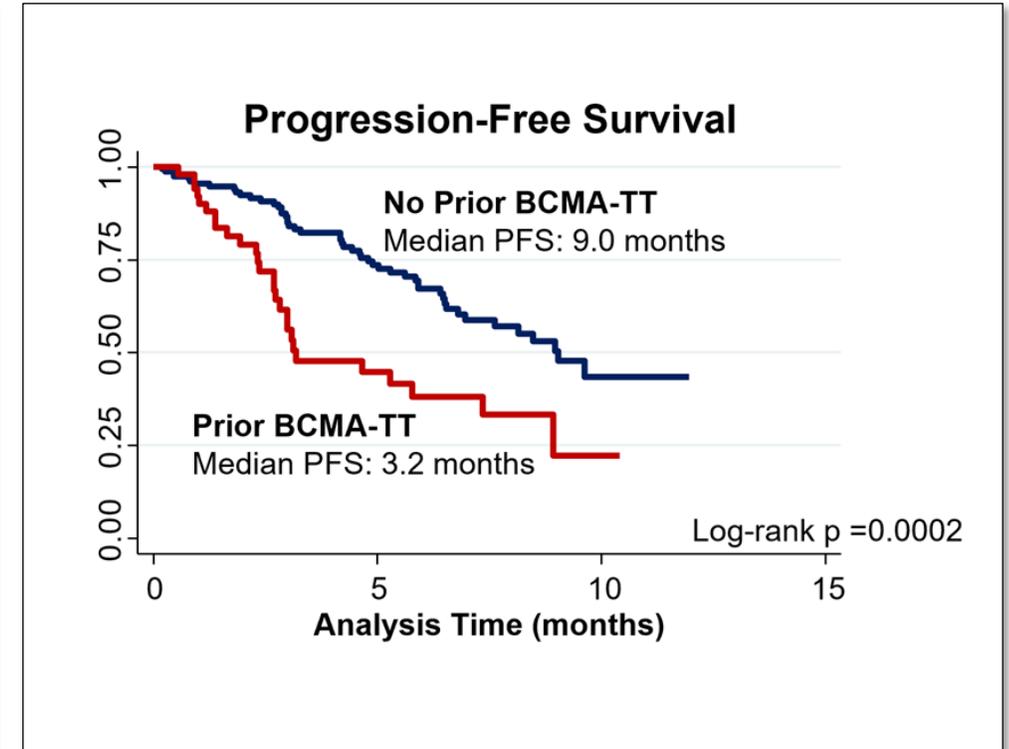
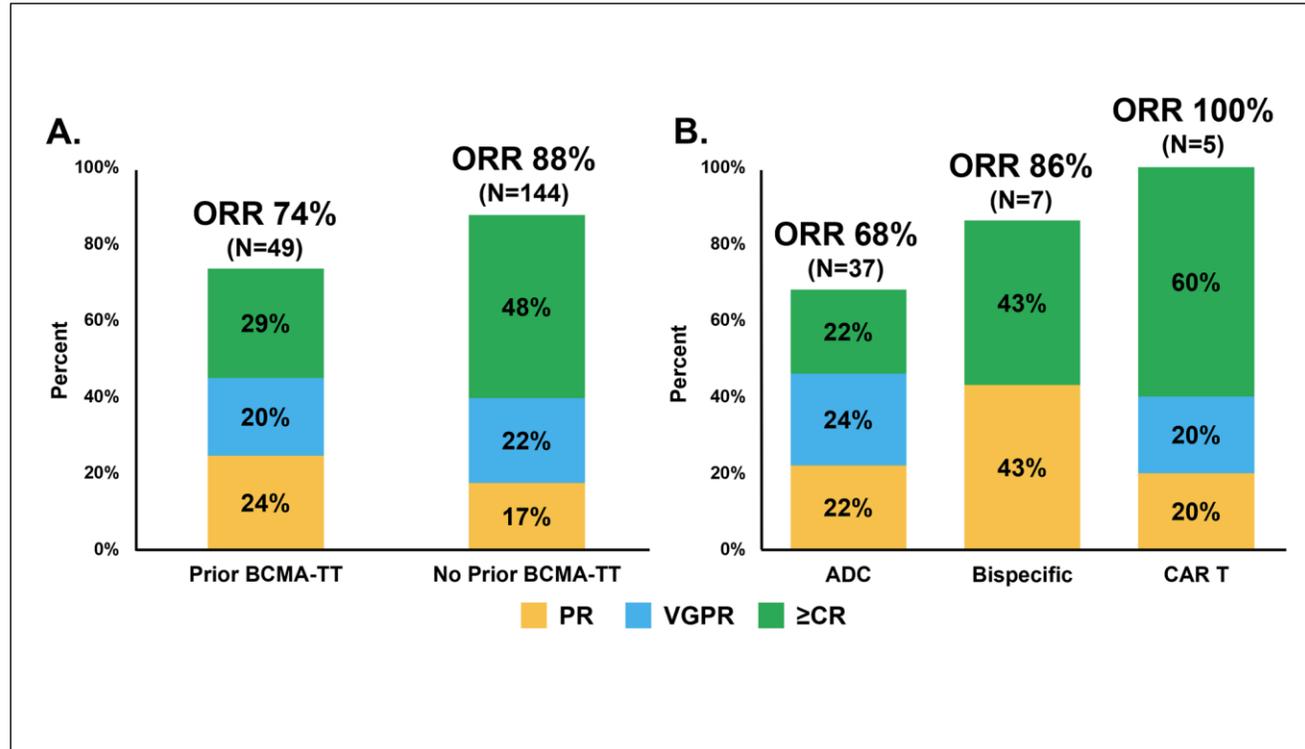
- N = 20, 13 prior ADC, 7 bispecific TCE
- ORR 60% (36.1-86.1)
- mDOR 11.5 mo (7.9-NE) mPFS 9.5 mo (0.99-NE)

## Timing of B-cell maturation antigen (BCMA)-targeting treatment

| Total cilta-cel N = 18*  |                   |                     |
|--|-------------------|---------------------|
| Treatments   | Responders n = 12 | Nonresponders n = 6 |
| <b>Duration of last ant-BCMA treatment, days</b>                       |                   |                     |
| Median   | 29.5              | 63.5                |
| Range  | 1-277             | 22-527              |
| <b>Time from last anti-BCMA treatment to apheresis, days</b>           |                   |                     |
| Median   | <b>161.0</b>      | 56.5                |
| Range  | <b>26-695</b>     | 40-895              |
| <b>Time from last anti-BCMA treatment and cilta-cel infusion, days</b> |                   |                     |
| Median   | <b>235.0</b>      | 117.5               |
| Range  | <b>62-749</b>     | 95-944              |

\*Two patients died before confirmed disease evaluation and were excluded from the analysis

# BsAB => CART: Response Rates to Ide-Cel in prior BCMA – The Real World



Ide-cel + prior BCMA vs Ide-cel + NO prior BCMA

- mPFS: 3.2 vs 9.9 mo Prior BCMA vs NO prior BCMA
- Prior BCMA independent predictor for PFS (HR 2.91) and OS-p=0.005

## CART => BsAb: Pooled MagnetisMM studies (Elranatamab, n=87): prior CART (n=36)

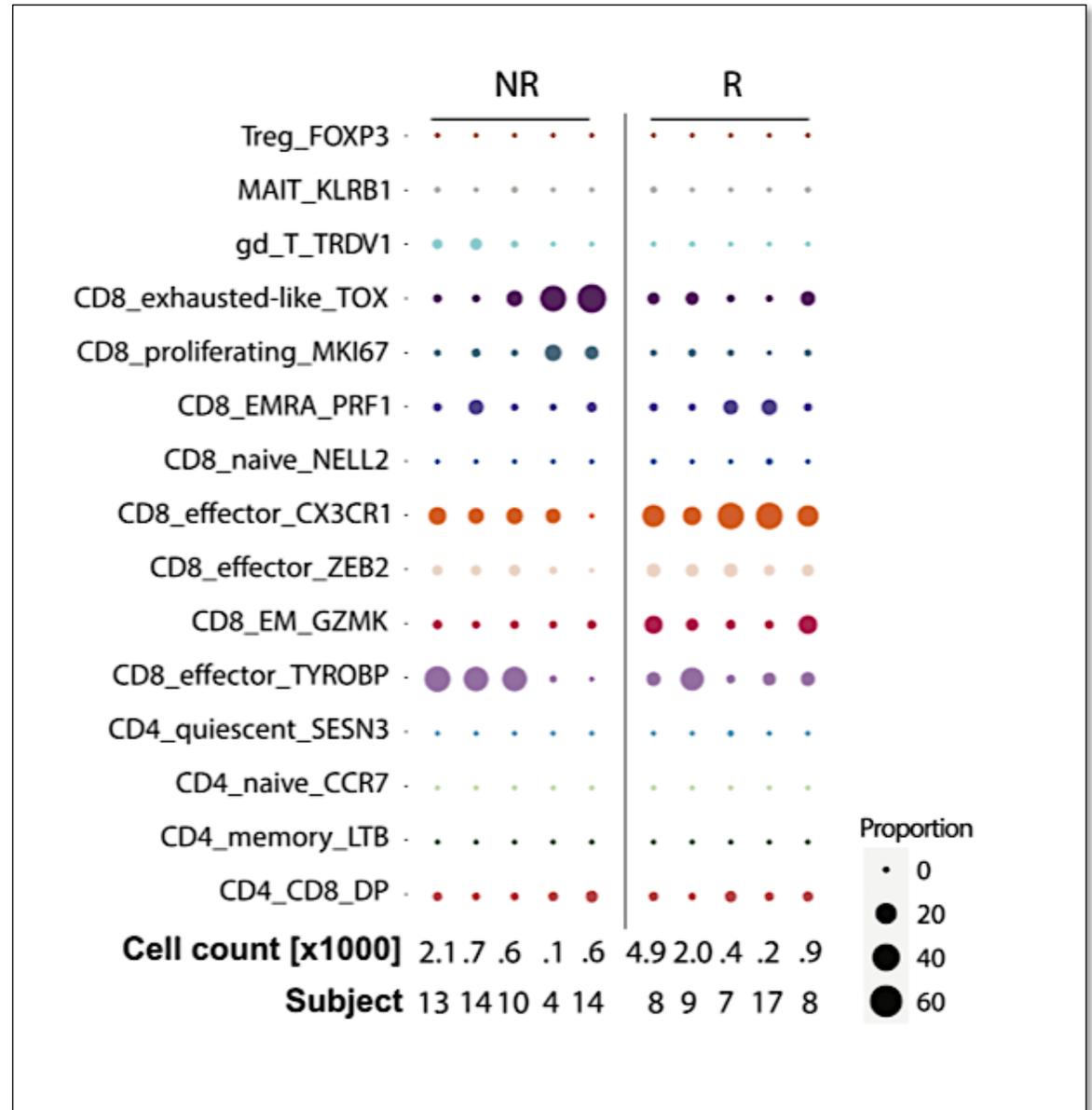
MagnetisMM-1, MagnetisMM-2, Magnetis MM-3, MagnetisMM-9

|            | MagnetisMM-3<br>(no prior BCMA)*           | Any Prior BCMA, n=87         | Prior ADC, n=59                 | Prior CART, n=36         |
|------------|--|------------------------------|---------------------------------|--------------------------|
| ORR        | 61.0%                                      | 46%                          | 42.4%                           | 52.8%                    |
| sCR/CR     |  | 18.4%                        | 18.7%                           | 19.5%                    |
| VGPR       |  | 24.1%                        | 20.3%                           | 27.8%                    |
| PR         |  | 3.4%                         | 3.4%                            | 5.6%                     |
| Median PFS | NR (95% CI, 9.9-NE)                        | 5.5 mo<br>(95% CI, 2.2-10.0) | 3.9 mo (95% CI, 1.9-6.6)        | 10.0 mo (95% CI, 1.9-NE) |
| Median DOR | NR (95% CI, NE-NE)<br>*median f/up 14.7 mo | 17.1 mo (95% CI, 9.8-NE)     | 13.6 months<br>(95% CI, 6.8-NE) | NE (95% CI, 9.8-NE)      |

- Median prior lines of therapy 7 (range 3-19)
- 62.1% were prior BCMA-therapy refractory
- Median f/up 11.3 mo

# Immune Landscape May Drive Responses to TCE

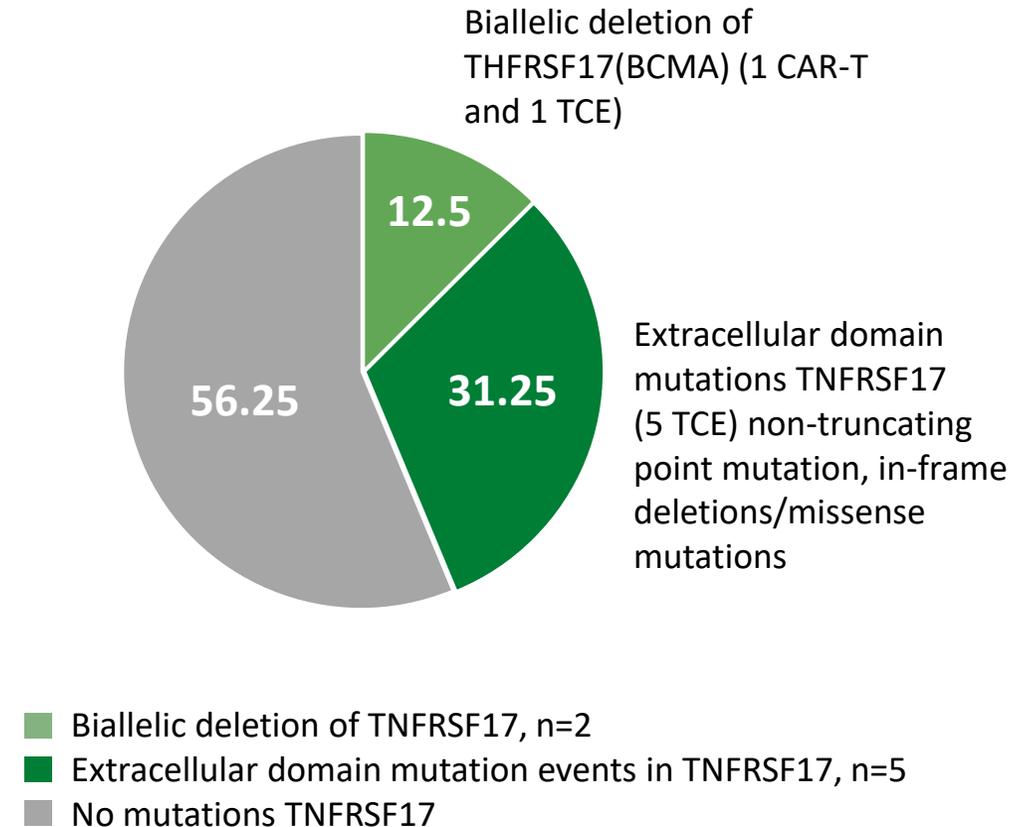
- Responders associated with large clonal expansion of CD8+ effector
- Expansion many occur through activation of naïve T-cells
- Non-clinical responders exhibit an abundance of exhausted T- cells that may not necessarily predict response to CAR-T cells



# Loss of Antigen: 16/24 progressors after anti-BCMA BsAb or CART: 7/16 BCMA mutations

- 30 patients treated with anti-BCMA and/or anti-GPRC5D CAR-T/T-Cell therapy undergoing bulk and single-cell whole-genome sequencing and copy number variation analysis
  - 24 patients post anti-BCMA
    - 5 CAR-T, 15 TCE, 3 Both
    - 16 patients progressors
  - 9 patients post anti-GPRC5D TCE
    - 4 patients with biallelic mutations post-GPRC5D
- Previous reports of biallelic loss of TNFRSF17, 6% post Ide-cel
- Lee et al. reporting 42.8% mutational events in TNFRSF17 (BCMA) post anti-BCMA TCE

## Anti-BCMA CAR-T and/or TCE, n = 16 progressors



## Summary – „Flowing“ Topic, as novel products against various targets are emerging & BsAb and CART cells move into earlier therapy lines

- Insufficient data to give recommendations on BsAb & CART sequencing
- **In BCP-ALL: BsAb first, CART second:** the majority of patients will have received blinatumomab within 1st Line therapy; CART indication in relapse; T cell fitness and response to blinatumomab associated with CART response; relevance of CD19 antigen loss through blinatumomab also in relation to the time interval to CART ill defined
- **In FL, BsAb & CART according to approval & pt choice;** BsAb and CART are targeting different antigens, so antigen loss not an issue; very limited data on the impact of sequencing on efficacy; both products with an excellent safety profile
- **In LBCL: CART first, BsAb second:** CD19 CART cells can cure in 3rd Line, achieve long term remission in 2nd Line, with an acceptable safety profile; CD20 BsAb with limited long term FU and RWE data sets
- **In MM: CART first, BsAb second:** higher response rates with CART, but antigen loss after BsAb reduces response rate of CART; relevance of target antigen loss vs T cell fitness needs to be determined with BsAb approval against GPRC5D, and GPRC5D directed CART evolving

## Question: Goal of Therapy

With aggressive vs indolent Lymphoma, what is the Goal of Therapy?

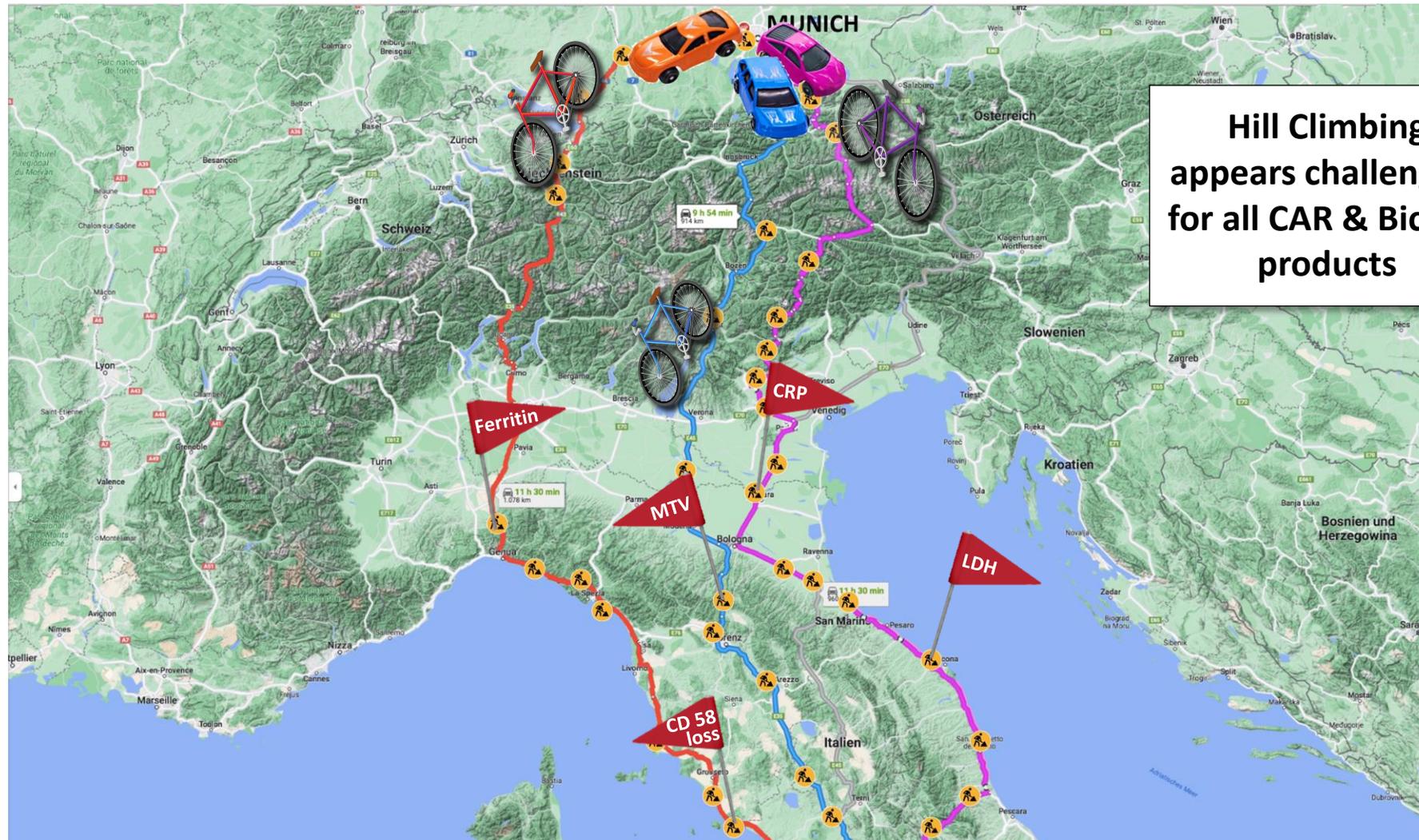
- **Curative vs Palliative**

**What Considerations are important?**

- Logistics / Feasibility
- Efficacy
- Toxicity
- Sequence
- Combinatorial Therapy



# The Road Determines the Success of CAR T cell & Bispecifics in Lymphoma



We do not know which CAR or Bispecific is most suitable for defined Construction Sites

# Acknowledgements

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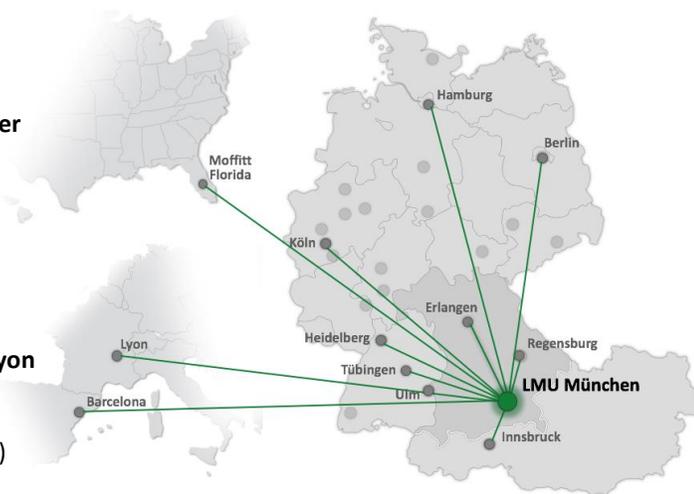
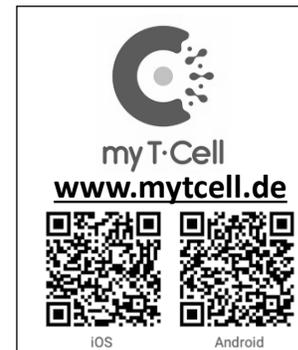
## LMU – Department of ATMZH, Neurology, Neurosurgery, Radiology, Nuclear Medicine, IZB

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Roni Shouval**



**Past IACH Meeting,  
Faculty Dinner  
October 6<sup>th</sup>, 2023 in Paris**

**Hoping for Peace in  
Israel and Palestine.**

Ich habe sehr viel Spaß im Krankenhauses Ich werde wieder gesund

Ich liebe meine Freundin Esse lebe ohne Krebs

Ich vermissen meine Katze Heute haben wir schlechtes Wetter Du schaffst das

Bist allergisch gegen Ärzte Felix fährt mit der Eisenbahn nach Hause.

## For our Patients worldwide & in Israel-Palestina-Ukraine

Mein Lieblingspferd heißt Cosmos Ich liebe mein Sohn David Heute haben wir schlechtes Wetter

Ich habe Durst Ein kränklicher Mensch wird schneller gesund.

Nice to meet you! Mein Name heißt STRACHN? What does the fox say?

Kitzle nie einen schlafenden Drachen Mein Käfer wurde schön Lächelt.

Meine Frau wird mich oft besuchen Heute ist ein sehr schöner Tag