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ABSTRACTS COLLECTION

The 47th Annual Meeting of the European Society for Blood and Marrow Transplantation: Physicians Award Winners (O001- O009)

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Physicians award winners

Van Bekkum Award

O001.

POST-transplantation cyclophosphamide vs. antithymocyte globulin after ric regimen allo-hct: first analysis of a prospective randomized multicenter trial in recipients of 10/10 matched donors

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Background: Graft-versus-host disease (GVHD) remains a major contributor to mortality and morbidity after allogeneic hematopoietic cell transplantation (allo-HCT). The updated recommendations suggest that rabbit antithymocyte globulin or anti-T-lymphocyte globulin (ATG) should be used for GVHD prophylaxis in patients (pts) undergoing matched-unrelated donor (MUD) allo-HCT. More recently, using post-transplant cyclophosphamide (PTCY) in the haploidentical setting has resulted in low incidences of both acute (aGVHD) and chronic GVHD (cGVHD).

In this prospective, randomized, phase 2 trial (ClinicalTrials.gov Identifier: NCT02876679), we set out to compare the efficacy of PTCy vs. ATG for GVHD prophylaxis in the setting of fludarabine-busulfan reduced-intensity conditioning (RIC). The primary endpoint was the assessment of the composite endpoint of GVHD-free, relapse-free survival (GRFS) at 12 months after allo-HCT. Endpoints included acute and chronic GVHD, disease-free survival (DFS), overall survival (OS) and non-relapse mortality (NRM), at 12 months.

Methods: Hematological pts with a matched sibling donor (MSD) or a 10/10 MUD and for which a RIC allo-HSCT was indicated, were included. All patients received a conditioning regimen of FB2 (fludarabine +2 days of busulfan at 3.2 mg/kg/d iv). Pts randomized to PTCy received 50 mg/kg/day at days +3 and +4 combined with cyclosporin A (CsA) from day +5. Pts randomized to ATG received ATG (thymoglobuline®) 2.5 mg/kg/day at days −2 and −1 with CsA from day −3. The stem cell source was peripheral blood.

Results: In total, 80 pts were randomized (43 in PTCy arm and 37 in ATG arm) between 2017 and 2019. Median age was 64.4 y (range: 21–71), 56 pts (70%) were male. 47.5% pts were transplanted for acute myeloid leukemia, 17.5% for myelodysplastic syndrome, and 14% for lymphoma. 77.8% were in complete remission at transplant. ECOG was ≤1 in 78% of the patients. The donor type was MSD in 31 pts (39%) and MUD

in 49 pts (61%). Baseline patient and transplantation characteristics were equally distributed between the two arms. The cumulative incidence (CI) at 6 months of grade II–IV GVHD was 34.9% [95% confidence interval (CI): 21–49.1] in recipients of PTCY vs. 24.3% [95% CI: 11.9–39.1] in the ATG arm ($p = 0.53$), and grade III–IV was 9.3% [95% CI: 2.9–20.3] and 2.7 [95% CI: 0.2–12.3] respectively ($p = 0.24$). The 1-year CI of cGVHD was 26.0 [95% CI: 13.8–40] in PTCY recipients vs. 30.2 [95% CI: 16.1–45.5] in CsA recipients ($p = 0.56$). The 1-year estimated PFS was 68.5% [95% CI: 51.6–80.5] and 67.1% [95% CI: 49.4–79.8] in the PTCy group and ATG groups, respectively ($p = 0.68$). The 1-year estimated OS was 78.9% [95% CI: 63.4–88.4] in the PTCy group and 80.4% [95% CI: 63.1–90.2] in the ATG group ($p = 0.93$). NRM was 14% [95% CI: 5.6–26.1] in PTCy recipients vs. 22.1% [95% CI: 10.2–36.8] in ATG recipients ($p = 0.49$). The 1-year estimated GRFS in the PTCy and ATG groups was 52.2% [95% CI: 36–66.2] and 42.2% [95% CI: 26.1–57.5], respectively ($p = 0.28$).

Conclusions: The use of PTCY for GVHD prophylaxis resulted in similar outcomes to those seen with ATG for patients who underwent an FB2 RIC regimen allo-HCT with a 10/10 HLA-matched donor.

Clinical Trial Registry: ClinicalTrials.gov Identifier: NCT02876679

Disclosure: P.Chevallier and I.Yakoub-Agha: received honorarium from Sanofi

Other authors have nothing to disclose

Basic science award

O002.

Abstract already published

Presidential symposium

O003.

Maribavir vs. investigator-assigned therapy (IAT) for the treatment of transplant recipients with refractory/resistant (R/R) cytomegalovirus infection: efficacy data from a randomized phase 3 open-label study

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Background: Maribavir has multi-targeted anti-cytomegalovirus (CMV) activity through UL97 protein kinase inhibition; efficacy and safety data from a Phase 3 open-label study of maribavir vs. IAT for treatment of hematopoietic cell/solid organ transplant (HCT/SOT) recipients with R/R CMV infection are reported.

Methods: HCT/SOT recipients (≥12 years) with CMV infection (screening viral load [VL] ≥2730 IU/mL/≥910 IU/mL CMV DNA [blood/plasma]; two consecutive tests ≥1 day apart) refractory to previous therapy (failure to achieve >1 $\log_{10}$ decrease in CMV DNA after ≥14 days' anti-CMV treatment), with/without genotyped resistance, were included. Patients (HCT/SOT and screening CMV VL stratification) were randomized 2:1 (interactive response technology) to oral maribavir 400 mg BID or IAT (valganciclovir/ganciclovir, foscarnet, cidofovir, or foscarnet + valganciclovir/ganciclovir) for 8 weeks with 12 weeks' follow-up. Primary endpoint: confirmed CMV viremia clearance (plasma CMV VL <137 IU/mL, two consecutive tests ≥5 days apart) at end of Week 8. Key secondary endpoint: achievement of CMV viremia clearance and symptom control at end of Week 8, maintained through Week 16 (≥8 weeks off-treatment). Between-group differences, adjusted for baseline CMV VL (low, <9100; intermediate/high, ≥9100 IU/mL [plasma]; central laboratory) and HCT/SOT, were compared (primary/key secondary endpoints; Cochran–Mantel–Haenszel tests; significance, $p \leq 0.05$). Primary endpoint subgroup analyses were performed.

Results: Overall, 352 patients were randomized (235 maribavir; 117 IAT). Age range: 19–79 years; 59.9% SOT and 40.1% HCT. 140 (99.3%) HCT recipients were allogeneic (60.7% unrelated donor; 45.0% received myeloablative conditioning). Proportion of patients with CMV genotypic resistance at baseline: 121/235 (51.5%) maribavir, 69/117 (59.0%) IAT. A significantly higher proportion of patients in the maribavir than IAT group achieved viremia clearance (difference [95% CI], 32.8% [22.80, 42.74]; $p < 0.001$) (Figure). Treatment differences (maribavir vs. IAT) in various subgroups, including those with baseline resistance, were generally consistent with the main analysis (Table). The key secondary endpoint was met ($p = 0.013$) (Figure). The safety analysis set included 350 patients (234 maribavir, 116 IAT). Any treatment-emergent adverse events (TEAEs) (% patients): 97.4% maribavir, 91.4% IAT. For maribavir ($n = 234$) /IAT($n = 116$)/(val)ganciclovir ($n = 56$)/foscarnet ($n = 47$)/cidofovir ($n = 6$): % patients with TEAEs of acute kidney injury were 8.5%/9.5%/1.8%/21.3%/0%, and neutropenia

were 9.4%/22.4%/33.9%/14.9%/0%; treatment-related TEAEs of acute kidney injury were 1.7%/7.8%/0%/19.1%/0%, and neutropenia were 1.7%/13.8%/25.0%/4.3%/0%. TEAEs leading to study drug discontinuation: 13.2% maribavir, 31.9% IAT. Two treatment-related serious TEAEs led to death (one patient per treatment group).

Figure. Patients achieving (A) primary and (B) key secondary endpoints

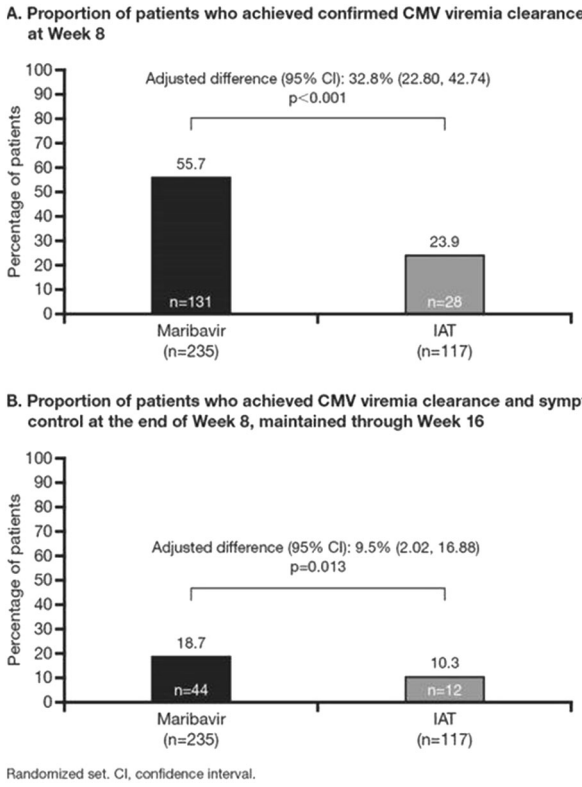

Table. Subgroup analyses of randomized patients achieving viremia clearance[a]

Subgroup analyzed	Maribavir *n*	Maribavir Responders[a] *n* (%)	IAT *n*	IAT Responders[a] *n* (%)	Adjusted difference in proportion of responders % (95% CI)[b]
Transplant type					
SOT	142	79 (55.6)	69	18 (26.1)	30.5 (17.31, 43.61)
HCT	93	52 (55.9)	48	10 (20.8)	36.1 (20.92, 51.37)
Study drug assignment[c]					
Maribavir	235	131 (55.7)			
Ganciclovir/valganciclovir			56	15 (26.8)	31.7 (18.63, 44.78)
Foscarnet			47	9 (19.1)	36.4 (23.37, 49.40)
CMV DNA viral load at baseline					
Low	153	95 (62.1)	85	21 (24.7)	37.4 (25.41, 49.37)
Intermediate/high	82	36 (43.9)	32	7 (21.9)	21.8 (3.93, 39.67)
Resistance status at baseline[d]					
Yes	121	76 (62.8)	69	14 (20.3)	44.1 (31.33, 56.94)
No	96	42 (43.8)	34	11 (32.4)	12.6 (−6.24, 31.43)

CI confidence interval.

[a]Primary endpoint; confirmed CMV viremia clearance (plasma CMV VL < 137 IU/mL, two consecutive tests ≥5 days apart; COBAS®–CAP/CTM) at end of Week 8.

[b]Estimate may be statistically unreliable if sample size in any applicable stratum (transplant type and CMV DNA level) is <5.

[c]Six patients received cidofovir and seven received combination therapy as IAT (data not shown); one patient did not receive a dose of IAT.

[d]At baseline, 18 patients in the maribavir group and 14 patients in the IAT group could not be genotyped (central laboratory).

Conclusions: Maribavir demonstrated superior efficacy vs. IAT in clearing viremia in transplant recipients with R/R CMV infection, with consistent findings across multiple patient subgroups. A higher proportion of patients receiving IAT reported premature study drug discontinuation due to TEAEs than maribavir.

Clinical Trial Registry: Clinicaltrials.gov: NCT02931539

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Catherine Cordonnier: Departmental research funding: Merck and Shire, a Takeda company; personal fees for advisory board and speaker bureau participation: Merck.

Johan Maertens: Consultant and speaker's bureau participation: Amgen, Astellas Pharma, Basilea Pharmaceutica, Bio-Rad Laboratories, Cidara Therapeutics, F2G, Gilead Sciences, Merck, Pfizer, Schering-Plough, SCYNEXIS, Shire, a Takeda company; research grants: Bio-Rad Laboratories, Gilead Sciences, Merck, Pfizer.

Jo-Anne Young: Institutional research grants: Ansun Biopharma, Janssen, Merck, Shire, a Takeda company.

Jingyang Wu and Aimee Sundberg: Employees of and hold stock/stock options: Shire Human Genetic Therapies, Inc., a Takeda company.

O004.

Calcineurin inhibitor-free graft-versus-host disease (GVHD) prophylaxis in hematopoietic cell transplantation

(HCT) with myeloablative conditioning regimens (MAC) and hla-matched donors: results of the BMT CTN 1301

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Background: Calcineurin Inhibitor (CNI)-based regimens are standard GVHD prevention yet CNI-free approaches using T cell depletion, either by ex vivo CD34 selection or in vivo post-transplant cyclophosphamide (PTCy), demonstrate low rates of chronic GVHD.

Methods: BMT CTN 1301 is a phase III trial that randomized patients aged ≤ 65 years with acute leukemia or myelodysplasia (blasts <5%) and an HLA matched related or unrelated donor to receive a CD34-selected peripheral blood stem cell (PBSC) graft without post-transplant immune suppression (IS), PTCy after a bone marrow graft (BM) without additional IS or tacrolimus/methotrexate (Tac/MTX) after BM (control). Primary endpoint was chronic GVHD (moderate/severe) relapse-free survival (CRFS) at 12 months post enrollment. Secondary endpoints were overall survival (OS), GVHD, relapse-free survival (RFS), relapse, transplant-related mortality (TRM), IS-free survival, EBV and CMV reactivation, and quality of life (QOL). Patients unable to receive treatment per protocol (e.g., inadequate PBSC cell dose for CD34 selection or donor non-compliance with marrow collection) received Tac/MTX with PBSC. Analysis of primary endpoint was based on intent to treat and was adjusted on age, donor type, performance status, disease and disease risk.

Results: Among 346 patients enrolled, 327 received HCT, 300 per protocol. CD34 selection had the highest rate of noncompliance with only 89/104 (86%) patients receiving per-protocol therapy. Rates of CRFS at 1 year were 60.2% for CD34 (hazard ratio [HR] vs. control 0.8, $p = 0.23$), 60.3% for PTCy (HR 0.86, $p = 0.41$) and 56.6% for control; the HR for CD34 vs. PTCy was 0.9, $p = 0.72$. Corresponding rates of OS were 75.7% (HR 1.74 vs. control, $p = 0.02$), 84.6% (HR 1.02, $p = 0.95$) and 84.2%. HR for CD34 vs. PTCy for OS was 1.77 ($p = 0.02$). TRM rates at 1 year were 16.5% (HR 2.76 vs. control, $p = 0.01$), 12% (HR 2.01 vs. control, $p = 0.09$) and 7%, for CD34, PTCY and control, respectively. Corresponding rates for relapse were 19.4% (HR 0.91, $p = 0.74$), 9.2% (HR 0.52, $p = 0.04$) and 22.9%, for CD34, PTCY and control, respectively. No differences were noted between the 3 groups in QOL assessments using the SF 36, FACT-BMT and MDASI at baseline, day 100, day 180, 1 and 2 years.

Conclusions: There was no difference in CRFS across treatment arms. Patients receiving CD34-selected grafts had lower overall survival driven by TRM, which offset any benefit from lower chronic GVHD. PTCy alone with BM did not reduce the rate of acute or chronic GVHD compared to Tac/MTX with a BM graft. Tac/MTX and CNI-free PTCy with BM are equivalently effective strategies for GVHD prophylaxis after myeloablative conditioning using HLA-matched donors.

Clinical Trial Registry: NCT02345850

Disclosure: This clinical trial was co-sponsored by Miltenyi Biotec

O005.

Results of a phase III randomized, multicenter study comparing omidubicel with standard umbilical cord blood transplantation (UCBT) in patients with high-risk hematologic malignancies following myeloablation

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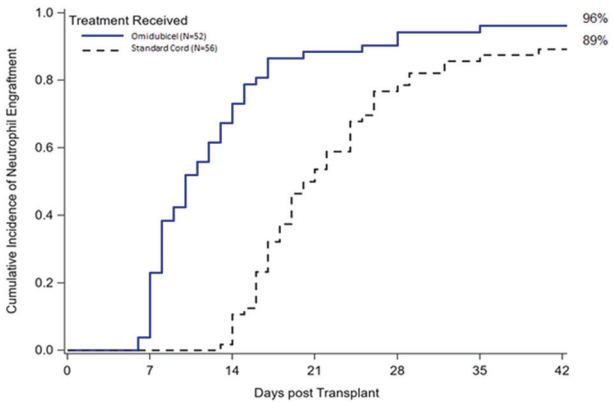
Background: Omidubicel is a cryopreserved cellular product derived from an entire single UCB unit expanded ex vivo that substantially increases CD34+ cell content and has demonstrated in a phase I-II trial rapid and durable hematopoietic reconstitution. Omidubicel could accelerate engraftment, decrease early transplant-related complications and reduce hospitalization, abrogating delayed engraftment, the major drawback of UCBT. We report herein the results of a phase III trial aimed to evaluate the efficacy of omidubicel compared to standard UCB in subjects with hematologic malignancies.

Methods: Subjects were randomized to receive omidubicel or standard UCB with 1 or 2 UCB units (control arm). Stringent EBMT criteria for single-unit UCBT were followed. Three myeloablative conditioning regimens were allowed; two TBI-based [TBI1200-1350cGy, thiotepa (T) 10 mg/kg, and fludarabine (F) 160 mg/m2 or TBI1200-1320cGy, F 75 mg/m2, and cyclophosphamide 120 mg/kg], and one TBI-free, [T 10 mg/kg, busulfan (B) 9.6 mg/kg, and F 150 mg/m2 (TBF)]. GvHD prophylaxis consisted of a calcineurin inhibitor and MMF. Primary endpoint was time to neutrophil engraftment (ANC > 500/μl) at 42 days. Secondary endpoints were platelet engraftment (>20,000/μl) at 42 days, grade 2–3 bacterial or invasive fungal infection at 100 days, and days alive and out of hospital in the first 100 days after transplantation. All endpoints were analyzed on an intention-to-treat basis.

Results: Between Jan 2017 and Jan 2020, 125 subjects were randomized (33 sites, 7 countries) to omidubicel ($n = 62$) or standard UCB ($n = 63$; single, 33% or double, 67%). Median age was 41 years (range, 13–65). Most patients had AML (48%) or ALL (33%). The study population was diverse (16% Black, 14% Asian, 13% Hispanic – Latino, and 3% multiracial). Baseline characteristics were well-balanced across the two arms. Median follow-up was 10 months (range, 1–19 months). Median CD34+ cell dose for omidubicel recipients was 9×106/kg (124-fold CD34+ cell expansion) and 0.3×106/kg for controls ($P < 0.0001$). Median time to neutrophil engraftment was 12 days (95% CI, 10–15 days) in omidubicel recipients and 22 days (95% CI,19–25 days) in controls ($P < 0.001$, Figure). Omidubicel recipients had a higher incidence of 42-day platelet engraftment ($P = 0.028$), a lower incidence of grade 2–3 bacterial/invasive fungal infection ($P = 0.027$) and spent less time in hospital during the first 100 days following transplant (median, 39 vs. 52 days; $P = 0.005$) than controls, Viral infections at 6 months ($P = 0.04$) and 1 year ($P = 0.02$) were also lower with omidubicel. Cumulative incidence of grade II/IV, grade III/IV acute GvHD, and 1-year incidence of chronic for omidubicel and control arms were not statistically different. Non-relapse mortality at 180 days (11% vs. 22%), 1-year relapse rate (27% vs. 20%), and 1-year probability of overall survival (73% vs. 62%) for omidubicel and control arm did not significantly differ.



Conclusions: Hematopoietic engraftment with omidubicel was faster, reduced early transplant-related complications, and achieved a substantial clinical benefit as compared to standard UCBT. The results of this clinical trial demonstrate that omidubicel represents a major therapeutic advance and should be considered the standard of care for patients eligible for UCBT.

Disclosure: Nothing to declare

O006.

Elivaldogene autotemcel (ELI-CEL; LENTI-D) gene therapy for cerebral adrenoleukodystrophy: updated results from the phase 2/3 study and safety outcomes report from the phase 3 study

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Background: Earlier results from the ALD-102 study of elivaldogene autotemcel (eli-cel; Lenti-D) gene therapy showed that 88% of patients with cerebral adrenoleukodystrophy (CALD) met the primary endpoint of survival free of major functional disabilities (MFD) at 24 months. Here, we provide updates on the fully enrolled ALD-102 study and initial data from study ALD-104 investigating busulfan/fludarabine myeloablative protocol instead of busulfan/cyclophosphamide.

Methods: Boys with CALD (≤17 years) underwent apheresis collection following hematopoietic stem cell (HSC) mobilization with granulocyte colony-stimulating factor (G-CSF) ± plerixafor (Table 1). Post-conditioning, boys received eli-cel (autologous CD34+ HSCs transduced with Lenti-D lentiviral vector encoding ABCD1 cDNA). After ALD-102/ALD-104 (2 years), monitoring continues in LTF-304 (additional 13 years). Data are median (min–max).

Results: As of January 2020, follow-up for 32 patients in ALD-102/LTF-304 was 30.0 (9.1–70.7) months. Twenty patients completed ALD-102 and enrolled in LTF-304, and 9 additional patients (maximum follow-up 22.1 months) were still in ALD-102; all without MFDs. The primary efficacy endpoint was met in 20/23 (87%) evaluable patients; 2 were withdrawn and 1 died after rapid disease progression and multiple MFDs.

As of February 2020, 13 additional patients received eli-cel in ALD-104 with 6.1 (2.2–10.3) months follow-up. Neutrophil engraftment occurred at 13 (11–41) days in ALD-102 ($n = 32$) and 13 (12–31) days in ALD-104 ($n = 13$). Platelet engraftment (PE) occurred at 32 (16–60) days in ALD-102 ($n = 32$) and 27 (18–108) days in ALD-104 ($n = 12$). Two clinically stable ALD-104 patients had an ongoing pancytopenia SAE (considered possibly eli-cel-related), one with PE on Day 108 and the other with available platelet values indicative of PE on Day 104; neither pancytopenia met criteria for failed engraftment. An additional ongoing SAE in ALD-104 was transverse myelitis (eli-cel-unrelated, partially responsive to steroids/plasmapheresis). In ALD-102, 3 AEs were possibly eli-cel-related: BK viral cystitis ($n = 1$) and vomiting ($n = 2$).

The safety/tolerability profile of eli-cel treatment regimen was primarily reflective of the known effects of mobilization/apheresis and conditioning. There was no graft failure, graft-versus-host disease, replication competent lentivirus, or insertional oncogenesis. Benign clonal expansion determined by insertional site analysis was observed in one ALD-102 patient, who was clinically well at last available visit (Month 62).

Conclusions: As of February 2020, 45 boys with CALD received eli-cel. The treatment showed a favorable benefit/risk profile with up to 71 months follow-up in ALD-102/LTF-304. Updated data from eli-cel studies with more patients and longer follow-up will be presented.

Table 1. HSC mobilization/apheresis in eli-cel studies.

	ALD-102 ($N = 32$)	ALD-104 ($N = 13$)
G-CSF dose/cycle, μg/kg	60.0 (40.0–100.0)	50.0 (33.0–70.0)
G-CSF average dose/day, μg/kg	10.0 (8.9–12.5)	10.0 (6.6–10.0)
Plerixafor (0.24 mg/kg) recipients,[a] *n* (%)	11 (34%)	13 (100%)
Mobilization cycles, *n*	1 (1–1)	1 (1–1)
Apheresis procedures per mobilization cycle, *n*	2.0[b] (1.0–4.0)	1.0[b] (1.0–3.0)
Total CD34+ cells collected, cells × 10^6/kg	17.0 (12.2–29.6)	23.5 (14.9–59.1)

Data are median (min–max).

[a]ALD-102 (optional), ALD-104 (required).

[b]G-CSF was administered for 4–6 days for first apheresis, with ≤3 additional apheresis days (each including G-CSF administration) performed/mobilization cycle.

Clinical Trial Registry: The data included in the abstracts are from studies ALD-102 (NCT01896102), LTF-304 (NCT02698579), and ALD-104 (NCT03852498), which are sponsored by bluebird bio, Inc.

Disclosure:

Kühl, Jörn-Sven: Honoraria (bluebird bio, Inc).

Duncan, Christine; De Oliveira, Satiro: None to declare.

Eichler, Florian: Consultant (Ionis Pharmaceuticals, SwanBio Therapeutics, Alnylam, Pfizer, Origin Biosciences); financial support to conduct clinical trials (bluebird bio, Inc., Minoryx Therapeutics); co-founder (SwanBio Therapeutics).

Thrasher, Adrian: Co-founder/consultant/ownership interest (Orchard Therapeutics); consultant (Rocket Pharmaceuticals, Generation bio, bluebird bio, Inc., 4Bio Capital Partners, Sana Biotechnology, Autolus Ltd.).

Sevin, Caroline; Chiesa, Robert: Consultant (bluebird bio, Inc.).

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Smith, Nicholas: Consultant (Avexis); research funding (bluebird bio, Inc., Abeona); equity ownership (837Bio); Advisory board member (Rare Finds Foundation, Sanfilippo Children's Foundation, and Batten Disease Support and Research Foundation).

Kenney-Jung, Daniel: Research funding (NIH).

Dalle, Jean-Hugues: Consultant/honoraria/ Advisory board member (Jazz Pharmaceuticals); consultancy/honoraria (Astellas, Bellicum, bluebird bio, Inc., Chimerix, GILEAD, Incyte, MEDAC, Novartis, Sanofi).

He, Shuang; Dietz, Andrew: Employment/ownership interest (bluebird bio, Inc.)

McNeil, Elizabeth: Former employee (bluebird bio, Inc.); currently employed by Passage Bio.

Aubourg, Patrick: Research funding (bluebird bio, Inc).

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O007.

A prognostic score including mutation profile and clinical features for cmml undergoing stem cell transplantation

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Background: The inclusion of mutation status improved risk stratification for newly diagnosed patients with chronic myelomonocytic leukemia (CMML). Stem cell transplantation is a potentially curative treatment option, and patient selection is critical, because of relevant transplant-related morbidity and mortality. We aimed to evaluate the impact of mutation status together with clinical presentations on posttransplant outcome.

Methods: This international multicenter study included a total of 240 CMML patients from 10 centers undergoing first allogeneic stem cell transplantation, diagnosed at time of transplant according to the criteria of the 2016 revised WHO classification of myeloid neoplasms. Patients with CMML which had already progressed to acute leukemia at time of transplantation were excluded. Samples for mutation analyses were taken at time of transplant and were sequenced for 19 previously identified genes. The primary outcome of overall survival was defined as time from date of transplantation to death from any cause. The distribution of survival was estimated by the Kaplan-Meier method and compared by log rank test. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) using Cox regression were applied for variables in univariable and multivariable analyses. Accuracy and discrimination of the final model was evaluated. Performance of the model was checked using cross-validation.

Results: 240 patients were included. The median follow-up was 5.5 years (95% CI, 4.0–7.0 years). At time of transplant, CMML classification according to WHO was 0 in 10% (24 patients), 1 in 50% (119 patients), and 2 in 40% (97 patients). The recipient-donor relation of the transplant was matched related in 21%, matched unrelated in 54%, mismatched related in 3%, and mismatched unrelated in 22% of patients. Graft type was mainly peripheral blood (93%) and 56% of patients received reduced intensity conditioning compared with 44% of patients who received myeloablative conditioning.

A significant association with worse survival was identified for the presence of mutations in ASXL1 and/or NRAS. In multivariable analysis, ASXL1- and/or NRAS-mutated genotype (hazard ratio [HR], 1.63), marrow blasts >2% (HR, 1.70), and increasing comorbidity index (continuous HR, 1.16) were independently associated with worse survival. A prognostic score (CMML-transplant score) was developed, and the following points were assigned: 4 points for an ASXL1- and/or NRAS-mutated genotype and blasts >2%, respectively, and 1 point each for an increase of 1 in the comorbidity index. The CMML-transplant score (range, 0–20) was predictive of survival and non-relapse mortality ($P < 0.001$, respectively). Up to 5 risk groups were identified, showing 5-year survival of 81% for a score 0–1, 49% for a score 2–4, 43% for a score 5–7, 31% for a score 8–10, and 19% for a score >10. The score retained performance after validation (concordance index, 0.68) and good accuracy after calibration. Predictions were superior vs. existing scores designed for the nontransplant setting, resulting in significant risk reclassification.

Conclusions: This CMML-transplant score, incorporating mutation and clinical information, was prognostic in patients specifically undergoing transplantation and may facilitate personalized counseling.

Disclosure: Nothing to declare.

O008.

Immune escape driven by somatic mutations in class I/II HLA alleles in AML relapsing after allogeneic HSCT: a piece of the puzzle

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Background: Curative potential of allogeneic hematopoietic stem cell transplantation (HSCT) in myeloid malignancies is principally related to the graft-versus-leukemia (GvL) effect exerted by donor-derived immune effectors on leukemic cells. However, perturbation/attenuation of T cell-mediated GvL responses may drive post-transplant relapses. Decreased expression of HLA alleles (due to HLA down-regulation) along with the occurrence of genomic aberrations in HLA region (6p copy-neutral loss of heterozygosity (LOH) or 6pdel) have been described in haploidentical/mismatched and matched contexts as mechanisms contributing to leukemia relapse. Here, we hypothesize that somatic mutations in class I–II HLA alleles may lead to immune escape from GvL, similarly to 6pLOH or HLA haploinsufficiency, decreasing the presentation of immunodominant peptides on leukemic blasts.

Methods: We performed a comprehensive genetic characterization of specimens sequentially collected from a cohort of 25 patients with AML and MDS relapsing after HSCT. Specifically, we applied a deep-targeted NGS panel to study HLA region along with 173 genes known to have a role in leukemogenesis/cancer ontogeny. Fifty-seven paired/serial samples (25 at AML/MDS diagnosis, 25 at relapse after HSCT and 7 at relapse after chemotherapy) were analyzed.

Results: Overall, we found the acquisition of 8 disruptive HLA somatic mutations in 6 patients at post-transplant relapse (24%), 4 in class I and 4 in class II loci. None of those events were found in samples at diagnosis or at post-chemotherapy relapse, suggesting an immune-driven pressure. Those somatic hits accounted for 4 intronic indels, 1 exonic frameshift insertion, one splicing site and 2 point mutations in 3` and 5` untranslated regions (UTRs). Median VAF was 17% (range 2–58%). Of note is that all HLA mutant patients received a matched HSCT (4 MRD and 2 10/10 MUD) suggesting that this mechanism is independent from the deletion and the loss of an immune privileged mismatched allele. Interestingly, median time to relapse was 514 (range 119–935) days for HLA-mutated patients vs. 126 (62–543) for HLA wild type cases ($p = 0.00042$), consistent with the hypothesis that the establishment of immune-tolerance, and the presence of a GvL effect (less likely in early relapses) are required for the selection of those mutations.

When somatic genotype of these patients prior and after transplant was studied, we found that 68% of post-HSCT relapses were associated with a new genomic configuration with either loss of previous events or acquisition of new subclonal mutations in myeloid or cancer related genes. Although mutational burden in myeloid-associated genes was similar between HLA mutated and HLA wild type patients in samples after HSCT, patients relapsing with HLA mutations had an increased frequency of somatic events in genes encoding for transcription factors and epigenetic regulators involved in immune modulation (EZH2, EP300, GATA2, DDX41, TET2).

Conclusions: Results shown here represent an important proof-of-concept for the role played by somatic mutations in HLA genes in the setting of post-HSCT AML/MDS relapses. These events, in analogy with the deletion or copy-neutral LOH, may promote immune escape relapses resistant to immunologic manipulations and may coexist or be an alternative pathway to the progression/relapse characterized by acquisition of myeloid subclonal driver mutations.

Disclosure: Nothing to declare

Jian Jian Luan Award

O009.

Standard-of-care CAR-T cell therapy for large B-cell lymphoma: real world data Germany

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Background: In 2018 the European Medicines Agency (EMA) approved axicabtagene ciloleucel and tisagenlecleucel for the treatment of relapsed/refractory (r/r) large B-cell lymphoma (LBCL) in Europe. In Germany, reimbursement of commercial CAR-T cell therapies is linked to mandatory reporting of baseline and outcome data to the DRST, which is the National partner organization of the EBMT. The purpose of this study was to perform the first outcome analysis on CD19-targeted CAR-T cell therapy used as standard of care (SOC) for r/r LBCL in Germany.

Methods: Eligible were all patients receiving above mentioned approved CAR-T products for SOC treatment of r/r LBCL from December 2018 through September 2020 and registered with the DRST. Baseline patient, disease, and transplant data were collected from MED-A Cellular Therapy forms. Centers were contacted to provide additional treatment and follow-up information. Main outcomes analyzed were patient characteristics, toxicities, hospitalization time, response, non-relapse mortality, and survival endpoints.

Results: 203 patients consecutively received SOC CAR-T cells in 16 centers, 98 patients axicabtagene ciloleucel and 105 patients tisagenlecleucel. Patients' median age was 60 (range, 19–83) years. 69 were female and 134 were male. 167 (82%) patients had diffuse large B-cell lymphoma (DLBCL), 15 (7%) transformed follicular lymphoma, 9 (4%) primary mediastinal B-cell lymphoma, and 7 (3%) other high grade B-cell lymphoma, 3 follicular lymphoma, 1 Burkitt lymphoma and 1 primary CNS DLBCL. Patients received a median of 3 (range, 2–8) prior lines of therapy. 6 patients had previous allogeneic, 19 previous autologous transplant. 74% (151/203) of patients were refractory to the last line of treatment.

82% (161/203) patients needed bridging therapy between the time of apheresis and start of lymphodepleting chemotherapy. Median hospital stay for CAR-T cell therapy were 21 (range, 9–128) days. CRS of any grade was reported in 137/203 (67%, 20/203 (10%) grade 3–4) and ICANS of any grade in 55/203 (27%, 14/203 (7%) grade 3–4). 47/203 (23%) were transferred to ICU during their inpatient treatment. 7 (3%) patients died due to non-relapse mortality. 130 patients are alive and 73 patients died. Overall response was evaluable in 197 patients. Overall response rate to CAR-T cell treatment was 60% with 57 CR (29%), and 61 PR (31%). SD as best response was seen in 27 (14%) and progressive disease in 52 patients (26%). With a median follow-up for patients alive of 183 (range, 30–648) days, 129 patients (64%) relapsed or progressed. Kaplan–Maier estimated overall survival was 53% and disease-free survival 20% at 1 year.

Conclusions: With a limited follow-up, the German experience with SOC CAR-T cells in LBCL is in keeping with the approval trials in terms of safety, whereas our efficacy data appear to be inferior to published results. More mature data will be presented at the meeting.

Disclosure: Consultancy Novartis and Gilead