POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

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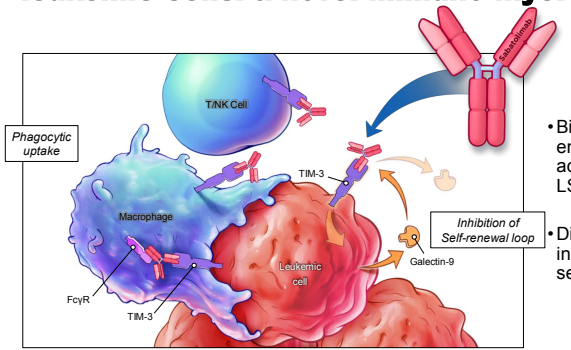
AML and BPDCN

59 TIM-3 Inhibitor Sabatolimab for Patients with Acute Myeloid Leukemia (AML) with Measurable Residual Disease (MRD) Detected after Allogeneic Stem Cell Transplantation (AlloSCT): Preliminary Findings from the Phase Ib/II Stimulus-AML2 Study

Background and rationale

- TIM-3: inhibitory receptor expressed on immune cells and leukemic stem cells and blasts but not on normal hematopoietic stem cells
- Sabatolimab: novel monoclonal antibody targeting TIM-3 -> reactivates immune system against myeloid malignancies by enhancing immune cell function and inhibiting leukemic cell self-renewal -> **enhance graft versus leukemia effect**
- Phase Ib/II STIMULUS-AML2 trial is evaluating sabatolimab ± azacitidine in patients with AML who attain hematologic CR but are MRD+ after alloSCT
- Current report details preliminary results of the safety run-in of sabatolimab monotherapy

Sabatolimab targets TIM-3 on immune and leukemic cells: a novel immuno-myeloid therapy



Sabatolimab

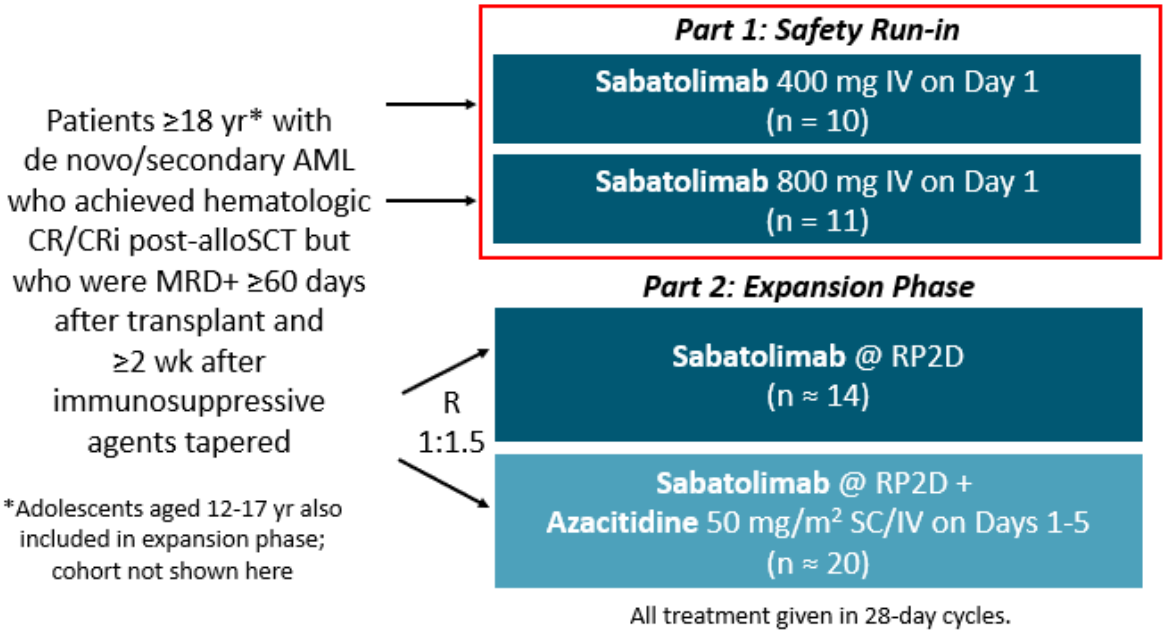
- Binds TIM-3 on immune cells, enhancing antileukemic immune activation and phagocytic killing of LSCs and blasts[1-4]
- Directly targets TIM-3 on LSCs, inhibiting TIM-3/galectin-9–driven self-renewal[1,2]

FcγR, Fc gamma receptor.
1. Acharya N, et al. *J Immunother Cancer*. 2020;8(1):e000911; 2. Sabatos-Peyton C, et al. SITC 2020. Abstract 439; 3. Borate U, et al. *HemaSphere*. 2020;4(suppl 1):Abstract S185; 4. Borate U, et al. EHA 2020. Oral presentation.

Zeiser R. et al; Abstract #59

59 TIM-3 Inhibitor Sabatolimab for Patients with Acute Myeloid Leukemia (AML) with Measurable Residual Disease (MRD) Detected after Allogeneic Stem Cell Transplantation (AlloSCT): Preliminary Findings from the Phase Ib/II Stimulus-AML2 Study

- Multicenter, open-label, phase Ib/II trial



- Primary endpoint for safety run-in: treatment-emergent DLTs, including acute or chronic GVHD during first 2 cycles
- Primary endpoint for safety run-in and dose expansion: no hematologic relapse after 6 cycles of therapy

Zeiser R. et al; Abstract #59

59 TIM-3 Inhibitor Sabatolimab for Patients with Acute Myeloid Leukemia (AML) with Measurable Residual Disease (MRD) Detected after Allogeneic Stem Cell Transplantation (AlloSCT): Preliminary Findings from the Phase Ib/II Stimulus-AML2 Study

Preliminary efficacy data

- 7 (33.3%) patients remain on treatment and in hematologic CR at time of data cutoff

- In sabatolimab 400 mg arm:
  - 3 of 10 patients still in CR after >1 yr on treatment
    - 2 patients had received 14 cycles, 1 had received 15 cycles

- In sabatolimab 800 mg arm:
  - 4 of 11 patients in CR
    - 1 patient had received 5 cycles, 1 had received 6 cycles, and 2 had received 7 cycles

Zeiser R. et al; Abstract #59

547 Durable Outcomes with Manageable Safety Leading to Prolonged Survival with Tagraxofusp for Treatment-Naive Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm: Updated Results from a European Named Patient Program

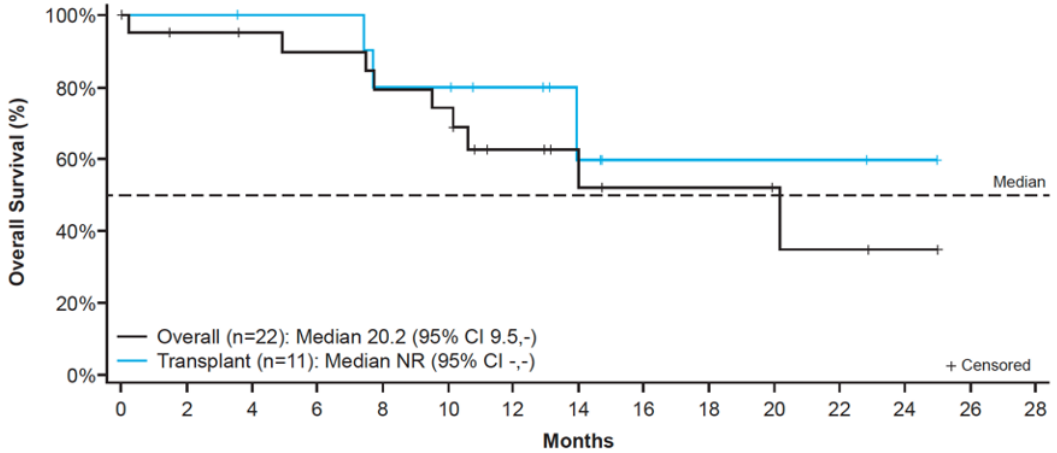
- 22 pts with treatment naive BPDCN -> 10% with CNS disease
- Median age 68 years (21-82)
- Median number or cycles: 3 (1-8)
- ORR 89% -> CR rate 67%, PR rate 22%
- 11/22 underwent allo HSCT
- 2 years of follow-up, median OS 20 months

- not reached in transplanted pts
- 11 months in non transplanted

- Treatment-related AE:

- Thrombocytopenia: 7/22 pts
- Capillary leak syndrome: 10/22 pts (9 in cycle 1)

Figure: Overall Survival*

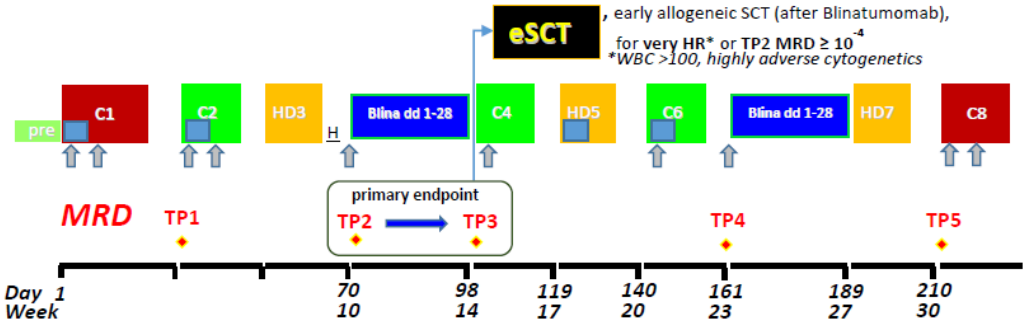


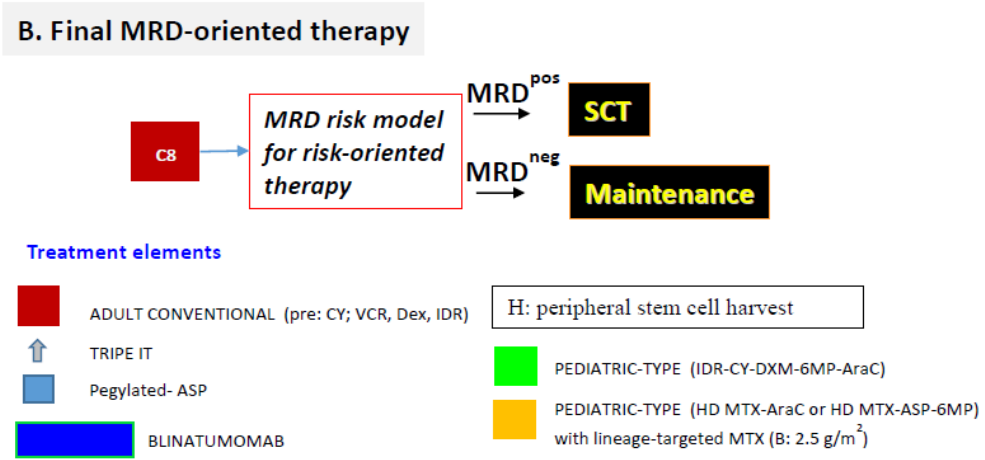
*OS is defined as time from start of TAG to death

Angelucci E. et al; Abstract #547

ALL

826 Sequential Chemotherapy and Blinatumomab to Improve Minimal Residual Disease in Adult Ph-B-Lineage Acute Lymphoblastic Leukemia. Final Results of the Phase II Gimema LAL2317 Trial





- 149 pts, median age 41 years (18-65)

- 31 pts classified as Ph-like according to BCR/ABL like predictor

- 12 pts with KMT2A-r; 5 pts with TCF3::PBX1 transcript

- primary endpoint : impact of blinatumomab in increasing early MRD negativity at the end of week 14 (TP3)

Chiaretti S. et al; Abstract #826

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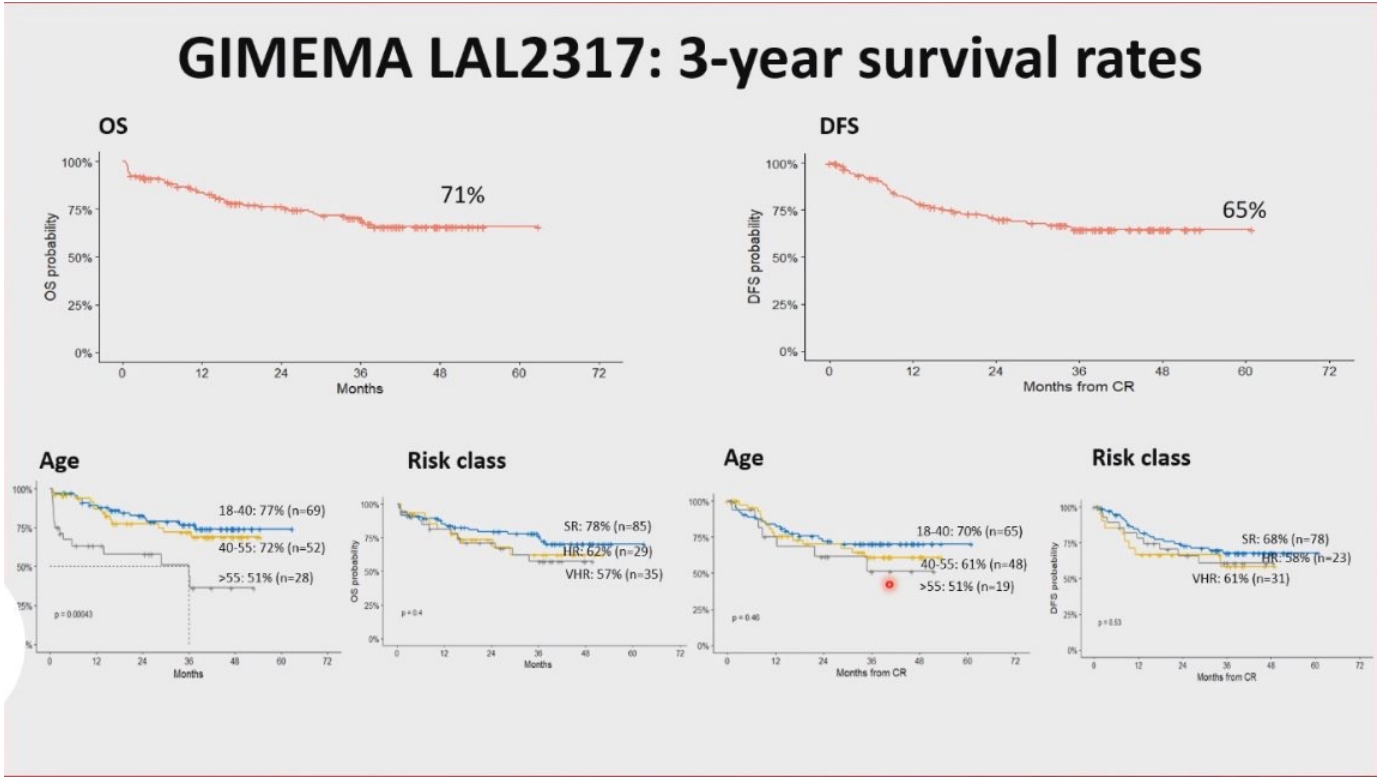


- Univariate analysis for OS:

- Age (p < 0.001)
- CR achievement (p < 0.001)
- TP2 MRD (p = 0.002)

- Univariate analysis for DFS:

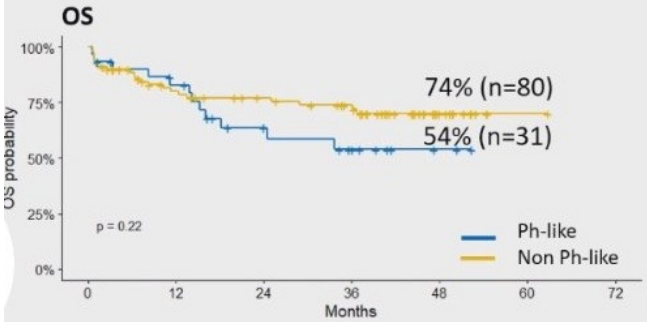
- Ph-like (p= 0.026)
- TP2 MRD (p < 0.001)

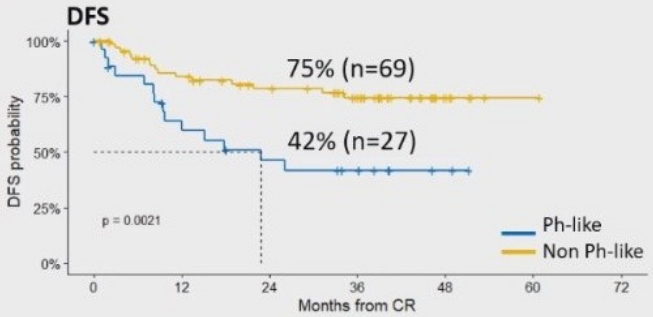
Chiaretti S. et al; Abstract #826

826 Sequential Chemotherapy and Blinatumomab to Improve Minimal Residual Disease in Adult Ph-B-Lineage Acute Lymphoblastic Leukemia. Final Results of the Phase II Gimema LAL2317 Trial

GIMEMA LAL2317: Focus on Ph-like

MRD at TP2 (HD3)	Overall (n=81, %)	Ph-like (n=22, %)	Non Ph-like (n=59, %)
MRD-negative	59 (73)	15 (68)	44 (75)
MRD-positive	22 (27)	7 (32)	15 (25)
MRD at TP3 (blinatumomab #1)	**n (%)**		
MRD-negative	78 (96)	22 (100)	56 (95)
MRD-positive	3 (3.7)	0	3 (5.1)





Chiaretti S. et al; Abstract #826

GIMEMA LAL2317: Conclusions

- Primary objective achieved: 93% of patients achieved a MRD negativity after the 1st cycle of blinatumomab.
- 23/30 (77%) MRD-positive cases at TP2 became MRD-negative after blinatumomab.
- Blinatumomab efficacy was shown at all ages.
- The 3-year OS and DFS are 71% and 65%.
- A significant survival improvement observed in patients aged 40-55. In elderly patients, inferior survival is partly related to deaths in induction.
- Relapses were mostly enriched by Ph-like cases, whose outcome was nevertheless improved compared to historical controls.
- A further caveat is represented by *MEF2D* rearrangements.

Chiaretti S. et al; Abstract #826

964 Dose Reduced Chemotherapy in Sequence with Blinatumomab for Newly Diagnosed Older Patients with Ph/BCR::ABL Negative B-Precursor Adult Lymphoblastic Leukemia (ALL): Preliminary Results of the GMALL Bold Trial

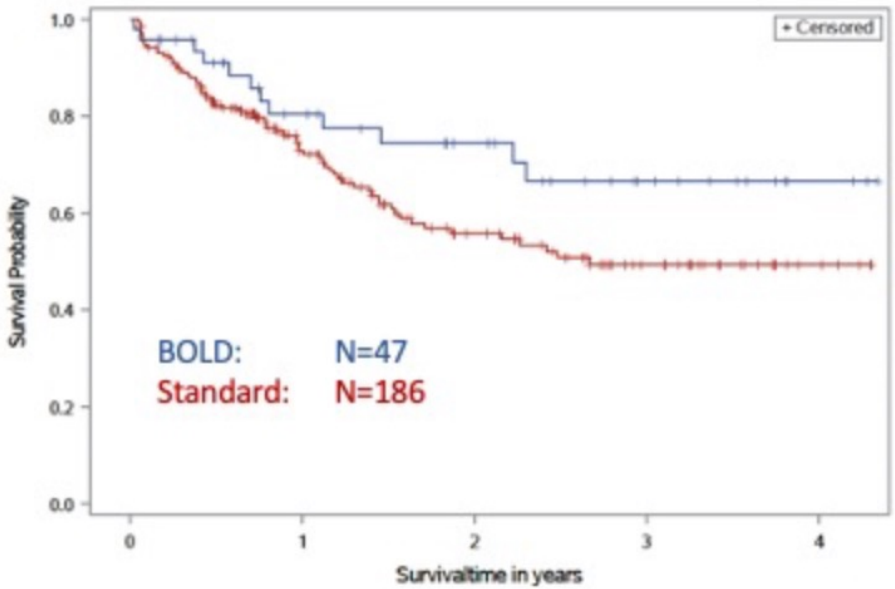
- Patients aged 56-76 years (median age 66)
- 40% with comorbidities according to Charlson Score: diabetes (13%), myocardial infarction (10%) or vascular disease (10%)
- Treatment scheme:
  - Induction: 1 chemo cycle + 1 blinatumomab cycle
  - 3 further blinatumomab cycle alternating with age-adapted consolidating cycles (according to GMALL protocol for older pts)
  - blinatumomab replaced three cycles of standard consolidation chemo
- Primary endpoint: CR after induction
- Key secondary endpoint: molecular response

Goekbuget N. et al; Abstract #964

964 Dose Reduced Chemotherapy in Sequence with Blinatumomab for Newly Diagnosed Older Patients with Ph/BCR::ABL Negative B-Precursor Adult Lymphoblastic Leukemia (ALL): Preliminary Results of the GMALL Bold Trial

- Authors compared BOLD Trial results to standard therapy for older pts with Ph-ne ALL (Goekbuget et al, ASH 2022)
- CR rates after induction were 85% vs 78% for BOLD vs standard therapy ($p > 0.05$)
- Molecular CR rates in pts with hematologic CR were 82% in BOLD arm vs 55% in standard therapy arm (p=0.006)
- 3-years OS: 67% in BOLD arm vs 49% in standard therapy arm
- Authors' conclusions:
  - Better MRD negativity rates with blinatumomab
  - OS and remission duration better even omitting several chemo cycles
  - Low mortality in induction and consolidation

Figure 1: Overall Survival BOLD vs GMALL Standard of Care



Goekbuget N. et al; Abstract #964

1029 Real-World Outcomes of Brexucabtagene Autoleucel (brexu-cel) for Relapsed or Refractory (R/R) Adult B-Cell Acute Lymphoblastic Leukemia (B-cell ALL): Evidence from the CIBMTR Registry

- Prospective evaluation in the CIBMTR Registry
- 197 pts infused with brexu-cel from July 2021 to May 2023 in 67 US centers -> 138 evaluable for outcomes analysis
- Median follow-up 5.9 months
- 55% with poor cytogenetic disease
- 79% had at least one comorbidity
- 44% had less than 5% on bone marrow blasts -> 49 pts were MRD negative at infusion
- **91% of patients would have been ineligible to ZUMA-3**
- Day 100 CR/CRi: 76%
- 63% of pts non in CR at infusion achieved CR/CRi
- 6-months RFS: 53%
- 6-months OS: 78%
- 31% of responders received allogeneic transplant
- Grade ≥ 3 CRS and ICANS in 9% and 24%
- **Response and safety outcomes similar to ZUMA-3**

Bezerra E. et al; Abstract #1029

1030 Brexucabtagene Autoleucel in Adults with Relapsed/Refractory B-Cell ALL: Outcomes and Novel Insights from the Real-World Outcomes Collaborative of CAR T in Adult ALL (ROCCA)

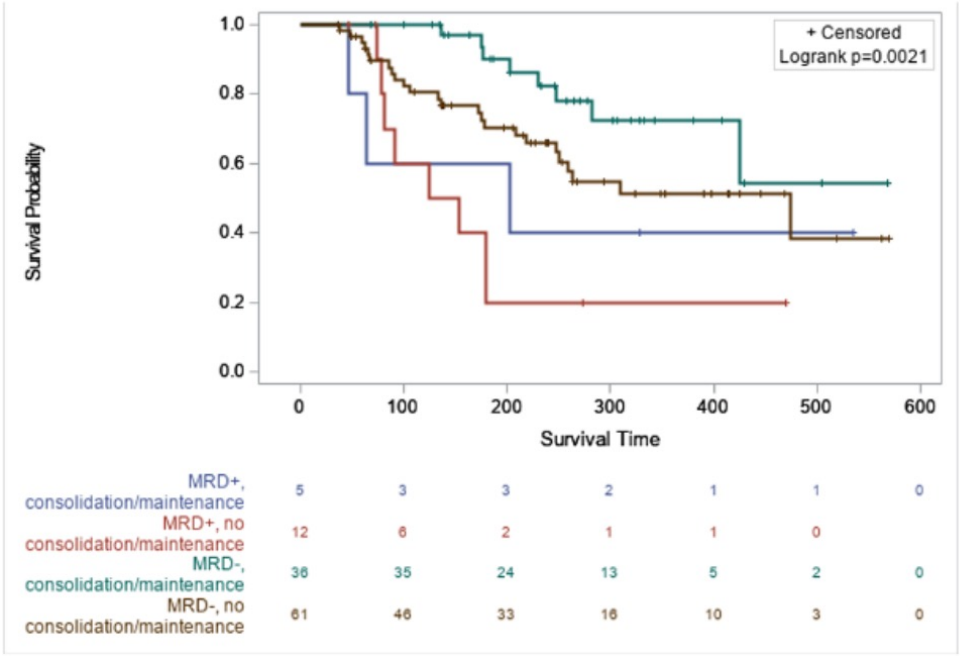
- Multicenter real-life study from 25 US centers
- 152 patients, median age 46 (range 18-81) -> 133 evaluable for assesment
- 67% Ph negative ALL
- Disease status at apheresis: 57% of patients had high burden disease; 23% were MRD positive, 15% were MRD negative
- Toxicity: 82% of CRS (9% of G3-4); 55% ICANS (32% G3-4)
- 5% of patients died of toxicity/infection before day +28

Roloff G.W. et al; Abstract #1030

1030 Brexucabtagene Autoleucel in Adults with Relapsed/Refractory B-Cell ALL: Outcomes and Novel Insights from the Real-World Outcomes Collaborative of CAR T in Adult ALL (ROCCA)

- Median follow-up 8.4 months
- 90% of pts achieved CR (82% MRD-ve) -> **response rate comparable to ZUMA-3**
- 12-months PFS and OS were 47% and 61%, respectively
- No difference between pre CAR T disease burden and post CAR T PFS/OS
- Landmark analysis on post CAR T therapies in patients alive and in CR at 2 months (113 pts, Fig. 1) -> 25 pts allografted
- Patients receiving consolidating/maintenance therapy post CAR T had superior outcome -> even among MRD-ve patients (Fig. 1)

Figure 1. PFS by Post-CAR MRD Response and Use of Post-CAR Consolidation/Maintenance



Roloff G.W. et al; Abstract #1030

770 Phase 1/2 Dose-Escalation/Dose-Expansion Study of Anti-CD7 Allogeneic CAR-T Cells (WU-CART-007) in Relapsed or Refractory (R/R) T-Cell Acute Lymphoblastic Leukemia/ Lymphoblastic Lymphoma (T-ALL/LBL)

- **WU-CART-007** -> anti CD7 allogeneic CAR-T with CRISP/Cas9 deletion of CD7 and T-cell receptor alpha constant to prevent fratricide killing (Leedom et al. ASH 2021)

- 18 patients, median age 33.5 years (20-68)
  - 28% relapsing post alloHSCT
  - 28% with extramedullary disease
  - median bone marrow blasts count 60% (5-98%)

- **4 CAR-T doses**: 100 X 10^6 (DL1); 300 X 10^6 (DL2); 600 X 10^6 (DL3); 900 X 10^6 (DL4, RP2D)

- 2 different lymphodepletion scheme adopted:
  - standard lymphodepletion: Flu 30 mg/m2/day x 3 days + Cy 500 mg/m2/day x 3 days
  - enhanced lymphodepletion: Flu 30 mg/m2/day x 4 days + Cy 1000 mg/m2/day x 3 days -> for DL4 patients

Ghobadi A. et al; Abstract #770

770 Phase 1/2 Dose-Escalation/Dose-Expansion Study of Anti-CD7 Allogeneic CAR-T Cells (WU-CART-007) in Relapsed or Refractory (R/R) T-Cell Acute Lymphoblastic Leukemia/ Lymphoblastic Lymphoma (T-ALL/LBL)

SAFETY

- Grade ≥3 Treatment-related AE in 8/18 patients
- CRS in 14/18 patients -> 73% of G1-2, one single G3 event
- G1 ICANS in one single patients (at DL3)
- **No GvHD or prolonged T-cell aplasia**
- **No anti-HLA antibody against donor**

EFFICACY -> dose dependent activity

- DL1: no activity
- DL ≥2 (12 pts): CR+CRi+CRh 58% (86% of MRD negativity) -> 2 allografted patients
- RP2D (DL4): CR+CRi+CRh 60% (3/5 pts)

Enrollment ongoing

Ghobadi A. et al; Abstract #770

Thank you for your attention