ABSTRACTS COLLECTION

The 49th Annual Meeting of the European Society for Blood and Marrow Transplantation: Physicians Award Winners (O001-O008)

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Physicians award winners

Presidential Symposium

13 - Infectious Complications

O001

IMPROVED OUTCOMES OVER TIME AND HIGHER MORTALITY IN CMV SEROPOSITIVE ALLOGENEIC STEM CELL TRANSPLANTATION PATIENTS WITH COVID-19: AN IDWP STUDY FROM THE EBMT REGISTRY

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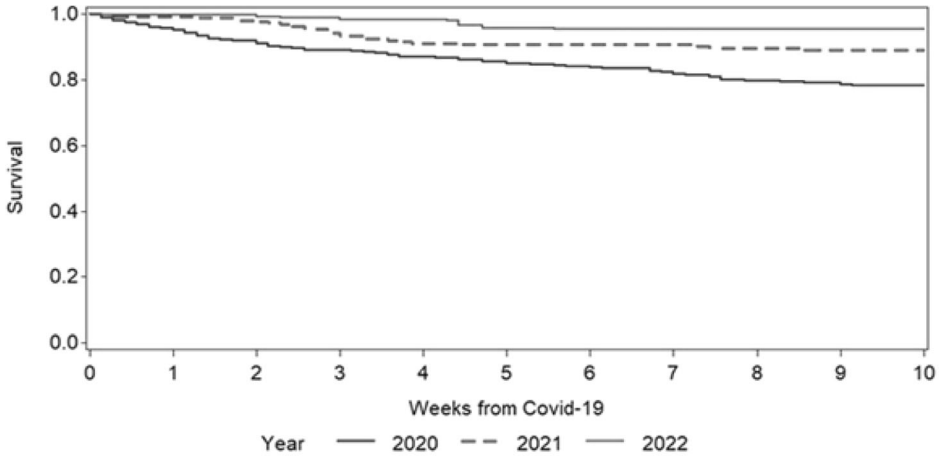
Background: COVID-19 has been associated with high morbidity and mortality in allogeneic hematopoietic stem cell transplant (allo-HCT) recipients. An early EBMT registry study showed a mortality of almost 30% for patients diagnosed during the first months of the pandemic. Since then, many advances have been achieved regarding management as well as new variants have emerged including the Omicron variant having in a healthy population lower morbidity and mortality. The aim of this analyses was therefore to study the outcome of COVID-19 in allo-HCT patients diagnosed from February 2020 to July 2022 to determine if the outcome has improved and if the risk factors are the same for severe and fatal COVID-19 also during the most recent period.

Methods: This prospective survey merged newly collected COVID-19 specific data with MED-A data existing in the EBMT registry. All patients gave informed consent for their data to be included. The COVID-19 specific case record forms have changed during the pandemic as knowledge have been gained. Criteria for inclusion were that the patient should be PCR positive for SARS-CoV-2 regardless of symptoms and have undergone an allo-HCT at any time before the diagnosis of COVID-19. From the beginning of 2021, a positive SARS-CoV-2 antigen test was also accepted for inclusion. For this analysis, patients diagnosed with SARS-CoV-2 infection before July 15, 2022, were included and patients needed to have at least six weeks of follow-up.

Results: 986 patients were included in the analysis. The median age was 50.3 years (min–max; 1.0–80.7). The median time from most recent HCT to diagnosis of COVID-19 was 20 months (min–max; 0.0–383.9). The median time was 19.3 (0.0–287.6) months during 2020, 21.2 (0.1–324.5) months during 2021, and 19.7 (0.1–383.9) months during 2022 (p = NS). 145/986 (14.7%) patients died; 124 (12.6%) due to COVID-19 and 21 of other causes. Only 2/204 (1%) fully vaccinated patients (defined as having received at least two doses with the 2nd dose given >14 days before diagnosis of COVID-19) died from COVID-19. There was a successive improvement in overall survival over time. Children had a better outcome than adults (95.4; 95% CI 89.3–98.1 vs. 83.6; 95% CI 80.6–86.1; $p = .004$). In multivariate analysis, increasing age (HR 1.33 (95% CI 1.20–1.48); $p < .0001$), worse performance status (HR 3.16 (2.10–4.76; $p < .0001$)), contracting COVID-19 within the first 30 days (HR 5.13 (2.91–9.02; $p < .0001$)) or 30–100 days after HCT (HR 2.11 (1.29–3.43, $p = .003$)), ongoing immunosuppression (HR 1.90 (1.23-2.93; $p = .004$)), pre-existing lung disease (HR 2.15 (1.32–3.50; $p = .003$)), and recipient CMV seropositivity (2.02 (1.26–3.25, $p = .004$)) had negative impact on overall survival while patients contracting COVID-19 in 2020



Year	Pts.	Deaths	2-week OS	4-week OS	6-week OS	12-week OS
2020	473	100	90.8 (87.9-93.1)	87.0 (83.5-89.7)	83.8 (80.0-86.9)	77.3 (72.7-81.3)
2021	265	31	97.7 (94.9-99.0)	91.1 (86.8-94.1)	90.7 (86.3-93.7)	88.1 (83.0-91.8)
2022	248	12	99.2 (96.8-99.8)	98.4 (95.7-99.4)	95.3 (91.6-97.4)	95.3 (91.6-97.4)

($p < .0001$) or 2021 ($p = .027$) had worse overall survival than patients with COVID-19 diagnosed in 2022 (Figure 1).

Conclusions: Although the outcome of COVID-19 has improved, patients having risk factors were still at risk for severe COVID-19 including death also during the time when the main circulating variant was Omicron.

Disclosure: Nothing to declare.

4 - CAR-based Cellular Therapy – Clinical

O002

FACTORS ASSOCIATED WITH DURATION OF RESPONSE AFTER CD19 CAR T-CELL THERAPY FOR RELAPSED/REFRACTORY CLL: 5-YEAR FOLLOW-UP UPDATE

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Background: CD19-targeted chimeric antigen receptor-modified (CD19 CAR) T-cell therapy is transforming the treatment landscape of relapsed/refractory (R/R) B cell malignancies. We previously described high rates of durable responses in patients with R/R chronic lymphocytic leukemia (CLL) treated on a phase I/II clinical trial of CD19 CAR T cells (NCT01865617; Turtle, JCO 2017). We now report comprehensive analyses of factors associated with duration of response (DOR) with a 68-month median follow-up.

Methods: We included 49 patients with R/R CLL and/or Richter's transformation ($n = 10$) treated on a phase I/II clinical trial of defined-composition CD19 CAR T-cell therapy (1:1 ratio of CD8 + :CD4 + CAR T cells). Patients received CAR T cells without concurrent ibrutinib ($n = 30$; stopped prior to lymphodepletion [LD]) or with concurrent ibrutinib ($n = 19$; started at least 2 weeks prior to leukapheresis; Gauthier, Blood 2019). Disease response was assessed per 2018 iwCLL criteria. Measurable residual disease (MRD) in bone marrow (BM) was evaluated by multiparameter flow cytometry (MFC) and *IGH* next-generation sequencing (NGS; clonoSEQ assay). CAR T-cell enumeration was assessed by MFC. Serum cytokine concentrations (20 analytes) were measured by Luminex assay. Univariate associations between outcomes and 41 patient, disease, and treatment-related variables, and longitudinal serum cytokine measurements were assessed using Cox regression.

Results: Median age was 61 years (range, 55–67) (Table 1). Forty-six patients (94%) had complex karyotype and/or 17p deletion. Forty-six patients (94%) received cyclophosphamide/fludarabine LD. Two patients died prior to re-staging; in the response-evaluable cohort ($n = 47$), median follow-up was 68.3 months (IQR, 54.3–81.6). Overall and complete response rates at day + 28 were 70% and 17%, respectively, and the median duration of response (DOR) was 22.2 months (95% CI, 10.7–not reached). MRD-negativity at day + 28 by MFC occurred in 33/47 (70%). In patients with MRD-negativity by MFC and available data, MRD negativity by NGS occurred in 18/29 (62%). In NGS MRD-negative responders, the median DOR was 56.8 months (95% CI, 39.5–not reached). In all evaluable patients, the 5-year OS and PFS were 35.5% (95% CI, 24.0%–52.5%) and 23.3% (95% CI, 13.3%–40.9%), respectively.

In univariate Cox regression, day + 28 MRD-negativity by MFC (HR = 0.03, 95% CI, 0.01–0.18, $p < 0.001$), day + 28 MRD-negativity by NGS (HR = 0.21, 95% CI, 0.07–0.61, $p = 0.004$), higher peak CD8 + CAR T-cell expansion (HR = 0.49, 95% CI, 0.24–1.00, $p = 0.05$), and lower peak MIP-1β (HR = 3.12, 95% CI, 1.13–8.65, $p = 0.029$) were associated with longer DOR. Peak MIP-1β remained associated with DOR (HR = 3.55, 95% CI, 1.25–10.1, $p = 0.017$) in a multivariable Cox model including pre-

LD CLL cells in BM, tumor cross-sectional area, peak CD8 + CAR T-cell expansion, and day + 28 MRD by MFC.

Table 1. Demographic, disease, and response characteristics of all infused patients (*n* = 49).

Age, median (range)	61 (55–67)
Male sex	33 (67%)
ECOG PS	
0	24 (49%)
1	25 (51%)
History of Richter's transformation	10 (20%)
Number of prior therapies, median (range)	5 (1–10)
High-risk cytogenetics	46 (94%)
Complex karyotype ($n = 1$ missing)	36 (75%)
17p deletion	33 (67%)
Pre-LD absolute lymphocyte count(1×10^9/L)	1.6 (0.2–58.9)
Pre-LD absolute CLL cell count, blood (1×10^9/L)	1 (0–76.7)
Percentage of CLL cells in bone marrow	60 (0–90)
Tumor cross-sectional area (mm^2)	2988 (0–20,406)
Maximum SUV ($n = 12$ missing)	5.1 (0–27.5)
Bulky disease	13 (27%)
Lymphodepletion	
Concurrent Cy/Flu	27 (55%)
Sequential Cy/Flu	3 (6%)
Other	19 (39%)
CAR T-cell dose level (cells/kg)	
2×10^5	5 (10%)
2×10^6	43 (88%)
2×10^7	1 (2%)
Day + 28 response (2018 iwCLL criteria)	
($n = 2$ died prior to day+28)	
CR	3 (6%)
CRi	5 (10%)
PR	25 (51%)
PD	11 (22%)
SD	3 (6%)
Day + 28 BM response by MFC ($n = 2$ missing)	33 (70%)
Day + 28 BM response by NGS ($n = 20$ missing; 4 MRD-negative by MFC and 16 MRD-positive by MFC)	18 (62%)
Cytokine release syndrome (Lee 2014 criteria)	
Any	40 (82%)
0	9 (18%)
1	15 (31%)
2	18 (37%)
3	5 (10%)
4	1 (2%)
5	1 (2%)
Neurotoxicity (CTCAE v4.03)	
Any	16 (33%)
0	33 (67%)
1	0 (0%)
2	3 (6%)
3	12 (24%)
4	0 (0%)
5	1 (2%)

Conclusions: Sustained remissions can be achieved in high-risk R/R CLL patients after defined-composition CD19 CAR T-cell therapy. Day+28 MRD and in vivo CAR T-cell peak expansion were predictors of DOR. In addition, higher peak serum MIP-1β levels, a known biomarker of BCR signaling, was strongly and independently associated with shorter DOR.

Clinical Trial Registry: NCT01865617.

Disclosure: Emily Liang: none.

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Aude Chapuis: **Advisory boards:** Affini-T, Metagenomi, SignalOne Bio, TScan Therapeutics. **Consulting:** BioNTech, Ridgeline Discovery GmbH. **Equity interest:** Adaptive Biotechnologies Corporation, Affini-T, Metagenomi, SignalOne Bio, TScan Therapeutics. **Patents:** Adaptive Biotechnologies Corporation, Affini-T, Amazon.com, Cullinan, ElevateBio, Lonza Walkersville, Celgene.

Mazyar Shadman: **Consulting, advisory boards, steering committees, or data safety monitoring committees:** Abbvie, Genentech, AstraZeneca, Pharmacyclics, Beigene, Bristol Myers Squibb, Morphosys/Incyte, TG Therapeutics, Kite Pharma, Eli Lilly, Adaptimmune, Mustang Bio, Merck, Fate therapeutics, MEI pharma and Atara Biotherapeutic. **Research funding:** Mustang Bio, Celgene, Bristol Myers Squibb, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, Beigene, AstraZeneca, Sunesis, Atara Biotherapeutics, Genmab, Morphosys/Incyte, Vincerx.

Brian Till: **Patents/royalties:** Mustang Bio. Consulting: Mustang Bio and Proteios. **Research funding:** Bristol Meyers Squibb and Mustang Bio

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Filippo Milano: none.

Hans-Peter Kiem: none.

Cameron Turtle: **Research funding:** Juno Therapeutics/BMS, Nektar Therapeutics. **Scientific and clinical advisory boards:** Precision Biosciences, Eureka Therapeutics, Caribou Biosciences, T-CURX, Myeloid Therapeutics, ArsenalBio, Century Therapeutics, Kyverna. **Ad hoc advisory boards/consulting (last 12 months):** GlaxoSmithKline, Decheng Capital, Nektar Therapeutics, Allogene, Sobi, Legend Bio, Syncopation Life Sciences. **Stock options:**

Precision Biosciences, Eureka Therapeutics, Caribou Biosciences, Myeloid Therapeutics, ArsenalBio. **Patents:** CJT has the right to receive payment from Fred Hutch as an inventor on patents related to CAR T-cell therapy.

David Maloney: **Ad hoc consultant, having received honoraria**: BMS, Caribou Biosciences, Inc., Celgene, Genentech, Incyte, Juno Therapeutics, Kite, Lilly. **Research Funding**: Fred Hutchinson Cancer Research Center, has received research funding, including salary support, from the following companies for clinical trials on which DGM is a principal- or sub-investigator: Kite Pharma, Juno Therapeutics, Celgene, Legend Biotech. **Patents**: DGM has the rights to royalties from Fred Hutch for patents licensed to Juno Therapeutics/BMS. **Stock options:** A2 Biotherapeutics, Navan Technologies. **Memberships with compensation:** A2 Biotherapeutics, Member of the Scientific Advisory Board; Navan Technologies, Member of the Scientific Advisory Board; Chimeric Therapeutics, Member of the Scientific Advisory Board; Genentech, Member and Chair of the Lymphoma Steering Committee; BMS, Member of the JCAR017 EAP-001 Safety Review Committee; BMS, Member, CLL Strategic Council; ImmPACT Bio, Member, Clinical Advisory Board, CD19/CD20 bi-specific CAR-T Cell Therapy Program; Gilead Sciences, Member, Scientific Review Committee, Research Scholars Program in Hematologic Malignancies; Interius Biotherapeutics, Inc, Clinical Advisory Board. **Memberships without compensation:** BMS, Member of the JCAR017-BCM-03 Scientific Steering Committee.

Jordan Gauthier: **Ad hoc consultant, having received honoraria:** Sobi, Legend Biotech, Janssen, Kite Pharma, MorphoSys**. Research funding:** Sobi, Juno Therapeutics (a BMS company), Celgene (a BMS company), Angiocrine Bioscience.

12 - Graft-versus-host Disease – Clinical

O003

AN EARLY ENDPOINT FOR ACUTE GRAFT VERSUS HOST DISEASE CLINICAL TRIALS

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Background: The overall clinical response rate (CR + PR) after four weeks of treatment is a validated surrogate for overall survival (OS) and has been widely adopted as the primary endpoint for trials of primary treatment for acute GVHD. Analysis of patients with the MAGIC database showed that the addition of second-line therapy to patients that do not respond to primary treatment is made within the first two weeks of treatment for ~65% of patients, highlighting the need to make decisions earlier. We hypothesized that the combination of the serum biomarker based MAGIC Algorithm Probability (MAP), and clinical response two weeks after treatment could provide a composite endpoint that would be at least as good as the clinical response at four weeks in predicting patient OS.

Methods: We prospectively collected serum samples and clinical staging from 1138 HCT patients who received systemic treatment for acute GVHD in one of 23 MAGIC centers between 2015 and 2021. We computed MAPs at 2 weeks from serum biomarkers as previously described (Srinagesh, Blood Adv, 2019) and clinical responses at two (w2) and four weeks (w4) after treatment. We used cox proportional hazards regression models to predict patient OS and compared them with time-dependent AUCs for censored event times.

Results: We separated the patient population into a training set ($n = 569$) to develop the model and evaluated it in a validation set ($n = 569$). In the training set, w4 non-response was associated with worse OS than response (HR:3.1, $p < 0.001$). In the w2 model, patients with clinical response and low MAP (complete combined response [CCR]) had the best OS, whereas patients in the other groups had increasingly worse OS: low MAP but no clinical response (good partial combined response [GPCR], HR:1.6, $p = 0.017$), high MAP and clinical response (poor partial combined response [PPCR], HR:4.0, $p < 0.001$) and high MAP and no clinical response (non-response [NR], HR:6.0, $p < 0.001$).

We then evaluated both models in the validation set. Responders at w4 ($n = 172$) had better OS than non-responders ($n = 397$) at 18 months (74% vs. 46.9%). But the combined w2 response separated the patients into four groups with significantly worse OS as response decreased. 18 months OS for patients with CCR ($n = 355$) was 76.9%, for patients with GPCR ($n = 125$) 64%, for patients with PPCR ($n = 35$) 39.7%, and for patients with NR ($n = 54$) 14.5%. Comparison of the time-dependent-AUC curves showed that w2 consistently displayed significantly higher AUC predicting OS for 18 months. The w2 model was superior to the w4 model when evaluating key subsets of the validation set based on GVHD grade, Minnesota risk groups, and patient age.

Conclusions: The combination of clinical response and MAP, a laboratory measure of GI crypt damage, at two weeks after treatment categorizes patients into four subgroups with distinct long-term outcomes. Importantly, this combination correctly reclassifies half of clinical non-responders as late responders who will experience excellent survival. We conclude that this combination after two weeks of treatment is feasible, providing an accurate and early prediction of long-term outcomes for patients with acute GVHD.

Disclosure: J. F. and J.L. are co-inventors on a GVHD patent and receive royalties. This work was supported by the National Institutes of Health and the National Cancer Institute (grant PO1CA03942). The authors thank the patients, their families, and the research staff for participating.

4 - CAR-based Cellular Therapy – Clinical

O004

CTX110 ALLOGENEIC CRISPR-CAS9–ENGINEERED CAR T CELLS IN PATIENTS WITH RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA: RESULTS FROM THE PHASE 1 DOSE ESCALATION CARBON STUDY

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Background: Allogeneic (allo) CAR T cell therapies in patients (pts) with Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL) may offer advantages over autologous (auto) CAR T products including "off-the-shelf" availability, no leukapheresis, an improved safety profile and the option for additional infusions. CTX110® is an investigational allo CD19-directed CAR T cell product engineered using CRISPR/Cas9-editing to disrupt the endogenous T-cell receptor (TCR) alpha constant (TRAC) locus to prevent TCR expression, and the β_2-microglobulin gene to eliminate major histocompatibility complex (MHC) class I expression.

Methods: CARBON (NCT04035434) is a phase 1, open-label, multicenter, global study evaluating the safety and efficacy of CTX110 in adult pts with R/R LBCL with ≥2 prior lines of therapy. Pts received standard lymphodepleting chemotherapy (LDC) with fludarabine 30mg/m^2 and cyclophosphamide 500mg/m^2 for 3 days, followed by CTX110. Clinically active doses of CTX110 ranged from 300×10^6 to 600×10^6 CAR$^+$ T cells. Pts who achieved initial benefit and subsequently progressed could receive an additional infusion of CTX110 preceded by LDC. Additionally, four pts with an initial Day 28 response of ≥stable disease (SD) received a second planned infusion on Day 35. Primary endpoints included safety and overall response rate (ORR) per Lugano 2014 Criteria. Secondary endpoints included complete response (CR) rate, duration of response and overall survival (OS).

Results: As of August 19, 2022, 34 pts with LBCL were enrolled for dose escalation and 32 received CTX110. Median time from enrollment to LDC was 2 days. Among pts who received ≥ 1 infusion

Cell dose (CAR + T Cells) Dose Level (*N*)	30×10^6 DL1 (3)	100×10^6 DL2*(3)	300×10^6 DL3 (6)	450×10^6 DL3.5 (6)	600×10^6 DL4 (14)	Total
Age, median (range)	52 (50-61)	64 (58–74)	69 (62–74)	67.5 (25–74)	64 (35–75)	64 (25–75)
ECOG 0	2 (66.7)	1 (33.3)	2 (33.3)	4 (66.7)	4 (28.6)	13 (40.6)
ECOG 1	1 (33.3)	2 (66.7)	4 (66.7)	2 (33.3)	10 (71.4)	19 (59.4)
DLBCL, NOS	1 (33.3)	2 (66.7)	2 (33.3)	4 (66.7)	8 (57.1)	17 (53.1)
HGLBCL w MYC/BCL2 and/ or BCL6 rearrangements	0	1 (33.3)	1 (16.7)	1 (16.7)	2 (14.3)	5 (15.6)
Grade 3b FL	0	0	0	0	1 (7.1)	1 (3.1)
Transformed FL	1 (33.3)	0	2 (33.3)	1 (16.7)	3 (21.4)	7 (21.9)
Other†	1 (33.3)	0	1 (16.7)	0	0	2 (6.2)
≥3 prior lines of therapy	1 (33.3)	2 (66.7)	2 (33.3)	3 (50.0)	7 (50)	15 (46.9)
Baseline SPD > 50cm^2, *n* (%)	1 (33.3)	1 (33.3)	2 (33.3)	1 (16.7)	6 (42.9)	11 (34.4)
Refractory, *n* (%)	3 (100)	3 (100)	2 (33.3)	1 (16.7)	8 (57.1)	17 (53.1)
Baseline LDH > ULN, *n* (%)	1 (33.3)	2 (66.7)	2 (33.3)	5 (83.3)	7 (50)	17 (53.1)
Best ORR, *n* (%)	0	1 (33.3)	4 (66.7)	4 (66.7)	9 (64.3)	18/27 (66.6)**
CR, *n* (%)	0	1 (33.3)	2 (33.3)	4 (66.7)	4 (28.6)	1127 (40.7)**
CRS, *n* (%)	1 (33.3)	2 (66.7)	2 (33.3)	3 (50)	10 (71.4)	18 (56.3)
Gr ≥ 3 CRS	0	0	0	0	0	0
ICANS, *n* (%)	0	1 (33.3)	0	0	2 (14.3)	3 (9.4)
Gr ≥ 3 ICANS	0	0	0	0	2 (14.3)	2 (6.2)
Gr ≥ 3 Infection, *n* (%)	1 (33.3)	0	1 (16.7)	0	2 (14.3)	4 (12.5)

*1 patient received two CTX110 infusions with the first infusion at DL2 and the second at DL3, and achieved CR after each infusion.
**Response rates were based on subjects who received at least one CTX110 infusion at DL > = 3 (*N* = 27).
†1 patient enrolled in DL1 had Richter's transformation of CLL, and 1 patient in DL3 had both grade 3b follicular lymphoma and germinal center B-cell like-DLBCL.
CAR chimeric antigen receptor, *CLL* chronic lymphocytic leukemia, *CR* complete response, *CRS* cytokine release syndrome, *DL* dose level, *DLBCL* diffuse large B-cell lymphoma, *ECOG* Eastern Cooperative Oncology Group, *FL* follicular lymphoma, *Gr* grade, *GvHD* graft versus host disease, *HGBCL* high-grade B-cell lymphoma, *ICANS* immune effector cell-associated neurotoxicity syndrome, *LDH* lactate dehydrogenase, *NHL* non-Hodgkin lymphoma, *NOS* not otherwise specified, *ORR* overall response rate, *PS* performance status, *SPD* sum of the products of diameters, *ULN* upper limit of normal.

of CTX110 at doses of ≥ 300×10^6 CAR T cells (DL ≥ 3; $N = 27$), best ORR and CR rates were 18/27 (67%) and 11/27 (41%) respectively (Table); the 6-mo CR rate was 19% (5/27) and there are 3 patients in CR past 24 months with the CR ongoing. For the 13 pts who received a second infusion of ≥300×10^6 CAR T cells, CAR T cell expansion was observed in all pts. Following CTX110 infusion, there was no graft versus host disease (GvHD) nor infusion reactions. Any grade (Gr) cytokine release syndrome (CRS) was reported in 18/32 (56%) pts with no CRS Gr ≥ 3. Any grade immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in 3/32 pts (9.4%), including 2 cases of Gr ≥ 3. Gr ≥ 3 infections occurred in 4/32 pts (12.5%) including 1 pt who died with HHV6 encephalitis. There were 7 pts who experienced serious adverse events that were attributed to CTX110. No increased toxicity was observed with re-infusion of CTX110.

Conclusions: CTX110 at DL ≥ 3 or higher resulted in clinically meaningful ORR, CR rates, and durable remissions, accompanied by a favorable safety profile in pts with R/R LBCL. Nearly half of all patients who achieved a CR maintained it out to at least 6 months. CTX110 offers a potential novel off-the-shelf treatment option with a median time from enrollment to LDC of 2 days. Repeat CTX110 infusions were well tolerated and showed further clinical benefit. CTX110 will continue to be evaluated in an expansion phase of the study.

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23 - Haemoglobinopathy

O005

EFFICACY AND SAFETY OF A SINGLE DOSE OF EXAGAMGLOGENE AUTOTEMCEL FOR TRANSFUSION-DEPENDENT B-THALASSEMIA AND SEVERE SICKLE CELL DISEASE

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Background: Exagamglogene autotemcel (exa-cel) is a cell therapy designed to reactivate fetal hemoglobin (HbF) via non-viral, ex vivo CRISPR/Cas9 gene-editing in autologous CD34+ hematopoietic stem and progenitor cells (HSPCs). Early data from two pivotal trials showed a single dose of exa-cel increased HbF and total Hb sufficiently to eliminate red blood cell (RBC) transfusions in patients (pts) with transfusion-dependent β-thalassemia (TDT) and vaso-occlusive crises (VOCs) in patients with sickle cell disease (SCD). We report efficacy and safety data from the first 75 pts dosed with exa-cel.

Methods: Following pharmacokinetic-adjusted busulfan myeloablation and exa-cel infusion, pts (12–35y) are monitored for engraftment, total Hb, HbF, *BCL11A* edited alleles, transfusions, VOCs (SCD only), and adverse events (AEs). Data presented as mean (min-max) unless noted.

Results: 44 pts with TDT (age 21.3 [12–35] y) and 31 pts with SCD (age 22.5 [12–34] y) were infused with exa-cel at data cut (follow-up 12.3 [1.2–37.2] mo and 9.6 [2.0–32.3] mo, respectively). 26/44 pts with TDT (59.1%) had β^0/β^0 or a β^0/β^0-like genotype (β^0/IVS-I-110, IVS-I-110/IVS-I-110). In the 2-yr period before screening, pts with TDT received 36.0 (15.0–71.0) units RBC/yr and pts with SCD had 3.9 (2.0–9.5) severe VOCs/yr. After exa-cel infusion, all pts engrafted neutrophils and platelets. Median time to neutrophil and platelet engraftment was 29 and 43 days in pts with TDT and 27 and 32 days in those with SCD, respectively.

42 of 44 pts with TDT stopped RBC transfusions (duration 0.8–36.2 mo); 2 pts had not stopped transfusions but had 75% and 89% reductions in transfusion volume. By Month 3, increases in HbF and mean total Hb levels (> 9 g/dL) were achieved, with mean total Hb levels increasing to >11 g/dL thereafter and were maintained.

All pts with SCD ($n = 31$) no longer had severe VOCs after exa-cel infusion (duration 2.0–32.3 mo). Mean proportion of HbF was >20% by Month 3, increasing to ~40% at Month 4 and stable thereafter, with mean total Hb levels >11 g/dL after Month 3.

Pts with TDT and SCD with ≥1 yr follow-up had stable proportions of edited *BCL11A* alleles in bone marrow $CD34^+$ HSPCs and peripheral blood mononuclear cells.

Two pts with TDT had serious AEs (SAEs) considered related to exa-cel: one pt was previously reported and a second pt had delayed neutrophil engraftment and thrombocytopenia (both considered related to exa-cel and busulfan). All SAEs resolved. No pts with SCD had SAEs considered related to exa-cel. There were no deaths, discontinuations, or malignancies.

Conclusions: Exa-cel infusion led to elimination of transfusions in almost all patients with TDT and elimination of VOCs in all patients with SCD, with associated clinically meaningful increases in HbF and total Hb that were maintained over time. Proportions of CRISPR/Cas9-edited *BCL11A* alleles remained stable after more

than 1 year, indicating long-term HSCs were successfully edited. Safety profile was generally consistent with busulfan myeloablation and autologous transplant. These results indicate exa-cel has the potential to be the first CRISPR/Cas9-based therapy to provide a one-time functional cure for TDT and severe SCD.

Clinical Trial Registry: CLIMB THAL-111 (NCT03655678) and CLIMB SCD-121 (NCT03745287).

Disclosure: **Franco Locatelli:** Speaker's bureau SOBI, Neovii, Medac, Jazz Pharmaceuticals, Novartis, Miltenyi, BlueBird bio, Bellicum, Gilead, and Amgen. Advisory boards Bellicum, Amgen, Neovii, Novartis, Sanofi, and Vertex Pharmaceuticals.

Haydar Frangoul: Consultancy for Editas Medicine, Rocket Pharmaceutical (advisory committee), and Vertex Pharmaceuticals (advisory committee); speaker Jazz Pharmaceuticals.

Josu de la Fuente: Advisory committee Jazz Pharmaceuticals.

Donna Wall: Steering committee and institutional PI Vertex Pharmaceuticals; Steering Committee Novartis.

Maria Domenica Cappellini: Advisory committees Bristol Meyers Squibb, Sanofi Genzyme, Vertex Pharmaceuticals, Agios, and Silence.

Mariane de Montalembert: Advisory committees Novartis, Vertex Pharmaceuticals, Addmedica.

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Yael Bobruff, Chris Simard, Yang Song, Lanju Zhang, Suzan Imren, Bill Hobbs: Employees of Vertex Pharmaceuticals Incorporated.

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4 - CAR-based Cellular Therapy – Clinical

O006

IDECABTAGENE VICLEUCEL VERSUS STANDARD REGIMENS IN PATIENTS WITH TRIPLE-CLASS–EXPOSED RELAPSED AND REFRACTORY MULTIPLE MYELOMA: KARMMA-3, A PHASE 3 RANDOMIZED CONTROLLED TRIAL

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Background: Survival outcomes are poor in patients with relapsed and refractory multiple myeloma (RRMM) who are triple-class exposed (TCE) to immunomodulatory agents, proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies. As patients become TCE in earlier lines of therapy, treatment options are limited. Idecabtagene vicleucel (ide-cel) demonstrated deep durable responses in heavily pretreated TCE RRMM.

Methods: KarMMa-3 (NCT03651128), an international, open-label, randomized controlled trial, enrolled patients with RRMM who received 2–4 prior regimens, including an immunomodulatory agent, a PI, and daratumumab, and were refractory to the last regimen. Patients were randomized 2:1 to ide-cel or a standard regimen (investigator choice of daratumumab + pomalidomide + dexamethasone, daratumumab + bortezomib + dexamethasone, ixazomib + lenalidomide + dexamethasone, carfilzomib + dexamethasone, or elotuzumab + pomalidomide + dexamethasone based on prior regimen). Ide-cel was infused at a target dose of $150–450 \times 10^6$ chimeric antigen receptor-positive (CAR+) T cells ($\leq 540 \times 10^6$ cells allowed). Primary endpoint: progression-free survival (PFS) assessed by Independent Response Committee (IRC). Key secondary endpoints: IRC-assessed overall response rate (ORR) and overall survival. Other secondary endpoints: duration of response (DOR), health-related quality of life (QoL), pharmacokinetics, and safety. Efficacy assessed per ITT.

Results: Of 386 patients (ide-cel $n = 254$; standard regimens $n = 132$), 225 received ide-cel (median dose 445×10^6 CAR+T cells [range $175–529 \times 10^6$]) and 126 received standard regimens. Baseline characteristics, including median age (63 years), median time since diagnosis (4.1 years), median prior therapies ($n = 3$), triple-class (66%) and daratumumab (95%) refractoriness, and high-risk cytogenetics (44%), were generally balanced. Median follow-up from randomization to data cutoff was 18.6 months. Ide-cel significantly improved PFS versus standard regimens (median 13.3 vs 4.4 months; HR 0.49; $P < 0.0001$). Ide-cel significantly improved ORR vs standard regimens (71% vs 42%; $P < 0.0001$), with deeper (complete response, 39% vs 5%), more durable responses (median DOR 14.8 vs 9.7 months). PFS and ORR benefit of ide-cel was consistent across multiple patient subgroups. Post–ide-cel infusion, CAR+T cells underwent rapid multi-log expansion (median 11 days to maximum expansion). In the treated population, grade 3/4 adverse events (AEs) occurred in 93% and 75% of patients in the ide-cel and standard regimen arms, respectively, and grade 5 AEs in 14% and 6%; 5 treatment-related AEs in 3% and 1%. In ide-cel–treated patients, any-grade cytokine release syndrome occurred in 88%; grade 3/4 in 4%. Any-grade investigator-identified neurotoxicity occurred in 15% of patients; grade 3/4 in 3%. Ide-cel demonstrated clinically meaningful improvements

on patient-reported outcomes, including symptoms, functioning, and QoL versus standard regimens.

Conclusions: Ide-cel treatment resulted in a significant improvement in PFS and ORR, with deeper and more durable responses versus standard regimens. Ide-cel benefit was consistent across difficult-to-treat subgroups. The toxicity profile of ide-cel was consistent with prior studies. These results support the use of ide-cel in patients with early-relapse TCE RRMM, a population with poor survival outcomes.

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Clinical Trial Registry: ClinicalTrials.gov, NCT03651128.

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BA: research/honoraria/advisor: Amgen, BMS, GSK, Janssen, Sanofi, Takeda.

KP: research/consultant/honoraria: AbbVie, Allogene, Arcellx, BMS/Celgene, Caribou, Cellectis, Janssen, Karyopharm, Legend, Merck, Nektar, Oncopeptides, Pfizer, Poseida, Precision.

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AN: honoraria/advisor: Adaptive, Amgen, BeyondSpring, BMS, GSK, Janssen, Karyopharm, Oncopeptides, Pfizer, Sanofi, Secure, Takeda.

SM: research/advisor: AbbVie, Adaptive, Amgen, BMS, GSK, Janssen, Novartis, Oncopeptide, Pfizer, Regeneron, Roche, Sanofi, Takeda.

NC: honoraria: ClinicalCareOptions, Research-to-Practice.

LC: research/consultant/honoraria: AbbVie, Adaptive, Amgen, BMS, Ionis, Janssen, Pfizer, Sanofi.

RV: research/consultant: BMS.

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12 - Graft-versus-host Disease – Clinical

O007

BACTERIOPHAGE-MODULATED PRODUCTION OF INTESTINAL INTERFERON I-INDUCING METABOLITES IS ASSOCIATED WITH PROTECTION IN ALLOGENEIC STEM CELL TRANSPLANTATION PATIENTS

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Background: The intestinal bacteriome determines outcome in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-SCT). Besides bacteria, fungal and viral communities as well as microbiota-derived metabolites play a role. Yet, it is still unclear how dynamic shifts in these three communities

(1) influence production of intestinal microbiota-derived metabolites,
(2) are affected by antibiotics, graft-versus-host disease (GvHD) or fecal microbiota transplantation (FMT),
(3) contribute to clinical outcome of allo-SCT patients.

Methods: We performed a prospective, longitudinal study that combined transkingdom analysis (bacterial 16S rRNA, fungal 18S rRNA, viral metagenomic sequencing) of intestinal microbial communities with targeted metabolomics by mass spectrometry (MS) in allo-SCT patients ($n = 78$) at two different transplantation centers in Germany. Our goal was to identify microbiome signatures associated with the production of intestinal microbiota-derived metabolites. Multi-omics factor analysis (MOFA)-identified microbiome signatures were subsequently analyzed by metagenomic sequencing for

(1) species-level profiling of the taxonomic community composition and
(2) characterization of alterations in microbial genes and pathways during allo-SCT.

The expression of highly differentially abundant bacterial genes was validated by quantitative PCR (qPCR). We defined an intestinal metabolite profile which correlated with clinical outcome (overall survival (OS), transplant-related mortality (TRM) and gastrointestinal (GI) GvHD).

Results: By integrating bacterial, fungal and viral sequencing data with metabolite expression via MOFA, we identified two factors that described a microbiome signature of metabolite-producing bacteria from the *Lachnospiraceae*and *Oscillospiraceae* families and their corresponding bacteriophages, which correlated with the intestinal production of short-chain fatty acids (SCFAs), metabolites associated with induction of type-I interferon signaling (IIMs) and secondary bile acids. A high expression of these MOFA-identified factors correlated with reduced TRM and GvHD. We defined an intestinal metabolite profile comprised of specific immunomodulatory metabolites which was associated with improved OS and reduced TRM. Antibiotic exposure and GI-GvHD significantly impaired metabolite expression. By metagenomic sequencing, we observed that patients with sustained metabolite production after allo-SCT had a higher abundance of microbial genes associated with bacterial metabolic pathways, e.g. Butyryl–coenzyme A (CoA):acetate CoA-transferase (BCoAT), a bacterial enzyme required for biosynthesis of the SCFA butyrate. We validated the expression of BCoAT by qPCR, and observed high expression in early, but not late time-points across all patients samples. In addition, we detected BCoAT protein sequence in two bacteriophage genomes. As outlook, we demonstrate that single taxa domination and metabolite depletion in a patient suffering from GvHD could be rescued by transfer of metabolite-producing bacterial consortia via FMT. FMT led to resolution of steroid refractory GvHD and was accompanied by an increase of bacterial and viral diversity and restoration of intestinal SCFAs and IIMs.

Conclusions: Our study demonstrates that sustained local production of a specific metabolite profile is associated with better OS, reduced TRM and less GVHD in patients receiving

allo-SCT. Microbiome alterations by antibiotics or modulation by FMT can affect the identified bacterial/bacteriophage consortia, the expression of metabolite biosynthesis pathways and the intestinal production of IIMs thereby steering clinical outcomes. Our study provides a rationale for the development of engineered metabolite-producing consortia and defined metabolite combination drugs as novel microbiome-based therapies.

Disclosure: Nothing to declare.

26 - Lymphoma and Chronic Lymphocytic Leukaemia

O008

ALLOGENEIC TRANSPLANTATION IN ADVANCED CUTANEOUS T-CELL LYMPHOMAS: A PROPENSITY SCORE-MATCHED CONTROLLED PROSPECTIVE TRIAL

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Background: Advanced-stage cutaneous T-cell lymphomas (CTCL) are rare, usually refractory, and fatal diseases. Case series have suggested that allogeneic haematopoietic stem cell transplantation (HSCT) may improve the prognosis of advanced-stage CTCL.

Methods: In this prospective, multicentre, matched controlled trial, patients with advanced CTCL were allocated treatment according to the availability of a compatible related donor and assigned to allogeneic HSCT or nonallogeneic HSCT therapy. Propensity score 1:1 matching with replacement was used to handle confounding factors, with balance measured on standardized mean differences. The primary endpoint was progression-free survival.

Results: Patients with a sibling/matched unrelated donor were assigned to allogeneic HSCT (HSCT group, $n = 55$ [56% of 99 patients]) and patients without donor to nonallogeneic HSCT treatment (non-HSCT group, $n = 44$ [44% of 99 patients]). In the HSCT group, 51 patients (93% of 55 patients) were 1:1 matched to patients from the non-HSCT group. In the intention-to-treat analysis, median progression-free survival was significantly longer in the HSCT group versus the non-HSCT group: 9·0 months (95% confidence interval [CI], 6·6–30·5) versus 3·0 months (95% CI 2·0–6·3), with a hazard ratio (HR) of 0·38 (95% CI 0·24–0·62, $p < 0·0001$). Median overall survival was not reached in the matched HSCT group and 26·9 months (95% CI 16·1–NA) in the matched non-HSCT group (HR 0·54, 95% CI 0·27–1·11, $p = 0·092$). In the per-protocol population, HR for overall survival was 0·37 (95% CI 0·16–0·84, $p = 0·018$). There was a mean improvement in quality-of-life measurements over time in the HSCT group ($p = 0·0050$).

Conclusions: Allogeneic HSCT was associated with significantly longer progression-free survival in patients with advanced-stage CTCL.

Clinical Trial Registry: ClinicalTrials.gov: NCT02520908.

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Conflicts of interest: None to declare.