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HSC and stem cell mobilization

O011

A phase III, double-blind, randomized, placebo-controlled, multicenter clinical trial to study the safety, tolerability, efficacy, and immunogenicity of inactivated VZV vaccine (ZVIN) in recipients of autologous hematopoietic stem cell transplants (auto-HSCT)

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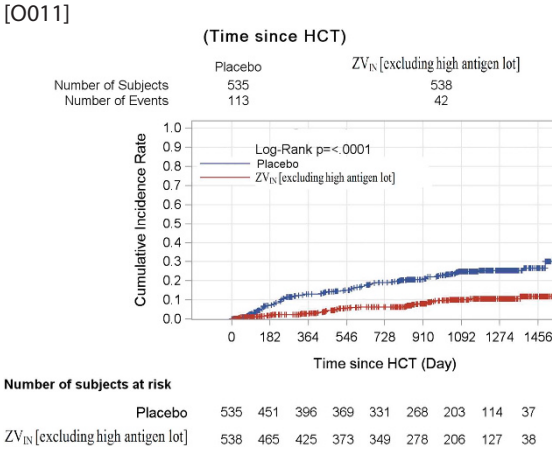
Inactivated varicella zoster virus (VZV) vaccine (ZVIN) is being developed for the prevention and amelioration of herpes zoster (HZ) and HZ-related complications in patients undergoing autologous hematopoietic stem cell transplants (auto-HSCT). Primary objectives are as follows: (1) assess safety and tolerability of ZVIN; (2) assess impact of ZVIN on HZ following auto-HSCT. Secondary objectives: (1) assess impact of ZVIN on moderate to severe HZ-associated pain, defined by $\geqslant\geqslant 2$ occurrences of a score of $\geqslant 3$ (0–10 point scale) on the zoster brief pain inventory (ZBPI) postvaccination; (2) assess impact of ZVIN on HZ complications, defined as hospitalization or prolongation of hospitalization due to HZ, dissemination of HZ manifested by disseminated rash with or without VZV viremia, neurological impairment due to HZ, or need for administration of intravenous acyclovir for treatment of HZ; (3) assess impact of ZVIN on postherpetic neuralgia (PHN), defined by pain in the area of HZ rash with a "worst pain in last 24 hours" score of $\geqslant 3$ on ZBPI that persists or worsens within 90 days after HZ rash onset . Adults ($\geqslant$18 years old) randomly received either ZVIN (560 subjects), ZVIN high antigen lot (160 subjects), or placebo (564 subjects), administered in a 4-dose regimen. Dose 1 was administered ~30 days prior to HCT. Doses 2 through 4 were administered ~30, ~60, and ~90 days post auto-HCT. Randomization was stratified by age ($<$ or $\geqslant$ 50 years old) and by duration of intended use of antiviral prophylaxis ($\leqslant$3 or $>$3 to $\leqslant$ 6 months). All subjects were actively followed for HZ for the duration of the study. Subjects who developed suspected HZ were followed for 6 months after onset of HZ. Cox proportional hazards model based on a modified intent-to-treat (MITT) population (all randomized patients who received $\geqslant 1$ dose of vaccine/placebo and underwent auto-HSCT) was used to compare the incidence of HZ, moderate to severe HZ-associated pain, HZ complications and PHN between ZVIN and placebo recipients. All subjects who received $\geqslant 1$ dose of vaccine/placebo and had follow-up data were included in the primary safety analysis. Subjects were monitored for serious adverse experiences (SAE) regardless of causality for the duration of the study. The majority of HZ cases were confirmed by PCR. Average follow-up time for HZ surveillance in MITT population was ~2.3 years postvaccination. Confirmed HZ occurred in 42 vaccine ($n=538$) and 113 placebo ($n=535$) recipients. Estimated VEHZ was 63.8%; (95% CI, 48.4–74.6%); adjusted for age and duration of antiviral prophylaxis, meeting the pre-specified primary hypothesis success criterion (that is, lower bound of 95% CI $<25\%$). Kaplan–Meier plot confirmed the lower cumulative incidence rate of HZ over time in the ZVIN group. Estimated VEPAIN was 69.5% (95% CI: 49.0%, 81.8%). Estimated VECOMPLICATIONS was 73.5% (95% CI: 49.8%, 86.0%). Estimated VEPHN was 83.7% (95% CI: 44.6%, 95.2%). Proportions of SAEs and vaccine-related SAEs were similar between vaccine and placebo groups (32.9% vs 32.7% (risk difference 0.2% (95% CI: − 5.1, 5.5)) and 0.8% vs 0.9% (risk difference − 0.1% (95% CI: − 1.4, 1.1))). None of the VZV rashes were PCR positive for vaccine strain. The results of a pivotal Phase III study (V212-001; NCT01229267; EudraCT2010-020150-34) demonstrate that ZVIN is efficacious and well-tolerated when administered to adult recipients of auto-HSCT.

Clinical Trial Registry:

Disclosure of conflict of interest: This study was funded by Merck & Co., Inc. (sponsor). In conjunction with the external study advisory committee (SAC) and the investigators, this study was designed, executed and analyzed by the sponsor. OAC, DJW, KMM and MJB were memebrs of the SAC and investigators. KH, SCS, LP, YZ, ISFC, JFS, SSK, JP, PWA and ZP were employees of the sponsor. AA was the cahir of the SAC. Presenting author is Cornely OA.

Figure 1: Kaplan–Meier Estimate of the cumulative incidence of confirmed Herpes-Zoster Cases.

[O011]



O012

High exposure to fludarabine in conditioning prior to allogeneic hematopoietic cell transplantation predicts for impaired CD4 reconstitution and lower survival chances

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Fludarabine (Flu) is widely used in conditioning prior to allogeneic hematopoietic cell transplantation (HCT) in combination with busulfan (Bu). Whilst targeting Bu to optimal exposure has been shown to increase survival chances, to date there is no optimal exposure known for Flu. Therefore, patients of all ages receive a standardized dose of 160 mg/m^2 over 4 days on the same days as Bu. As Flu has strong cytotoxic and immunosuppressive properties, this study aims to relate Flu exposures with CD4 T-cell reconstitution (IR) and overall survival (OS). In this retrospective single-center study, the circulating metabolite of Flu (F-ara-A) was quantified in samples acquired for routine Bu therapeutic drug monitoring (TDM, from 2010) using a validated liquid chromatography mass spectrometry method. With these data a pharmacokinetic (PK) model was developed and validated using nonlinear mixed effects modelling (NONMEM 7.0). Next, AUC was determined as measure of exposure. For outcome analysis only patients undergoing their first HCT receiving fludarabine 160 mg/m2 and busulfan (targeted to 90 mg*h/L) over 4 days were included. Anti-thymocyte globuline (ATG) was given in the unrelated donor HCT (from day −9: 8mg/kg in adults and 10mg/kg in children). There were no limitations for age, cell source and indication. Main outcomes of interest were overall survival (OS) and IR over time. Statistical analyses included Kaplan–Meier estimates, cox proportional hazard models and linear mixed effect models. For the construction and validation of the PK model 227 patients were included (109 adults, 118 children). For the outcome analyses 141 patients were included (adults; $n = 83$, children; $n = 58$) treated for a variety of malignant ($n = 79$) and non-malignant disorders ($n = 58$), with a median age of 33 years (range 0.23–74). The available ATG exposure ($n = 82$) after HCT was similar in both groups. For the main outcome of interest OS, Flu-exposure was found to be a predictor. Patients with the highest exposure (Figure 1, upper quartile) showed inferior 2-year OS (32%) compared to the 3 lowest quartiles (62%, $P = 0.001$). Also in multivariate analyses Flu-exposure remained a predictor (HR = 2.22, $P = 0.03$), while age and indication (malignant/non-malignant) lost significance ($P = 0.61$, $P = 0.93$, respectively) With the linear mixed effect model a significantly slower IR for patients with the highest Flu-exposure was found ($P < 0.001$). Independently, increasing age had an additional significant contribution to slower IR ($P < 0.001$). High exposure to Flu significantly impairs CD4+ T-cell reconstitution and reduces survival chances after HCT. This is the first step in the definition of a target exposure for Flu in this setting. Dose individualization and/or TDM-based corrections towards the Flu target may reduce overexposure and improve survival chances after HCT.
Disclosure of conflict of interest: None.

O013

Previously published

O014

Impact of G-CSF mobilization on T-cell functionality: New aspects for adoptive immunotherapy

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Peripheral blood stem cells (PBSC) mobilized with granulocyte-colony-stimulating factor (G-CSF) have been increasingly used for hematopoietic stem cell transplantation (HSCT) with the benefits of a faster engraftment and less transplant-related mortality. PBSC products contain more than 10-fold higher number of T cells when compared to bone marrow (BM), leading in most trials to similar rates of acute graft-versus-host disease (aGvHD), but more chronic GvHD. Recently it was shown, that higher rates of viral infections/reactivations with the human cytomegalovirus occurred in PBSCT recipients early after transplantation, while antiviral immunity after 100 days was comparable to BM recipients. These differences may be due to a

Figure 1 (O012):

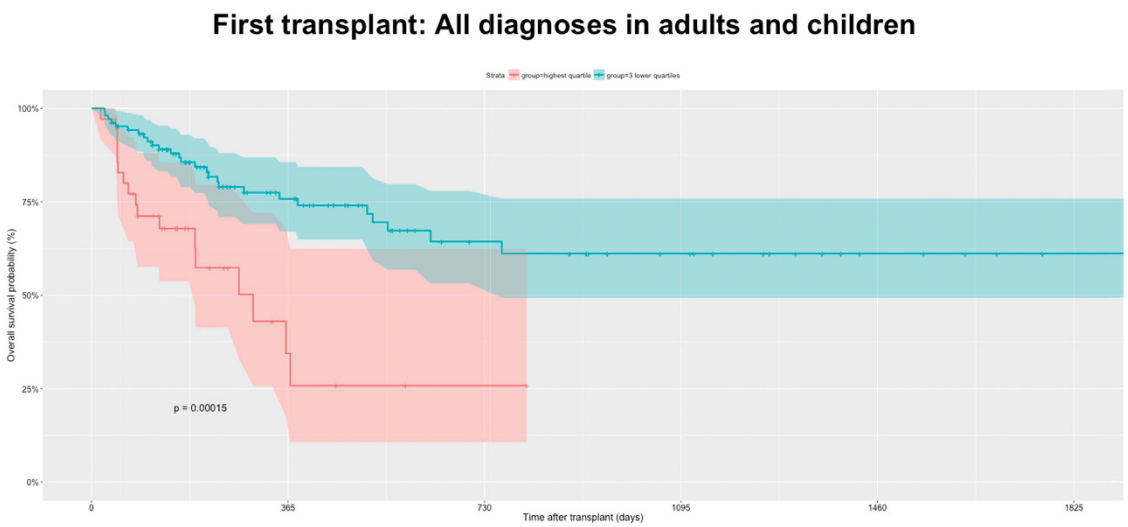

Figure 1: Overall survival after alloHCT in patients receiving busulfan (targeted to optimal exposure) and fludarabine (160mg/m2). Groups consist of patients in the highest quartile of F-ara-A AUC exposure (red) and the lower three quartiles (green). Kaplan-Meier estimates and 95% confidence intervals (CI) are displayed.

transient delayed T-cell immunity, since it was shown that G-CSF-treatment induces immunologic tolerance and negatively affect T-cell functionality. This study aimed to examine the influence of G-CSF administration on the function of CD8+ cytotoxic T cells (CTLs) with focus on (1) the mechanism by which G-CSF influences CTL functionality and (2) the evaluation of mechanisms responsible for this suppressive effect. Functionality of *in vivo* and *in vitro* G-CSF-treated CTLs was analyzed at mRNA and protein levels. Expression of activation marker and miRNA expression profiles, secretion of effector molecules and activation of signaling pathways were investigated after antigen-dependent (viral peptides) and -independent (anti-CD3/CD28) *in vitro* stimulation. Our results showed for the first time that CTLs directly affects by G-CSF, indicated by a reduction in their cytotoxicity, secretion of effector molecules and degranulation capacity, while the proliferative capacity was not hampered. Diminished CTL activation after G-CSF-treatment was indicated by decreased phosphorylation of ERK1/2 (−17%), Lck (−33%) and CD3ζ (−20%) as well as a reduced expression of miRNA-155 (−1.5-fold) and T-cell activation markers such as CD25, CD69 and CD137 (up to − 3.9-fold). Microarray analysis confirmed the down-regulatory effect on CTL activation markers such as CD25 (−5.1-fold), CD69 (−2.0-fold), CD57 (−5.2-fold), and CD137 (−6.3-fold). These results were associated with an impaired expression of effector molecules IFN-γ and granzyme B. Our findings demonstrate that G-CSF treatment directly affects essential elements of the CD8+ T-cell activation pathway leading to an impaired CTL functionality. This suggests that delayed CTL function triggered by G-CSF might be the reason for a similar risk of aGvHD and higher rates of viral reactivations early after HSCT compared to BMT. Cells of G-CSF-treated donors further might not be the best choice in cases where donor lymphocyte infusion or adoptive T-cell transfer is required for treatment of viral reactivation early after transplantation.
Disclosure of conflict of interest: None

O015
Plerixafor in poor mobilizers with non-Hodgkin's lymphoma: a multi-center time-motion analysis

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High-dose chemotherapy alongside peripheral blood stem cell (PBSC) infusion has become the standard of care in different hematologic malignancies. Successful engraftment after transplantation correlates with the CD34+ cell dose; the generally accepted minimum CD34+ cell yield to proceed to transplantation is $\geqslant 2\times10^6$ cells/kg. The current mobilization regimen with granulocyte colony-stimulating factor (G-CSF) still fails in 10–25% of patients. Plerixafor is able to rescue most of these patients from mobilization failure. The objective of this study was to highlight the impact of plerixafor on the cost and time spent on apheresis in patients defined as poor mobilizers. This was a non-interventional study in which patients were divided into two eras: (1) prior to approval of plerixafor and (2) after approval of plerixafor. Patient hospital records from ten centers in Germany, France, and Italy were reviewed and patients qualifying as poor mobilizers (circulating CD34+ cell count $<$ 20/μL) were included. The number of apheresis sessions, time spent on apheresis, CD34+ cell yield, and costs associated with apheresis were recorded. Patient charts were reviewed using standard time-motion technique and time spent for clinical assessment, medical record entry, management of supplies, apheresis, and other procedures were recorded. Costs were obtained prospectively during the plerixafor era in a subset of patients and quantified using micro-costing through interviews with local hospital administration. The primary endpoint of this study was time and effort to mobilize patients for autologous stem cell transplantation (ASCT), using two main variables: mean time to perform apheresis and cost per patient inferred to the hospital. 124 and 134 NHL patients were included during the pre-plerixafor and plerixafor era, respectively. During the plerixafor period, patients spent less time on apheresis (350 vs 463 minutes; Table 1). Poor mobilizers given plerixafor collected more CD34 + cells during the first apheresis session, leading to a decrease in the average number of apheresis sessions needed (2.2 vs 1.6). The total apheresis yield was unaffected, but costs associated with apheresis decreased from €6212 to €4457. Patients in the pre-plerixafor era had a significantly higher initial CD34+ cell count (12.6 cells/mL vs 8.7 cells/mL). A subgroup analysis in patients with initial CD34+ cell count <10 cells/mL showed that time on apheresis and apheresis sessions per patient were reduced; in addition, the total apheresis yield was higher in the plerixafor era (4.2×106 cells/kg vs 3.2×10^6 cells/kg; $P=0.02$). In this study plerixafor lessened the time-effort associated with the treatment of poor mobilizers and reduced apheresis costs.
Disclosure of conflict of interest: CC received research support, honorarium and hospitality from SANOFI S.A. and Honorarium from Terumo BCT. The remaining authors declare no conflict of interest.

O016
The value of post thaw CD34 count with and without DMSO removal in the setting of autologous stem cell transplantation

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[O015] Table 1. Time and cost associated with apheresis

	Initial CD34+ cells $<$ 20 cells/mL		*P**	*Initial CD34+ cells $<$ 10 cells/mL*		P-*value**
	Pre-plerixafor (n = 124)	*Plerixafor (n = 134)*		*Pre-plerixafor (n = 41)*	*Plerixafor (n = 88)*	
# apheresis sessions Mean (s.d.)	2.2 (0.9)	1.6 (0.7)	0.001	2.2 (0.9)	1.6 (0.6)	0.001
Minutes of apheresis Mean (s.d.)	463 (216)	350 (150)	0.001	456 (204)	361 (151)	0.01
Estimated apheresis cost (€) Mean (s.d.)	6212 (2674)	4457 (1860)	0.001	6174 (2455)	4622 (1845)	0.001

*Wilcoxon Rank Sum

Table 1 [O016]

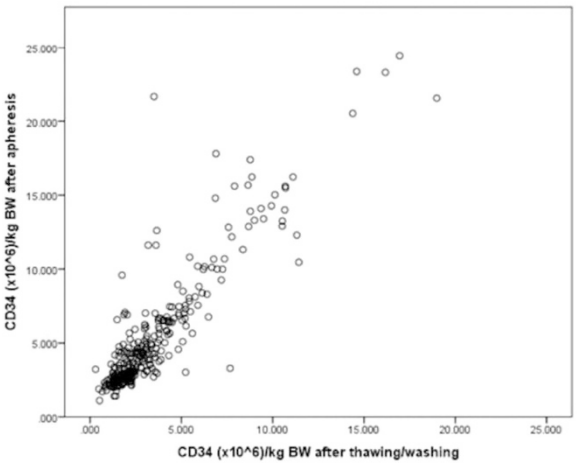
Table. Engraftment data (days after ASCT: median and the lower 10th and 90th percentile). Numbers (n) indicate numbers of ASCT.

Engraftment	ANC	p-value*	PLT	p-value*	RBC	p-value*
DMSO no removal (n=196)	16 (11-26)	0.456	16 (12-28)	0.047	14 (11-27)	0.003
DMSO removal (n=97)	15 (11-25)		19 (14-29)		17 (13-30)	
CD34 at apheresis						
- Low	18 (15-40)	< 0.0001	18 (15-27)	0.007	18 (11-29)	0.146
- Intermediate	16 (12-27)		17 (13-29)		16 (12-29)	
- High	14 (10-24)		16 (11-27)		15 (11-29)	
CD34 after thawing						
- Low	17 (13-28)	< 0.0001	18 (14-31)	< 0.0001	17 (12-30)	0.002
- Intermediate	16 (11-25)		17 (13-28)		16 (11-29)	
- High	13 (10-18)		14 (11-21)		14 (11-30)	
CD34 low after thawing but median/high after apheresis	16 (12-27)		18 (13-30)		17 (13-30)	

Low CD34: CD34 < 2x10^6/kg; Median CD34: CD34 ≥ 2 and < 5x10^6/kg; High CD34: CD34 ≥ 5x10^6/kg.
Abbreviations: ANC: neutrophil engraftment; PLT: platelet engraftment; RBC: red blood cell engraftment. D: days; DMSO: Dimethylsulfoxid.
* p-values < 0.05 are considered statistically significant.

CD34 count per kg patient body weight administered is considered an essential predictor of engraftment after autologous stem cell transplantation (ASCT). According to the recently published JACIE standards (6th edition) counts are generally measured upon cryopreservation at the end of processing. At our institution, CD34 count is routinely determined after processing and after thawing. The value of post-thaw CD34 count with and without dimethylsulfoxid (DMSO) removal has not been systematically analyzed so far. All adult patients transplanted at our institution between 2008 and 2015 were included in this retrospective study. Graft composition, clinical and engraftment data were collected through the electronic database of our institution and by chart review. Analysis were performed using IBM SPSS. All data are expressed as median and the lower 10th and 90th percentile if not otherwise specified. Between 01 January 2008 and 31 December 2015, 237 patients (155 males, 65%) underwent ASCT at our institution. Overall, 293 ASCT were performed. Median age at diagnosis was 55 years. The main indication was multiple myeloma. Different mobilization schemes were used, according to the underlying disease. Only 23 patients (9.7%) had more than one apheresis procedure because of poor mobilization. All grafts were stored with 7.5% DMSO and kept at − 175°C in liquid or vapour phase of liquid nitrogen. Median CD34 cell count after apheresis and after thawing was 3.96 (2.29–11.56) and 2.49 (1.31–7.26), respectively. In 97 ASCT (33%) DMSO was removed before infusion, either manually or with the automated Sepax system after validation of the procedure. Standard definitions of red blood cell (RBC, reticulocyte counts >30 G/L or $>$ 1% and independence of RBC transfusions), platelet (PLT, >50 G/L and independence of PLT transfusions) and neutrophils (ANC, >0.5 G/L) engraftment were used. Overall, there was no significant association between RBC, PLT and ANC engraftment and CD34 count either after apheresis or after thawing. We found a good correlation between CD34 count after apheresis and after thawing (Figure 1, Pearsons's correlation: 0.931). Washing significantly affected RBC and PLT engraftment but not ANC engraftment (Table 1). Engraftment was related to the stem cell dose at apheresis and at thawing (low CD34: CD34 $< 2\times106$/kg vs median CD34: CD34 $>$ 2 and $< 5\times10^6$/kg vs high CD34: CD34 $> 5\times10^6$/kg, Table). Patients receiving a graft with a low CD34 recovery (defined as CD34 $< 2\times10^6$/kg after thawing but $> 2\times10^6$/kg after apheresis) had a statistically significant delayed RBC, PLT, and ANC engraftment (RBC: 17 vs 15 days, $P=0.015$; PLT: 18 vs 16 days, $P=0.001$; ANC: 16 vs 15 days, $P=0.003$). There were only 8 patients with CD34 $< 2\times10^6$/kg at apheresis but 89 upon thawing, due to low CD34 recovery. Even though there are some losses that are significant and even though we found a correlation between lower CD34 doses and longer time to engraftment, the differences are not of sufficient clinical importance to justify regular, time consuming and expensive monitoring of post thaw CD34 counts used for ASCT. Additionally, many preanalytic, analytic and single institutional conditions (i.e. localization of thawing) eventually affect CD34 count. DMSO removal may affect engraftment and its use should be balanced against possible associated infusion side effects.

Figure 1 [O016]



Disclosure of conflict of interest: None.

O017

Safety and efficacy trial of escalation of plerixafor for mobilization of CD34+ Hematopoietic Progenitor Cells (HPCs) and evaluation of globin gene transfer in patients with sickle cell disease. preliminary results

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There is presently no curative therapy for SCD other than allogeneic hematopoietic progenitor cell (HPC)

transplantation. Incoming trials of autologous gene therapy approaches in patients with sickle cell disease (SCD) include the need of HPCs for gene transduction. However, the use of G-CSF for mobilization of HPCs is contraindicated in this patient population, having resulted in sickle crises and death in some patients. Plerixafor is an inhibitor of the CXCR4 chemokine receptor on HPCs and blocks binding of its ligand, stromal cell-derived factor-1α (SDF-1α). It is FDA-approved at doses of 240 μg/kg subcutaneously in combination with G-CSF for autologous HPC mobilization in non-Hodgkin lymphoma and multiple myeloma patients. We designed a multi center 3 +3 phase 1 study of dose escalation of plerixafor for mobilization of HPC in patients with SCD. The primary goal of this trial is to evaluate the safety of, and the optimal dose for the mobilization of HPCs with plerixafor alone. Plerixafor was supplied by Sanofi following their approval of the protocol. Because of the ethical considerations, and the risks associated with the mobilization of patients with SCD, the protocol was submitted to, and approved by the FDA; IND 122657. It was registered with ClinicalTrials.gov; identifier: NCT02193191. Nine patients with SCD were entered on the study to date. Patients' age was 21–36 years (median 30 years). Patients had a history of SCD complications including vaso-occlusive crises, acute chest syndrome, osteomyelitis, pulmonary hypertension, cerebral aneurysm, retinal ischemia, and skin ulcers. All but one patient were on hydroxyurea. The first three patients received a dose of 80 μg/kg. One patient had an adverse event, a vaso-occlusive crisis 47 h after completion of plerixafor. Therefore, three more patients were treated at the same dose of 80 μg/Kg with no adverse events. A second cohort of three patients received a dose of 160 μg/kg without adverse effects. The current cohort is being treated at the dose of 240 μg/kg. White blood cell counts (WBC), absolute neutrophil counts (ANC), absolute lymphocyte counts (ALC) (×10^9/L), CD34+ and CD34+CD38− cell counts were measured at the following time points: 0, 6–12 and 24–48 h post-treatment with Plerixafor, which allowed to identify the optimal CD34 peak time in SCD patients. The results were as follows: at dose level 1, WBC, ANC and ALC increased by a 1.8–2.4-fold, 1.0–2.0-fold and 2.4–3.8-fold, respectively for six patients. At dose level 2, WBC, ANC and ALC increased by a 1.9–2.5-fold, 1.6–1.9-fold and 1.7–2.5-fold respectively for 3 patients. There were no significant variations in the levels of hemoglobin and platelets. CD34 concentrations were: for level one 7–132 cells/mcl and for level two 27–251 cells/mcl. In summary, this is the first trial on the use of plerixafor for HPC mobilization in patients with SCD. Our data in 9 patients support the safety of plerixafor administration at doses of 80 and 160 μg/kg, which is especially significant, in view of the prior toxicity associated with G-CSF in this patient population. Plerixafor increased WBC, ANC and ALC to acceptable levels (1–3.8-fold), and, at the level of 160 μg/kg, allowed the mobilization of high numbers of CD34+ cells. This study will allow us to define the optimal conditions for effective globin gene transfer in an upcoming trial.

Clinical Trial Registry: NCT02193191; https://clinicaltrials.gov; FDA Protocol: IND 122657.

Disclosure of conflict of interest: None.

O018

Engraftment of donor cells after allogeneic stem cell transplantation: comparison and impact of chimerism in whole blood and peripheral CD3+ T-cells

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After allogeneic stem cell transplantation (allo-SCT), engraftment can be assessed by quantitative polymerase chain reaction (qPCR) using differing donor/recipient markers identified in peripheral blood cells DNA before transplant. Complete chimerism is considered in the presence of $>95\%$ donor DNA. We report on the concomitant examination of the proportions of donor and recipient DNA in whole blood (WB) and sorted $CD3^+$ T-cells on days +60 and +90, looking at their impact on survival independently as well as in the four possible combinations (full/full, mixed/mixed, full/mixed and mixed/full). Allo-SCT recipients between October 2009 and October 2016 were reviewed, focusing on those with both types of samples available on days +60 and/or +90. A cohort of 239 grafts was retrieved, with 52 evaluable on day +60 only, 67 on day +90 only and 120 on both. Chi square tests were used to compare incidences. Log rang test and Kaplan Meier were used to evaluate DFS and OS. The whole cohort comprised 62% of males and had a median age of 58 years old (20–74) at the time of allo-SCT. Reduced-intensity conditioning was used in 89% of the cases. Donors were familial (45%) or from registry (48%). Unrelated cord blood units were used in 18 cases. Post-transplant cyclophosphamide (PTCY) was used in 48 procedures (33 haplo-SCT and 15 matched donors). The median follow-up of the cohort was 5.8 years (95% CI: 3.1–5.8) and rates of relapse and death 27% and 31% respectively. The results of chimerism are given respectively on days +60 and +90. Complete WB chimerism was seen in 80% and 71% of the cases, and complete CD3+ chimerism in 53% and 51%. Both complete WB and CD3+ chimerism was present in 53% and 51% of the cases, while 27% and 20% were documented with full WB and mixed $CD3^+$ chimerism. Mixed chimerism was observed in both WB and $CD3^+$ cells in 14% and 22% of the cases. Finally, a small proportion of patients (6% and 7%) displayed an intriguing complete chimerism in $CD3^+$ cells yet mixed WB chimerism. None of these features appeared associated to disease lineage (lymphoid or myeloid) nor cord blood allo-SCT. Interestingly, of the 27 grafts with myeloablative conditioning, only 14 had full WB/$CD3^+$ engraftment. None of the four WB/CD3 chimerism combinations at the two time points had any impact on DFS. Surprisingly, although full or mixed WB chimerism had no impact on DFS and OS, the presence of a mixed CD3+ chimerism at day+90 was associated with a significantly better OS (median: 5.8 years (95%CI: -not reached) versus 3.1 years (95%CI: 2.2– 3.1); $P = 0.025$). All HG resulted in full CD3+ chimerism at both time points compared to non HG (52%, $P < 0.0001$). The same was almost true when considering PTCY procedures: 90% at day +60 and 92% at day +90. Of note, there was no influence on DFS nor OS of WB or CD3+ chimerism status when considering only HG or PTCY grafts vs others. In this large series, early WB chimerism status did not predict outcome. Surprisingly, mixed CD3+ chimerism at day+90 appears to be significantly associated with a longer OS, suggesting that remaining recipient memory lymphocytes could be beneficial. This result has to be confirmed prospectively. It remains also to define the place of donor lymphocyte infusions (DLI) to prevent relapse in patients with full or mixed CD3+ chimerism.

Disclosure of conflict of interest: None.

Infectious complications (1)

O019

Pegivirus in hematopoietic stem cell transplant recipients: a longitudinal prevalence study and association with immune reconstitution and clinical outcomes

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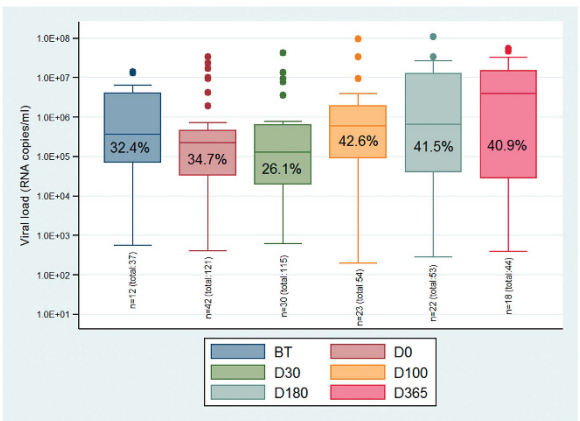
Human pegivirus (HPgV) is a Flavivirus infecting peripheral blood mononuclear cells(1). Viremic infection is identified in

up to 20% of healthy subjects. HPgV has been associated with an improved survival among HIV patients (1). Whether HPgV has a clinical or immunological impact in patients with hematopoietic stem cell transplantation (HSCT) is currently unknown. A next-generation sequencing study on the blood virome of allogeneic HSCT patients among a subgroup of patients enrolled in a single-center prospective cohort has identified HPgV as highly prevalent. This led to the screening of all patients transplanted in 2014 and 2015 using a specific real-time RT-PCR assay on stored plasma at days 0 and 30 after transplantation; according to specimens' availability, some patients were screened for four additional timepoints. We have assessed if HPgV infection has a detectable impact on immune reconstitution and clinical outcomes. X2 and Mann–Whitney tests were used for categorical and continuous variables, respectively, and log–rank test for survival analyses. Cumulative incidence estimates of infectious complications, graft–versus–host disease (GvHD) and relapse were calculated using the Gray test with death from other causes as a competitive event. 122 patients were included in the screening. Mean age of patients at HSCT was 49 year old. Timepoints of screening for HPgV were at a mean of − 19, 5, 32, 90, 179 and 339 days after HSCT. 53 of 122 patients were positive at least once (43.4%). A subpopulation of forty patients were screened for all timepoints, of whom 16 were positive at $\geqslant 3$ timepoints (40%); most of them were positive before transplantation. Taking positive results only, median viral load before transplantation, at d0, d30, d100, d180 and d365 were 3.6E+05, 2.2E+05, 1.3E+05, 6.0E+05, 6.5E+05 and 3.9E+06 copies/mL, respectively (Figure 1). Compared to HPgV-negative patients, CD4 and CD8 cell count 30 days after HSCT was significantly lower, and CD8 cell count at 6 months significantly higher among HPgV-positive patients. At one month, CD4 cells from HPgV-positive patients displayed a more differentiated phenotype compared to HPgV-negative patients, while there was no difference in CD8 cell subpopulation at any timepoint between both groups. Nevertheless, there was a higher rate of T-cell depletion among HPgV-positive patients, potentially confusing the results. There was no difference in overall survival, cumulative incidence of infection, GvHD and relapse at one year between both groups. Image/graph: Viral load of positive blood specimens at each timepoint. Total is the number of patients screened at each timepoint. N is the number of positive samples. %: percentage of patients positive for HPgV. BT: before transplantation; D: day Our results highlight that HPgV is part of the human virome of HSCT patients. Approximately 35% of patients are positive at baseline and the infection persist at high viral load up to one year. Although we didn't observe an association between HPgV infection and immune reconstitution nor clinical outcomes, larger prospective studies are required to assess the potential role of commensal viruses in HSCT patients.

Figure 1 [O019]



Disclosure of conflict of interest: None.

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O020

Meta-analysis of clinical outcomes associated with isavuconazole versus relevant comparators for patients with invasive aspergillosis

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Invasive aspergillosis (IA) is a major cause of morbidity and mortality in immunocompromised patients, especially in those with haematological malignancies or bone marrow transplants. Isavuconazole (ISAV) is the most recently approved antifungal agent for the treatment of adults with IA in the US and in the European Union. No head-to-head studies have compared treatment outcomes with ISAV against amphotericin B formulations, but mixed treatment comparison meta-analyses provide an opportunity to estimate the effects of one treatment against another. The objective of this study was to perform a meta-analysis to estimate the clinical outcomes of ISAV versus amphotericin B deoxycholate, liposomal amphotericin B and voriconazole for the treatment of patients with proven/probable IA. A systematic review and literature search of the Embase, MEDLINE, CDSR, DARE, NHSEED, HTA, CENTRAL, ICTRP and NGC databases was carried out to identify randomised controlled trials (RCTs) with comparators of ISAV. Studies were considered eligible for inclusion in this analysis if they provided information on the clinical effectiveness of either ISAV or any of the comparators in treating patients in the relevant population, were RCTs with human subjects and were published in English since 1995. A mixed-treatment comparison meta-analysis was performed using Bayesian modelling methods. A fixed-effect model was developed to assess the all-cause mortality (ACM) and overall response of ISAV from the phase 3 SECURE trial1 and relevant comparators in patients with proven/probable IA. Statistical significance was assessed using 95% posterior Credible Intervals (CrI). Odds ratios were calculated for the main outcomes using a logistic regression model. After identification, forty-one full-text articles reporting RCTs were assessed for eligibility; four studies met the eligibility criteria for inclusion in this analysis.1–4 In this meta-analysis, patients with proven/probable IA showed statistically significant differences in both ACM and overall response in favour of ISAV compared with amphotericin B deoxycholate. Differences with liposomal amphotericin B and voriconazole did not reach significance. Figure: All-cause mortality (A) and overall response (B) compared with isavuconazole from the primary analysis logistic regression model. In this study, mixed treatment comparison meta-analyses allowed for an estimate of the clinical outcomes of ISAV versus amphotericin B deoxycholate, liposomal amphotericin B and voriconazole to be assessed. ISAV was indicated to be statistically better than amphotericin B deoxycholate and comparable with liposomal amphotericin B and voriconazole. The results of this meta-analysis might support clinicians in their decision-making when considering therapeutic options for the treatment of IA.

Disclosure of conflict of interest: HR: personal fees for advisiory board – Astellas. Personal fees for advisory board and speaker's fees – Basilea, Gilead, Pfizer and MSD. Research grant – Pfizer. KD: Is an employee of Basilea. Holds stock options with Basilea. PN Pooley: Is an employee of PHMR who were paid by Basilea to perform a literature review and statistical anaylsis for this abstract and for other projects. PJ: Is an

employee of Basilea. Holds stock options with Basilea. EC: Is an employee of Basilea. Holds stock options with Basilea.

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O021

Molecular demonstration of a pneumocystis outbreak in stem cell transplant patients: evidence for transmission in the daycare center

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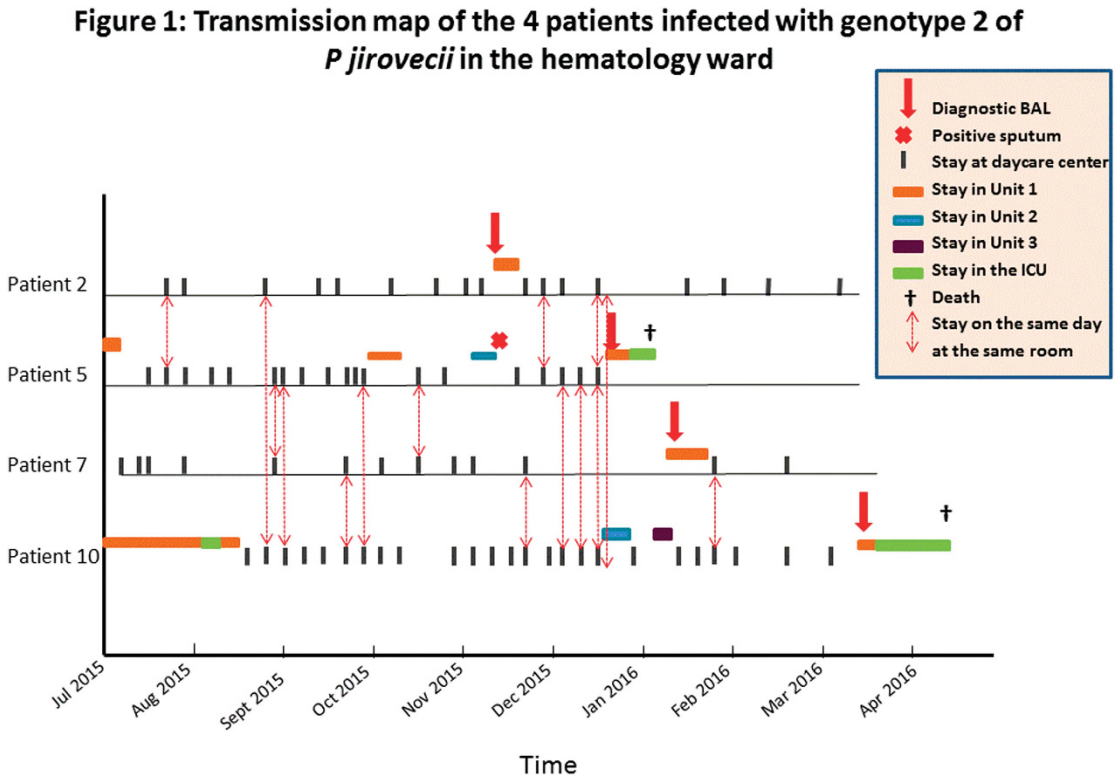
Molecular demonstration of a pneumocystis outbreak in stem cell transplant patients: Evidence for transmission in the daycare center Introduction: Pneumocystis jirovecii pneumonia (PCP) is a life-threatening infection in hematology. Ninety percent of the PCP patients are infected with several different strains of P. jirovecii. Although occasionally reported, the role of interhuman transmission of PCP when compared to reactivation is unclear. Due to the lack of molecularly documented relationship between cases in hematology, the recommendations of isolation of PCP patients in the hematology ward are so far not well evidence-based. During an outbreak of PCP in our department starting with the occurrence of 4 cases within 9 days, we investigated the possibility of an interpatient transmission by determining the genotype of the strains and the transmission map between these patients. Due to an unexpected high number of PCP in the hematology ward, we explored 12 consecutive patients with PCP documented with bronchoalveolar lavage from November 2015 to May 2016. Molecular typing of PCP was performed on DNA extracted from respiratory samples, using microsatellite marker genotyping1. The possibility of interpatient transmission was established from the hospital records on the basis of the patient presence in the same unit on the same day than another PCP patient. Patients: Among the 12 patients, 7 were allogeneic HSCT recipients. None was under TMP-SMX prophylaxis. Three patients were receiving atovaquone because of TMP-SMX intolerance, and one was under pentacarinate aerosols. Eight patients had no prophylaxis, because we had no specific local recommendation at this time for the underlying disease (mixed phenotype acute leukemia, $n=2$), because the disease was not considered at high risk (AML, $n=3$), or because prophylaxis was stopped several months ago at time of stopping immunosuppressive drugs after control of graft-versus-host disease ($n=2$). Three patients died from acute respiratory failure. Among the 12 PCP patients, the PCP genotype could not be determined in 3 of them due to insufficient amounts of DNA. Among the 9 remaining patients, one genotype (Gt2), unknown in our experience of genotyping more than 300 French and European P. jirovecii samples, was found in 4 patients. These 4 Gt2-patients, all allogeneic HSCT recipients, were diagnosed with PCP within 4 months. Three out of the five non Gt2-patients harbored mixtures of genotypes. The transmission map (Figure 1) shows that these 4 patients had multiple opportunities to meet with at least one of the 3 others (median: 6.5 times (range: 4–10)) at the daycare center. Our study shows that four allogeneic HSCT recipients were infected with a unique P. jirovecii genotype–an unusual feature for PCP–and additionally with a genotype so far unreported in Europe. These patients had several opportunities to meet at the day care center. This clearly supports for the first time a strong recommendation for isolation and respiratory precautions in case of PCP in the hematology ward.

Figure 1 [O021]



Disclosure of conflict of interest: None.

Reference

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O022
Previously published

O023
Outcome of allogeneic hematopoietic stem cell transplantation in children and adults with prior invasive fungal diseases

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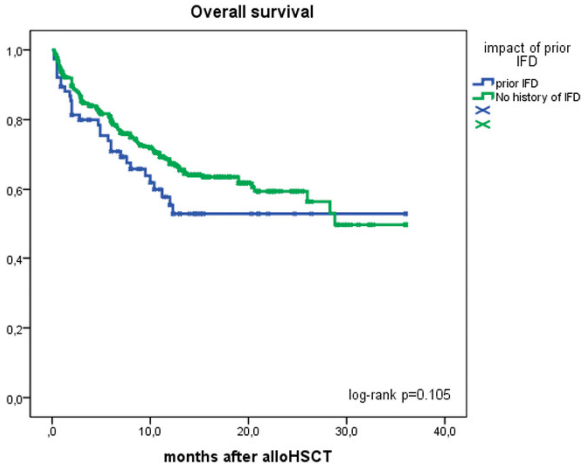
Invasive fungal diseases (IFD) are a major cause of morbidity and mortality in hematological patients, but recently prognosis of IFD has improved due to introduce new antifungals and diagnostic procedures. Number of patients with IFD who are candidates for allogeneic hematopoietic stem cell transplant (alloHSCT) increased. But there are no data on pediatrics alloHSCT with prior IFD. This study focuses on outcome of alloHSCT in children and adults with prior IFD. In prospective study, 504 alloHSCT recipients were included from Jan 2013 to Jul 2016. The median age was 24 y.o. (2 months – 76 years), children (< 18 yo) - 164, adults – 340, males – 52%. Most of pts were with high-risk acute leukemia (74.6%). AlloHSCT from MUD was performed in 58.5%, MRD – 22.5%, haplo – 19%, predominantly with RIC (67%). EORTC/MSG 2008 criteria for diagnosis and response to therapy were used. In pts with CT-scan lung lesions before alloHSCT bronchoscopy with BAL was used. 'Active IFD' means IFD diagnosed just before HSCT. Incidence of IFD before alloHSCT was 15% ($n = 76$). According to EORTS/MSG 2008 criteria 90.8% of pts had probable and 9.2% proven IFD. Etiology of IFD prior to HSCT were invasive aspergillosis (IA) – 75%, invasive candidiasis (IC) – 13%, mucormycosis (Mu) – 4%, pneumocystis pneumonia (PCP) – 1,3%, and combination of IA with Mu – 2 pts, IC – 1, PCP – 1. The main sites of infection were lungs – 95%, other localizations were predominantly in combination with lung involvement: sinuses – 9%, spleen – 6%, liver – 6%, and soft tissues – 3%. Antifungal therapy before alloHSCT was used in 75% pts with median duration – 2 months. Complete response to antifungal therapy was in 38.2% pts, partial response or stabilization – 35.5%, and 26.3% pts had "active IFD". After alloHSCT all pts received antifungal therapy or secondary prophylaxis according to IFD the etiology. Cumulative incidence of relapse or progression of IFD after alloHSCT was 14.5%. Active underlying disease at the moment of HSCT was the only risk factor for relapse or progression of IFD after alloHSCT (11.5% vs 21.1%, $P = 0.03$). We detected no significant differences in the cumulative incidence of acute, chronic GVHD and relapse in study group as compared to pts without history of IFD. 3-year OS after alloHSCT was 67.5%. The impact of prior IFD on overall survival in alloHSCT recipients was not statistically significant in all group (60.5% vs 68.7%, $P = 0.1$, Figure 1), and separately in children (50.0% vs 57.4%, $P = 0.3$) and adults (63.3% vs 74.6%, $P = 0.09$). The worst outcome was observed in pts with 'active IFD' and active underlying disease at the moment of HSCT (3-year OS – 20%, $P < 0.001$). However, in pts with "active IFD" and remission of underlying disease OS was similar to survival rate of pts without history of IFD (80% vs 68.7%, $P = 0.2$). Incidence of IFD before alloHSCT was 15%. Cumulative incidence of relapse or progression of IFD after alloHSCT was 14.5%. Prior IFD had no significant impact on transplant-related complications and overall survival in children and adults undergoing alloHSCT. Active underlying disease at the moment of HSCT was the only risk factor for relapse or progression of IFD and impair outcome of alloHSCT.

Figure 1 [O023]



Disclosure of conflict of interest: None.

O024
Gram-negative bacteremia in children after allogeneic hematopoietic stem cell transplantation (HSCT): a multinational study on behalf of Infectious Diseases Working Party of European Society for Blood and Marrow Transplant (EBMT-IDWP)

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Gram-negative rod bacteremia (GNRB) is an important cause of morbidity and mortality after HSCT. Data on GNRB in children are limited. We present the results of a prospective multinational IDWP study conducted from January 2014 to May 2015 focused on pediatric population. Data on all episodes of GNRB since the initiating of conditioning and during 3 months after the first allogeneic HSCT were collected prospectively. The following parameters were compared in children who developed vs those who did not develop at least one episode of GNRB: demography, underlying disease and its status, HSCT type and conditioning, fluoroquinolone prophylaxis and involvement of infectious control team in the unit;

presence of engraftment and GVHD were analyzed as time dependent variables. 539 allogeneic HSCT were performed in children (median age at HSCT 8.6 years, range 0.1–18; 352 (65.3%) males); in 27 centers from 18 countries (in Europe, Asia and Australia). Among them, 469 (87.7%) received myeloablative conditioning. Fluoroquinolone prophylaxis was provided in 6 centers, whereas an infectious control team was operating in 23 centers. The stem cells sources were: peripheral blood, 148 (27.5%); bone marrow, 321 (59.6%); cord blood, 70 (13%). The underlying diseases were acute leukemia, 277 (51.4%); myelodysplastic/myeloproliferative syndrome, 41 (7.6%); lymphoma 23 (4.3%), chronic leukemia, 7 (1.3%), solid tumors, 2 (0.4%); non-malignant diseases, 189 (35.1%). The pre-HSCT status of patients with malignant disease was first to second complete remission in 256 (75.3%), and other remission status or partial remission/active disease in 84 (24.7%) patients, respectively. Neutrophil engraftment was observed in 497 (97.6%) patients; at median time of 18 days (range 5–102) after HSCT. Acute grade II-IV GVHD was reported in 135 (26.9%) patients during the observation period. 100-day overall survival was 90.4% (95% CI: 87.1–92.9). The incidence of GNRB was 10.6% (57/539) with the isolation of: 46 (58.2%) Enterobacteriaceae, 32 (40.5%) nonfermentatives (including 12 Pseudomonas aeruginosa, 11 Stenotrophomonas maltophilia and 9 others), 1 (1.3%) other. In univariate analysis, the absence of neutrophil engraftment was the only risk factor associated with the development of GNRB; HR 5.2 (95% CI: 1.4–19.9), $P = 0.02$. Resistance to carbapenems was reported in 21/78 (26.9%) of GNR and multidrug resistance (resistance to 3 or more antibiotic classes) in 31 out of 78 (39.7%). 30-day mortality after GNRB episode was 4.4%. The risk of 100-day mortality after HSCT was higher in patients with GNRB, than in patients without GNRB, HR 2.7 (95% CI: 1.1–6.5), $P = 0.03$. In our multinational study, the rate of GNRB in children was lower than previously reported in adults. Neutropenia is the main risk factor for development of GNRB. Early diagnosis and prompt appropriate empirical and targeted therapy is crucial. The increasing rate of antimicrobial resistance, which for carbapenems is higher than the rate reported in adults, challenges treatment options. Although short term prognosis is relatively good, GNRB episode is associated with increased post-transplant mortality.

Disclosure of conflict of interest: None.

O025

Quantitative PCR in fresh gastrointestinal mucosa is faster, more objective, and more reliable than immunohistochemistry for the diagnosis of CMV gastrointestinal disease

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Diagnosis of CMV Gastrointestinal (GI) disease relies on detection of CMV in biopsy specimens by culture, immunohistochemistry (IHC), or observation of inclusion bodies, in presence of GI signs and symptoms. Unfortunately, there is a great variability in the interpretation of the results among observers. Results from quantitative PCR are more objective. However, PCR alone is considered not sufficient for the diagnosis of CMV GI disease because of a low predictive positive value (PPV). The aim of this study is to compare results of CMV detection obtained from IHC and inclusion bodies with those obtained from quantitative PCR. We analyzed a total of 157 GI endoscopic biopsy specimens from 103 patients who underwent an allo-SCT since May 2004 until June 2016. Endoscopic procedure was indicated due to GI symptoms such as diarrhea, bleeding, or abdominal pain. We compared results obtained by IHC and PCR techniques, first in 116 paraffin samples, and afterwards in 41 fresh samples. IHC was considered positive if >1 cell CMV+ was observed. PCR was considered positive if >1000 CMV copies/mL were detected (the same threshold used in blood samples for CMV infection). We analyzed sensitivity, specify, positive predictive value (PPV) and negative predictive value (NPV) of these two techniques, in both paraffin and fresh samples. In paraffin samples, 20 were diagnostic for CMV GI disease (based on the presence of GI symptoms, detection of CMV in GI mucosa by, at least one technique and clinical outcome after antiviral treatment). IHC was positive in 18 of them and PCR was positive in 16. There were 5 false positive (FP) for IHC and 6 FP for PCR. 4 of the 6 FP for PCR had a viral load $<2{,}000$ copies/mL. 1 of them was positive one week earlier than IHC became positive, so it could be an earlier diagnose of CMV GI disease by PCR. Comparing the 6 discordant results obtained by IHC and PCR, 2 samples were PCR+/IHC- and were considered false negative (FN) for IHC and 4 samples were IHC+/PCR- and were considered FN for PCR. When analyzing in paraffin samples for comparison of IHC vs PCR, sensitivity was 90% vs 80%, specify 95% vs 94%, PPV 78% vs 73%, and NPV 98% vs 96%. In fresh samples, 13 were diagnostic for CMV GI disease. IHC was positive in 10 samples; 1 of them was considered FP (in this sample PCR was negative). Thus, there were 3 FN for IHC. In contrast, PCR was positive in the 13 samples. When analyzing in fresh samples for statistical values for comparison of IHC vs PCR, sensitivity was 77% vs 100%, specify was 96% vs 96%, PPV was 91% vs 93%, and NPV was 90% vs 100%. These figures compare favourably, especially for PCR, with those obtained with both methods in paraffin samples. Median viral load in positive biopsy specimens for PCR in paraffin was 4,089 c/mL (range 1,176-311,406 c/mL) and in fresh mucosa median viral load was 361 500 c/mL (range: 4034 to $>$ 10 000 000 c/mL). Near 75% of the patients had a concomitant CMV infection in blood. Median viral load in blood was lower than in GI samples. CMV detection by PCR in fresh GI mucosa was more sensible and had a higher positive and predictive value than IHC performed in either fresh or in paraffin. Besides, PCR is faster and more objective than conventional IHC. PCR in fresh GI mucosa might replace IHC studies in paraffin embedded tissue for the diagnosis and response monitoring of CMV GI disease.

Disclosure of conflict of interest: None.

Figure 1 [O025]

Paraffin samples (N= 116)

No CMV GI Disease N= 96	IHC Neg	IHC Pos	No CMV GI Disease N= 96	PCR Neg	PCR Pos
	91 TN	5 FP		90 TN	6 FP
CMV GI Disease N= 20	IHC Pos	IHC Neg	CMV GI Disease N=20	PCR Pos	PCR neg
	18 TP	2 FN		16 TP	4 FN

Fresh samples (n= 41)

No CMV GI Disease N= 28	IHC Neg	IHC Pos	No CMV GI Disease N=28	PCR Neg	PCR Pos
	27 TN	1 FP		27 TN	1 FP
CMV GI Disease N= 13	IHC Pos	IHC Neg	CMV GI Disease N=13	PCR Pos	PCR Neg
	10 TP	3 FN		13 TP	0 FN

*TP: True positive; TN: True negative; FP: False Positive; FN: False Negative

O026

Proven and probable lower respiratory tract viral infection in acute leukemia patients and after hematopoietic cell transplantation predicts outcome

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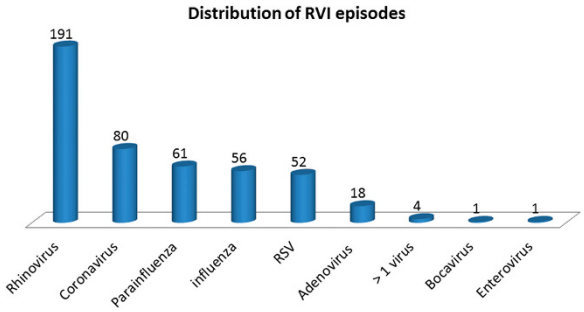
Respiratory viral infection (RVI) is common in patients with acute leukemia and following hematopoietic cell transplantation (HSCT) resulting in morbidity and also mortality. In this two center retrospective study, we evaluated adult patients with acute leukemia and/or after HSCT diagnosed with laboratory confirmed RVI between Sep 1st 2009 and Nov 1st 2014. The laboratory diagnosis was made on a sample collected from the respiratory tract with the multiplex PCR technique performed at each center. Each episode was classified as upper respiratory (URTI), possible (respiratory virus detection in a nasopharyngeal or sputum specimen but no BAL sample with new pulmonary infiltrates), probable (respiratory virus detection in a BAL sample, with lower respiratory tract symptoms, but without new pulmonary infiltrates), and proven (respiratory virus detection in positive BAL sample, with new pulmonary infiltrates with or without symptoms lower respiratory tract infection (LRTI). Multivariate logistic regression was performed on overall survival with clinical and demographic variables as covariates, and a backward selection procedure at the 0.05 significance level was used to build the final model. For RVI, a generalized mixed effects model was performed. 291 patients had 493 documented episodes of RVI. 228 patients had undergone HSCT and 63 patients had acute leukemia. The distribution of the different respiratory viruses is shown in Figure 1. 441 episodes (89.4%) were initially diagnosed as URTI and 52 (10.6%) as a LTRI. In addition 43 episodes were diagnosed as URTI and progressed to LRTI. There were 24 episodes of proven, 9 episodes of probable, 62 episodes of possible LRTI in 22, 9, and 47 patients, respectively. 47 of 56 influenza episodes were treated with oseltamivir, 34/54 RSV episodes were treated with ribavirin and 4/20 adenovirus episodes were treated with cidofovir. The highest proportion of Proven/Probable LRTI among all episodes was found for adenovirus 15% (3 out of 20) followed by parainfluenza 13.1 (8 out of 61), metapneumovirus 10.3% (3 out of 29), RSV 7.4% (4 out of 54), rhinovirus 5.7% (11 out of 191), influenza virus 3.6% (2 out of 56), and coronovirus 2.5% (2 out of 80). Out of the 291 patients, there were 20 deaths (6.9%). There were 16 deaths in HSCT patients (7.0%) and 4 deaths in acute leukemia patients (6.3%). Patients with Proven/Probable LRTI had significantly higher mortality compared to patients with possible LRTI/URTI ($P < .0001$). In HSCT patients, ANC < 500 cells/μL on the diagnosis date of the RVI was associated with increased risk of Proven/Probable LRTI ($P < 0.05$) while there was a trend for ALC < 300 ($P = 0.09$). No effect on the risk for Proven/Probable LRTI was seen by age, underlying diagnosis, acute or chronic GVHD, grade of GvHD, ongoing immunosuppression, or CMV viremia. Development of Proven/Probable LRTI caused by respiratory viruses increases the risk for mortality in HSCT and acute leukemia patients.

Disclosure of conflict of interest: None.

Figure 1 [O026]



Novel drugs and immunotherapies

O027

Drug resistant lymphocyte immunotherapy: Dose and schedule optimization

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We have recently developed a combined chemotherapy and cell based gene therapy strategy for high-grade primary gliomas that we have termed Drug Resistant Immunotherapy (DRI). Specifically, this approach consists of activated MGMT-transduced γδ T cells and NK cells targeted to NKG2D ligands upregulated on the tumor during chemotherapy-induced stress following exposure to the alkylating agent Temozolomide (TMZ). While TMZ kills sensitive GBM cells and modifies the tumor microenvironment, MGMT genetic engineering enables cytotoxic function of stress-antigen targeted lymphocytes in high concentrations of chemotherapy. Pharmacokinetics of both oral and intravenous TMZ reveal a rapid increase in blood concentration followed by a gradual decline. We have separately shown a rapid upregulation of NKG2DL on TMZ-resistant GBM lines *in vitro* over the first 4 hours followed by a decline over 24h raising the question as to the effect of DRI during maintenance dose TMZ. We hypothesized that intermittent exposure to TMZ with a higher concentration can drive efficacy of DRI even in TMZ-resistant tumors. Intracranial (IC) glioma xenografts were established using either primary (P) or a TMZ-resistant clone (T) of human glioblastoma (GBM) xenolines X12 (Classical) and X22 (Mesenchymal). Two treatment schema were studied. In the first, tumor-bearing mice were treated twice weekly with intraperitoneal (IP) 60 mg/kg TMZ and received intracranial (IC) of 1×10^6 MGMT-modified γδ T cells (DRI) on the alternating day between the TMZ injections. In the second schema, DRI-treated mice received TMZ on the same schedule but received intensified DRI 1×106 MGMT-modified γδ T cells IC concurrently with each TMZ injection. Control mice received MGMT-modified γδ T cells alone, TMZ alone or no therapy. Survival was assessed using Kaplan-Meier analysis. MGMT-modified γδ T cells alone did not improve survival overf untreated mice for either tumor or treatment schema. In the first schema, both TMZ/TMZ alone and TMZ/DRI/TMZ significantly improved survival over untreated controls ($P < 0.001$) for X12P, while TMZ/DRI/TMZ increased median survival from 57 to 75 days over TMZ/TMZ. Median survival of X12T mice treated with TMZ/TMZ was not improved over untreated controls; however, TMZ/DRI/TMZ did improve median survival over untreated controls ($P = 0.0147$) but only marginally over TMZ alone ($P = 0.0966$). In the second schema, mice that received TMZ+DRI concurrently showed significantly improved median survival over TMZ alone with 80% long-term survivors. For X12T, DRI+TMZ improved median survival from 22 days to 38 days over untreated

animals ($P = 0.0004$) and from 27 to 38 days over TMZ alone ($P = 0.017$) with 10% of animals showing long-term survival >119 days. Additionally, for TMZ-resistant tumors, Schema 2 showed significant improvement over Schema 1 ($P = 0.001$). TMZ eradicated tumors in all X22P animals. For X22T, Schema 2 significantly improved survival over untreated animals (20d vs 27d; $P = 0.0009$) while Schema 1 did not ($P = 0.0607$), however neither Schema resulted in improved survival over TMZ alone. In summary, the combination of chemotherapy-induced stress antigen expression and targeted DRI significantly improves survival in tumor-bearing immunodeficient mice. The positive effect on survival is increased when with intensified DRI is given within the first 4 hours of each TMZ injection.

Disclosure of conflict of interest: Incysus, Ltd. Scientific Advisory Board member and founding scientist.

O028

CD19-specific CAR T cells with a central memory and stem memory phenotype-automated generation in a closed, gmp-compatible system from peripheral blood of pediatric patients with acute lymphoblastic leukemia

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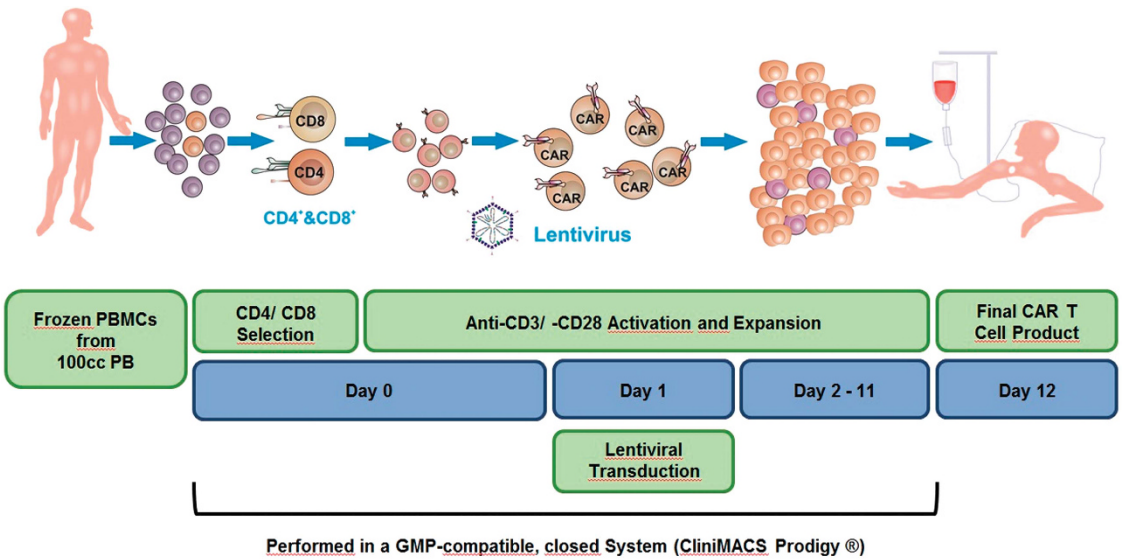
Chimeric antigen receptor (CAR) modified T cells targeting CD19 can induce sustained remissions in pediatric patients with relapsed and refractory B-precursor acute lymphoblastic leukemia (ALL) (1). Essential preconditions for treatment efficacy and prevention of CD19+ relapse are proliferation and persistence of CAR T cells in vivo. Central memory T cells (Tcm) and stem cell-like memory T cells (Tscm) are known to be the best candidates for a sustained *in vivo* expansion after T-cell therapy with small cell doses (2). A protocol for generation of anti-CD19 CAR T cells in a closed and GMP-compatible system (CliniMACS Prodigy®) was established. Mononuclear cells derived from 100cc peripheral blood of pediatric ALL patients served as starting material. After separation for CD4+/CD8+ cells, T cells were activated with anti-CD3/-CD28 beads and transduced with a lentiviral vector encoding the anti-CD19 single-chain variable fragment, a 4-1BB (CD137) co-stimulatory domain and the T cell receptor (TCR) zeta chain. After 12 days of IL-7/-15-based expansion, the final CAR T cell product was harvested from the device and analyzed for cellular composition, transduction rate and functionality by flow cytometry. Despite small pediatric blood samples with low initial cell numbers and a broad variety in cellular composition including high counts of malignant cells and a rather exhausted phenotype, a robust T-cell composition was achieved on day five after activation with a mean of 63% CD4+ and 37% CD8+ T cells. Mean transduction rate was 30%. No malignant cells or B cells were detected in flow cytometric analyses of the final product. The vast majority of CAR T cells were of a Tcm (47%) and Tscm (44%) phenotype leading to a strong proliferative potential of more than 100-fold expansion. When co-cultured with CD19+ target cell lines or patient-derived autologous CD19+ B cells, CAR T cells showed effective cytotoxic functionality with only little background of the un-transduced control. At an effector to target ratio of 5:1 up to 80% of the CD19+ target cells were killed. A significant release of Interferon gamma (IFN-γ), Tumor necrosis factor (TNF-α) and Interleukin-2 (IL-2) confirmed a strong and target-specific Th1 response. Secretion of Interleukin-6 (IL-6) upon contact to the antigen was not detected. In addition, reduced sensitivity to inhibitory signals was documented by low expression of programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and lymphocyte-activation protein 3 (LAG3). Generation of CAR T cells from small pediatric blood samples was feasible in a closed, GMP-compatible and fully automated system. Despite variety of cell numbers, cellular composition and T-cell phenotype in the starting sample, a uniform T-cell product of Tcm and Tscm could be produced with a balanced CD4/CD8 ratio leading to high expansion potential, good functionality and reduced sensitivity to inhibitory signals.

Disclosure of conflict of interest: Miltenyi Biotec GmbH, Bergisch Gladbach, Germany, provided FB and TF with reagents free of charge. AK and MA are employees of Miltenyi Biotec GmbH, Bergisch Gladbach, Germany.

Figure 1 [O028]



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O029

Checkpoint blockade with pembrolizumab induce graft-versus-host disease for patients with refractory acute leukemia heavily treated after allogeneic transplantation

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Refractory acute leukemia post allogeneic hematopoietic stem cell transplantation (allo-HSCT) carries a particularly grave prognosis. Immune checkpoint blockade with anti-PD1 antibody could theoretically induce graft-versus-host disease (GVHD) and possibly the graft-versus-leukemia (GVL) effect. Recently, anti-PD1 Nivolumab had shown activity against Hodgkin lymphoma relapse after allo-HSCT (ref 1), while checkpoint blockade with Ipilimumab had shown to induce marked immune reaction for patients relapse after allo-HSCT (ref 2). In this study, we aim to evaluate the treatment response and side effects of the anti-PD-1 antibody, pembrolizumab, in heavily treated patients with relapsed and refractory acute leukemia post allo-HSCT. Between Sep 2015 and Nov 2016, nine adult patients received pembrolizumab as salvage therapy for refractory acute leukemia (6 AML, 3 ALL) post allo-HSCT at National Taiwan University Hospital. The baseline patient characteristics, treatment responses and side effects were retrospectively reviewed. Progression-free survival (PFS) was evaluated with the Kaplan-Meier survival analysis. The pilot use of Pembrolizumab in this population had been approved by the hospital Research Ethics Committee. The median duration between allo-HSCT and the administration of the first dose of pembrolizumab in this study was 315 days (range 79-836). Before pembrolizumab administration, they had failed multiple lines of treatment after allo-HSCT (median 4, range 1-8), including repeated donor lymphocyte infusion, second allo-HSCT and chemotherapy, and only four of them had grade I acute GVHD. Pembrolizumab was given at the dose ranging from 1 to 1.6 mg/kg (7 patients received one dose, and 2 patients two doses). Immediate acute GVHD-like reaction occurred in all patients after pembrolizumab administration, including spiking fever ($N=7$, median 5 days, range 3–15 days), elevated hepatic enzymes ($N=7$), and skin rashes ($N=7$, 5 patients had $>75\%$ body surface area involved). No treatment related mortality was encountered. The overall response rate (ORR) was 44% (4/9), including two complete remissions (CR) (22%) and two partial remissions (PR). Regarding the two patients who ever achieved CR after pembrolizumab, one had developed Guillain–Barré syndrome (GBS) and immune-mediated esophageal stricture, which was controlled by plasmapheresis and endoscopic balloon dilation procedures, respectively; and the other one had extensive moderate chronic GVHD involving multi-organ. After a median follow-up of 3.2 months (range 0.5–15.5 months), three patients remain alive (one disease-free), while six had died of leukemia progression. The estimated 6-month PFS and was 26.7%, respectively. In this preliminary report, we observed that immediate and remarkable immune response, reminiscing aGVHD/cGVHD could occur after checkpoint blockade therapy. It should therefore to be used with caution, especially for those with ongoing or severe GVHD. Some responsive patients could be seen even in these heavily pre-treated refractory patients, particularly in those with severe and special immune response.

Disclosure of conflict of interest: None.

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[O029]

Table 1. Patient characteristics and treatment outcome/adverse effects after pembrolizumab therapy

UPN	Age/gender	Disease	Donor type	Timing [1] (day)	Lines Rx [2]	Dose (mg)	Duration of Fever > 39C (d)	aGVHD or other AE post pembro[3]	RR [4]	Current status[5]
1	39F	PMF --> AML	Sibling	141	3	50	7	Gr I, S0G0L1	PD	DOD, 3.2m
2	38F	Ph Pre-B ALL	MUD	678	3	50	0	Gr I, S0G1L1	PD	DOD, 0.7m
3	22M	CEL --> AML	Sibling	79	4	100	5	Gr III, S4G0L0	PD	DOD, 0.7m
4	47F	Pre-B ALL	Haplo-daughter	512	4	100	0	Gr II, S3G0L1& oral limited	SD, 3m	DOD, 4.6m
5	19M	AML	Haplo-mother	312	3	50	4	Gr I, S2L0-1, G0-1	SD, 0.5m	AWD, 0.5m
6	54F	AML	Haplo-son	602	4	50	15	Gr II, S3G1L1	PR, 2m	DOD, 1.9m
7	48F	AML	Sibling	134	1	50-50	3	Gr II, S2G0L1	PR/PD[6]	DOD, 4.2m
8	38F	T-LBL/L	Sibling (9/10)	315	8	50-12.5	12	Gr II, S3G1L1, plus GBS, esophageal stricture	CR, 5m	AWD, 15.5m
9	39F	AML	Haplo-mother	836	4	50	5	Gr II, S2G1L2 & cGVHD, exten. mod., oral, eye, skin	CR, 3m	AOD, 4 m

Abbreviations, PMF: Primary myelofibrosis, CEL: Chronic eosinophilic leukemia, Pembro = pembrolizumab; GBS = Guillain–Barré Syndrome (confirmed with sural nerve biopsy) T-LBL = T lymphoblastic lymphoma/leukemia. PD: progressive disease, PR: partial remission, CR: complete remission

[1] Timing of pembrolizumab post allo-HSCT.

[2] Before pembrolizumab, line of treatment after allo-HSCT, including DLI, 2nd PBSCT, chemotherapy, etc.

[3] aGVHD grading, S: skin, G, GI tract, L: liver.

[4] Best response and response duration.

[5] DOD: Died of disease; AWD: Alive with disease; AOD: alive without disease.

[6] After pembrolizumab administration, the patient achieved CR in BM, but PD on her granulocytic sarcoma.

O030

Vaccines are safe and effective after T-cell depleted CD34-selected allogeneic hematopoietic stem cell transplantation (Allo HCT)

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Myeloablative T-cell depleted (TCD) allogeneic HCT with CD34 selection is associated with decreased acute and chronic GVHD, and similar survival compared to unmodified grafts. However, there is delayed T-cell recovery and increased risk of infectious complications. Since this may also result in impaired vaccine response, we examined immune reconstitution and vaccine responses after TCD allo HCT. We retrospectively identified patients with hematologic malignancies from the institutional registry who received a first myeloablative TCD allo HCT between April 2012 and June 2015 and completed re-immunization per CDC guidelines. Patients were immunized based on immune recovery parameters: CD4 T >200 cells/μL, CD19 B cells >50 cells/μL, IgG >500 mg/dL, PHA $>50\,000$ cpm. Vaccine responses were determined based on comparison of pre- and post- vaccination titers. Patients were classified as responders, non-responders, immune by pre-vaccination titer, and not evaluable due to missing data (missing either pre or post-vaccination titers); descriptive statistics were used to summarize results for each vaccine. Adverse events due to vaccination were collected retrospectively. Total CD3, CD4, and CD8 T-cells, and naïve, central memory (CM), effector memory (EM), and effector subsets, as well as B cells were monitored by flow cytometry. 77 patients met inclusion criteria (median age, 52 years; range, 23–71; 54% males). TBI was used in 22 patients (29%), and 64 (83%) received an 8/8 matched graft (24 related (31%) and 40 unrelated (52%)). At 12 months post HCT, median CD3, CD4, CD8 T cell and B cell counts were 623, 284, 308 and 365, cells/uL, respectively. Effector memory cells were the predominant subset of CD4 (median 55.6%) and CD8 (median 40.2%) T cells (See Table 1 for details of immune subsets). Median time to vaccination was 15.2 months (7.6–34.3) after allo HCT. 68 patients completed the Haemophilus influenzae type b series vaccine and 80% of evaluable patients responded. Pneumococcal vaccination with Prevnar 13 was completed in 75 patients. All patients had lost their immunity prior to vaccination, but 40% responded to the vaccine. 72 patients completed the full Tdap vaccine series. Tetanus, diphtheria, and pertussis had respectively 75, 51 and 67% of responders among evaluable patients. Fewer patients received and completed the Hepatitis A and B vaccines. Responses occurred in 79 and 59% of evaluable patients, respectively. 63 patients received the Polio vaccine. With 81% retaining immunity, 100% of evaluable patients responded to the inactivated polio vaccine. No patients had any adverse events. Details of vaccine response are provided in Table 2. T cell recovery after myeloablative TCD allo HCT is characterized by early expansion of EM T cells and later rise in naïve T cells. While delayed compared to unmodified grafts, it attains normal values in most patients. Re-immunization with inactivated vaccines after myeloablative TCD allo HCT based on immune recovery is safe and effective, offering this population immunity to vaccine preventable diseases.

Disclosure of conflict of interest: None.

[O030]

Table 1: Immune reconstitution at one-year post CD34 selected allo HCT

	Cells/μL (Median, range)	% (median, range)
B cells	365 (0-1349)	
CD3	623 (97-5179)	
CD4	284 (51-1047)	
CD8	308 (22-4022)	
CD4 naïve	39 (2-240)	12.6 (0.4-65.6)
CD4 CM	42 (0-182)	19.5 (0-44.6)
CD4 EM	139 (5-475)	55.6 (1.8-92.2)
CD4 effector	13 (1-358)	3.6 (0.3-66.5)
CD8 naive	21 (1-191)	5.6 (0-63.0)
CD8 CM	5 (1-31)	1.5 (0-8.3)
CD8 EM	106 (3-1149)	40.2 (11.1-95.1)
CD8 effector	91 (6-1287)	29.6 (3-73.7)

O031

Nivolumab salvage therapy before and after allogeneic stem cell transplantation in relapsed/refractory hodgkin lymphoma

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Table 2: Vaccine response post CD34 selected allo HCT

	Response, n (%)			
Vaccine	Responder (% evaluable)	Non-responder (% evaluable)	Immunized (%total)	Not Evaluable (%total)
Haemophilus Influenzae (n=68)	35 (80%)	9 (20%)	22 (32%)	2 (3%)
Pneumococcal (12) (n=75)	30 (40%)	45 (60%)	0	0
Poliomyelitis (n=63)	4 (100%)	0	51 (81%)	8 (13%)
Tetanus (n=73)	27 (75%)	9 (25%)	33 (45%)	4 (5%)
Diphtheria (n=72)	33 (51%)	32 (49%)	0	7 (10%)
B. Pertussis (n=72)	34 (67%)	17 (33%)	16 (22%)	5 (7%)
Hepatitis A (n=39)	22 (79%)	6 (21%)	9 (23%)	2 (3%)
Hepatitis B (n=45)	20 (59%)	14 (41%)	9 (20%)	2 (5%)

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Hodgkin's lymphoma (HL), although considered a curable neoplasm in adults, could be associated with a very poor prognosis when refractory to primary induction therapy or when it relapses within 12 months from an autologous stem cells transplant (auto-SCT). The optimal treatment of patients with heavily pretreated/refractory HL is controversial. Options include: immunotherapeutic agents such as anti-CD30 Brentuximab (Bv), anti-PD1 antibody Nivolumab, Bendamustine (Benda), and allogeneic hematopoietic stem cell transplantation (allo-SCT). Several reports are available on safety and efficacy of Bv, and Benda before and after allo-SCT, 5 but data is scarce on the use of Nivolumab. We report a retrospective multicenter study to assess the outcomes of HL patients treated with Nivolumab pre or post allo-SCT. This study was conducted in two major centers in Lebanon, the American university of Beirut Medical Center (AUBMC) and Makassed university hospital. We identified and analyzed the outcome and toxicity in 11 adult patients (nine pre-allo-SCT; two post-allo-SCT) with HL treated with Nivolumab peri-allo-SCT. The primary endpoint of the study was objective response rate (ORR). Secondary endpoints included successful bridging to allo-SCT, safety, and toxicity of Nivolumab. Nivolumab Pre-allo The median age at diagnosis was 28 years (range, 20–38). All patients relapsed post ASCT with a median time to relapse of 7 months (range, 1–24 months). Eight patients (89%) failed further salvage post ASCT, prior to initiation of Nivolumab, the remaining patient was refractory to Bv and Benda prior to ASCT so he was immediately salvaged with Nivolumab. The median number of treatment lines prior to Nivolumab and between ASCT and Nivolumab were 5 (range, 4–7), and 1 (range, 0–2) respectively. And the median follow up from Nivolumab initiation and from allo-SCT was 14 (range, 8–24) and 7 (range, 3–17) months respectively. All patients received a median of 8 cycles (range, 6–20) of Nivolumab. The treatment was well tolerated. One patient developed recurrent fever at every infusion. The ORR was 100% with three (33%) and six (67%) patients achieving CR and PR respectively. All of them proceeded with an allo-SCT immediately after Nivolumab. The median time between the last Nivolumab dose and allo-SCT was 44 days (range, 23–100). After a follow up of 7 months (range, 3–17) post allo-SCT, all patients are alive, seven (78%) in CR, and two (22%) in stable disease. Interestingly, none of our patients progressed post allo-SCT. The 1-year Overall Survival (OS) and Disease free survival (DFS) have not been reached. Nivolumab post allo-SCT Two patients were treated with nivolumab for disease relapse post-allo-SCT. Two patients with refractory HL relapsed 10 and 9 months post allo-SCT Salvaged with Nivolumab 3mg/kg (1 dose) developed both a severe steroid refractory acute GVHD (10 and 28 days post therapy respectively). Both still in continuous CR at the last follow up. CONCLUSION: Albeit with the limits of a small observational retrospective study, our data suggests that Nivolumab can be an effective bridge to allo-SCT in patients with relapsed and refractory HL. Even though it does not affect stem cell engraftment, it may contribute to an increased incidence of acute GVHD when used pre and post allo-SCT.

Figure [O031]

Characteristics	N(%)
Age at diagnosis median (range)	28 (20-38)
Male / Female	6 (67)/ 3 (33)
Nodular Sclerosis/Unknown	8(89)/1 (11)
Stage	
IIA-IIB	3 (33)
IVB	5 (56)
Unknown	1 (11)
Interval auto relapse median (range) months	7 (1-24)
Nivolumab pre allo-SCT	9 (100)
Refractory to BV	7 (78)
Status at initiation of Nivolumab	
PD	7 (78)
PR	2 (22)
Best response to Nivolumab	
CR	3 (33)
PR	6 (67)
Progressed on Nivolumab	3 (33)
allo-SCT	9 (100)
Matched Related Donor	3 (33)
Haplo-identical Donor	6 (67)
Status at transplant	
CR	3(33)
PR	3(33)
PD	3(33)
CD34x10^6/kg median (range)	5.13 (4.19-10)
Conditioning	
TBF	5 (56)
Sequential	2 (22)
FB+ATG	1 (33)
Flu-cy-TBI	1 (33)
GVHD prophylaxis	
CSA	3 (33)
CSA+MMF	6 (67)
Complications post allo-SCT	
GVHD	
Acute GVHD grade II-IV	9 (100)
Chronic GVHD	3 (33)
Limited/extensive	2 (22)/ 1(11)
Infection	
CMV reactivation	7 (78)
EBV reactivation	1 (11)
HHV6	0 (0)
BKV	5 (56)
Other complications	
VOD	1 (11)
TTP	1 (11)
Last follow up	
Alive	9 (100)
CR	7 (78)
Stable disease	2 (22)

Disclosure of conflict of interest: None.

O032
Previously published

O033
S1P modulator FTY720 regulates osteoclast precursor mobilization and targets osteoclastogenesis in multiple myeloma systemic xenograft model

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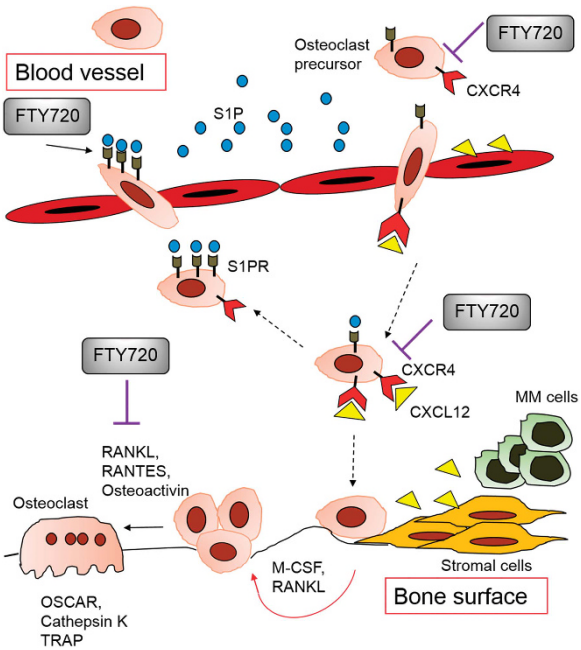
Sphingosine-1-phosphate (S1P), a lipid mediator enriched in blood, controls the dynamic migration of osteoclast (OC) precursors between the blood and bone. Bone disease is one of the hallmarks of multiple myeloma (MM) leading to substantial morbidity and disability. Bone lesions result from abnormally increased osteoclast (OC) formation and activation. Studying the underlying mechanism may help to develop new therapeutic targets to treat MM-associated osteolytic lesions. Previously we reported that S1P modulator FTY720 exhibits potent anti-myeloma effect *in vitro* and *in vivo* in novel disseminated xenograft model of MM. We report now the effect of FTY720 on localization and activation of OCs and their functional sequel in MM model. The *in vitro* effect of FTY720 was tested on OCs and OC precursors from healthy donors, and on bone marrow mesenchymal stromal cells (BMSCs). *In vivo* model of BM-disseminated human myeloma was used to evaluate FTY720 anti-MM and bone activities. The generated OCs expressed the genes encoding for S1P1 and

S1P2 receptors and enzyme SPHK1, tested by RT-PCR. Treatment with FTY720 significantly reduced *in vitro* formation of TRAP+ OCs, resulting in 90% inhibition following 1 μM treatment, and complete abolishment of OC formation at 2.5 μM FTY720 ($P < 0.0001$). Furthermore, FTY720 significantly reduced the expression of genes associated with OC activation. Thus, expression of osteoactivin, cathepsin K, NFATc1, OSCAR, RANK, RANTES, MT1-MMP and MMP9 genes were significantly down-regulated in FTY720-treated OC cultures ($P < 0.001$). In addition, FTY720 targeted the microenvironment components - MM cells and BMSCs, suppressing the expression of osteoclastogenic factors. Moreover, FTY720 altered the ability of myeloma and stroma cells to promote OC formation. Thus, FTY720 was able to disrupt the deleterious cross talk between the MM tumor cells and the OCs. Next, we evaluated the effect of FTY720 on OC activation *in vivo* taking advantage of our novel xenograft model of CXCR4-overexpressing MM cells that results in typical BM involvement by the MM cells accompanying with significant increase in number of TRAP+ murine OC. Treatment of MM-bearing mice with FTY720 (10 mg/kg) effectively targeted the MM cells in the BM milieu. Correspondingly, FTY720 significantly reduced mRNA levels of murine OC differentiation marker genes in BM, including those encoding cathepsin K, integrin β3, OSCAR, RANTES and RANKL ($P < 0.001$). These effect correlated with increased numbers of circulating CD11c+ and F4/80+ monocytes, with OC precursors in both cell populations. To investigate whether OC precursor migration is affected by FTY720, we evaluated the *in vitro* migration of human monocytes toward CXCL12, well-known chemo-attractant of OC precursors. FTY720 completely blocked CXCL12-induced migration of CD14+ cells and significantly reduced their surface CXCR4 expression. These results suggest novel mechanism of action of FTY720, affecting both S1P and CXCR4 pathways, reducing the attachment of the OC precursors to the bone and thus leading to their mobilization to the blood. Our observations uncover novel roles of S1P pathway in OC formation and activation in MM, delineating a novel mechanism of action of FTY720 targeting OC formation and migration *in vitro* and *in vivo* and providing preclinical rationale for its therapeutic application in patients with MM bone disease.

Figure 1 [O033]



Disclosure of conflict of interest: None.

O034

Decitabine enhances targeting of acute myeloid leukemia cells by umbilical cord blood CD34+ progenitor-derived NK cells in NOD/SCID/IL2Rgnull mice

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Combining NK cell adoptive transfer with hypomethylating agents (HMA) is an attractive approach for patients with acute myeloid leukemia (AML). While the direct anti-leukemic effects of HMA are recognized, the impact on the immune system in general and on NK cells in particular is not well established yet. Furthermore, data regarding their impact on NK cells are rather conflicting and mostly derived from *in vitro* studies. Here, we report a comparative study of azacitidine and decitabine in combination with NK cells generated ex vivo from umbilical cord blood (UCB)-derived CD34+ hematopoietic stem and progenitor cells (HSPC-NK cells). CD56+Perforin+ HSPC-NK cells were generated under stroma-free conditions in the presence of StemRegenin-1, IL-15 and IL-12 as previously reported (1,2). These SR1/IL15/IL12 expanded HSPC-NK cells exert efficient *in vitro* cytolytic activity and IFN-g production towards AML cells. Both HMA were tested for their potentiating effect on HSPC-NK cell mediated killing and targeting of AML cells *in vitro* and in THP1-bearing NOD/SCID/IL2Rgnull mice. Used azacitidine and decitabine concentrations were based on clinical practice and plasma concentrations achieved in patients. *In vitro*, low dose HMAs had minor effect on HSPC-NK cell proliferation and viability. HSPC-NK cells remained phenotypically activated and only the frequency in KIR+ NK cells was increased by HMA treatment under proliferative conditions. In functional assays, the highest concentration of azacitidine diminished NK cell reactivity towards K562 cells. In contrast, decitabine did not influence HSPC-NK killing nor IFN-γ production capacity. Moreover, using AML cell lines and primary AML blasts, we showed that the effects of HMA and HSPC-NK cells were at least additive against AML. *In vivo*, while both agents exerted a significant effect on AML progression, the persistence of adoptively transferred HSPC-NK cells was not affected with sustained expression of activating receptors, up-regulation of NKp44 expression and remarkable KIR acquisition. Most importantly, only decitabine potentiated HSPC-NK cell anti-leukemic activity *in vivo*. Interestingly, besides upregulation of NKG2D and DNAM-1 ligands on AML cells, decitabine enhanced mRNA expression of inflammatory cytokines, perforin, and TRAIL in HSPC-NK cells. In addition, treatment resulted in higher numbers of HSPC-NK cells in the bone marrow compartment, suggesting that decitabine could positively modulate NK cell trafficking and tumor targeting. Altogether, these data demonstrate that HSPC-NK cells and decitabine can potently cooperate to combat AML, and provide a strong rationale to explore this combination strategy to treat patients. Combining HSPC-NK cell adoptive immunotherapy with decitabine could serve as consolidating therapy for AML or even as bridge towards non-myeloablative allogeneic stem cell transplantation.

Disclosure of conflict of interest: None.

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Stem cell source

O035

Allogeneic bone marrow transplantation (BMT) without ATG versus allogeneic peripheral blood stem cell transplantation (PBSCT) with ATG in AML patients given grafts from HLA-identical siblings: a retrospective study by the ALWP of the EBMT

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A meta-analysis including data from 9 prospective studies have demonstrated that, in patients given grafts from HLA-identical siblings, the use of peripheral blood stem cell (PBSC) instead of bone marrow (BM) was associated with a lower risk of relapse translating to a better overall survival in patients with advanced disease but at the price of a higher incidence of extensive chronic GVHD (Stem cell trialists collaborative group, *J Clin Oncol* 2005). More recently, a prospective randomized study has demonstrated that ATG improved GVHD-free relapse free survival (GRFS) in patients given PBSC from HLA-identical siblings. This prompted us to compare the outcomes of AML patients given BMT without ATG versus PBSC with ATG in the setting of HLA-identical transplantation. The study population consisted of adult patients with AML transplanted with grafts from HLA-identical siblings from 2007 to 2015 at EBMT-affiliated centers with either BM without ATG or PBSC with ATG after myeloablative conditioning. Exlusion criteria consisted of *in vitro* T cell depletion, administration of alemtuzumab, and unknown disease status at transplantation. Data from 1587 patients given BMT without ATG ($n = 1187$) versus PBSC with ATG ($n = 400$) were included. In comparison to BMT recipients, PBSC patients were transplanted more recently and thus had a shorter follow-up ($P < 0.001$), were older ($P < 0.001$), were more frequently male patients ($P < 0.01$), were less frequently CMV-seronegative patients given grafts from CMV seronegative donors ($P = 0.02$), were more frequently transplanted for advanced disease ($P < 0.001$), received more frequently a conditioning regimen combining busulfan and fludarabine ($P < 0.01$), and received less frequently the association of cyclosporine and methotrexate for GVHD prophylaxis ($P < 0.001$). In multivariate analyses adjusted for conditioning and GVHD prevention and weighted by inverse of the propensity score obtained on age, patient sex, cytogenetic, year of transplantation, disease status and CMV serostatus, the use of PBSC with ATG was associated with a similar incidence of grade III–IV acute GVHD (HR 0.7, $P = 0.3$), a lower incidence of chronic GVHD (HR = 0.6, $P = 0.02$), a similar incidences of relapse (HR = 0.8, $P = 1$) and of nonrelapse mortality (HR = 0.9, $P = 0.6$), a trend for better leukemia-free-survival (HR = 0.8, $P = 0.06$) and better GRFS (HR = 0.7, $P = 0.02$) in comparison to BMT without ATG. These data suggest that PBSCT with ATG results in at least comparable outcomes than BMT without ATG in AML patients given grafts from HLA-identical siblings.

Disclosure of conflict of interest: None.

O036

Previously published

O037

Unrelated matched versus autologous transplantation in adult patients with good and intermediate risk acute myelogenous leukemia in first molecular remission

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Adult patients with standard risk Acute Myelogenous Leukemia (AML) in CR1 treated with chemotherapy have a better outcome if reaching molecular remission. Recent developments have suggested that Autologous Stem Cell Transplantation (ASCT) might bring benefit to patients autografted in molecular CR. In a previous EBMT study (Saraceni F *et al*), that compared allogeneic transplantation (HSCT) from unrelated donors (UD) to ASCT in AML in CR1 we demonstrated that 10/10 matched UD-HSCT was associated with the best LFS, while the OS was similar. Using the EBMT registry, we did a similar comparison restricted to patients transplanted in molecular CR1, with the hypothesis that in this better prognostic group, there might be no difference in outcome following ASCT vs 10/10 UD. From January 2005 to December 2015, 708 patients with non M3 AML, with available cytogenetics were either autografted (375) or allo transplanted with a matched UD (335) in molecular CR1. The follow up was 35 months in the autograft and 23 months in the UD10/10 allo group. In the autograft group, the time from diagnosis to transplant was shorter (155 versus 171 days, $P <$ 10–4) and peripheral blood was more often used (96% versus 75%, $P <$ 10–4). Patients were stratified using the ELN classification which takes into account cytogenetics and molecular markers; the outcomes were compared separately in three ELN AML risk groups: favourable, intermediate 1 and intermediate 2. ELN favourable group: 234 patients were autografted and 70 allografted. By univariate analysis, in the ASCT group, the NRM was lower (3.7% versus 19%; $P <$ 10–4), the RI higher (29% versus 17%, $P <$ 10–4), the LFS identical (67% versus 64%) and the OS was better than in the UD group (83% versus 62%; $P = 0.008$). By multivariate analysis, age was significant for LFS and OS and ASCT was associated with a better OS than UD transplant (HR: 2.09, CI 1.08–4.04; $P =$ 0.03). ELN intermediate group 1: 87 patients were autografted and 172 allografted. By univariate analysis, in the ASCT group, the NRM was lower (2.5% versus 11.8%; $P =$ 0.03), the RI higher (59% versus 18%, $P <$ 10–6),and both the LFS and the OS were lower than in the UD group (39% versus 70%; $P <$ 10–6) and (61% versus 74%; $P = 0.005$), respectively. By multivariate analysis, UD rather than ASCT, absence of FLT3ITD and presence of the NPM1 mutation were all significant favorable prognostic factors for both LFS (HR: 0.39; $P =$ 0.001; HR: 2.6, $P = 0.003$; HR:0.3, $P <$ 10–5 respectively) and OS (HR: 0.53; $P =$ 0.04; HR: 2.5, $P = 0.01$; HR:0.37, $P = 0.02$, respectively) . ELN intermediate group 2: 52 patients were autografted and 93 allografted. By multivariate analysis, there was no difference in any of the outcome indicators, NRM, RI, LFS and OS.When considering the high dose consolidation to be given to patients with AML in molecular CR1, using the ELN prognostic classification, good risk patients have a better benefit in terms of LFS and OS with ASCT, while patients in the intermediate risk 2 category have the same outcome post ASCT or UD transplants. In this category the absence of GVHD and the quality of life post transplant may favor ASCT. Patients in the intermediate risk 1 category do better with UD transplants. The ELN classification

which includes FLT3ITD in the intermediate risk 1 group may not apply as well following ASCT than as initially designed post chemotherapy.
Disclosure of conflict of interest: None.

O038
Cost-effectiveness analysis of haploidentical versus matched unrelated allogeneic hematopoietic stem cells transplantation in patients older than 55 years

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Due to limited donor availability, high comorbidities and cost issues, allogeneic hematopoietic stem cell transplant is not universally accessible. Regarding donor availability the use of unrelated donors can help mitigate this issue but can increase costs and time to transplant. Haploidentical related donors can be found for almost every patient but no economic evaluation has been previously conducted to compare these two alternative strategies to match sibling transplant. The aim of our study was to conduct a cost-effectiveness analysis of haploidentical vs matched unrelated transplant. This retrospective study included patients with hematological malignancies older than 55 years who underwent haploidentical or matched unrelated transplant between 2011 and 2013 in Marseille (Institut Paoli-Calmettes). The incremental cost-effectiveness ratio has been calculated using the mean overall survival and the mean transplant costs. Costs were calculated using a micro-costing strategy from the hospital perspective and a time horizon at two years. Mean and median OS and PFS were assessed using Kaplan–Meier estimator. Costs were discounted with a 4% rate. The incremental cost-effectiveness ratios (ICER), assessing effectiveness with OS and PFS, were calculated considering HRD-SCT as innovative and UD-SCT as the reference. The confidence regions of the ICERs were calculated with the Fieller's method. Sensitivity analyses were conducted using a ± 20% rate. Probabilistic and sensitivity analyses were performed on the incremental cost-effectiveness ratio. During inclusion, 29 patients underwent haploidentical transplant and 63 matched unrelated transplant. In haploidentical and matched unrelated transplant. Clinical results were already published (Blaise D *et al*, Biol Blood Marrow Transplant. 2015). The mean overall survival was respectively 19.4 (1.6) months and 15.1 (1.2) months ($P = 0.06$) and the mean cost was respectively 98 304 (40 872) € and 151 373 (65 742) € ($P < 0.01$) (Figure 1). In our study, HRD-SCT dominated UD-SCT with a better effectiveness at a lower cost. Sensitivity analysis showed that our results were robusts to changes in expensive drug's unit costs and hospitalisation unit costs. The incremental cost-effectiveness ratio was assessed to −148,485 (−1,265,550; −64,368) € per life year gained (Figure 2). Our study was associated with a "real world" practice observation, with data offering good external validity characteristics (i.e. the way to represent the real world data). Internal validity of data needs to be improved. A prospective economic study alongside a multicentric randomized clinical trial is actually ongoing to confirm these results and addressing quality of life assessment issue (MUDELDERLY, Pr Blaise). Among older patients suffering from hematological malignancies, haploidentical transplant is a promising alternative to matched unrelated transplant and first economic arguments supports its diffusion. If results shown by our study are confirmed, HRD-SCT in adults with hematological malignancies could significantly reduce the costs of allo-HSCT with equivalent or better survival and better donor availability.
Disclosure of conflict of interest: None.

[O038]

Figure 1: Cost results

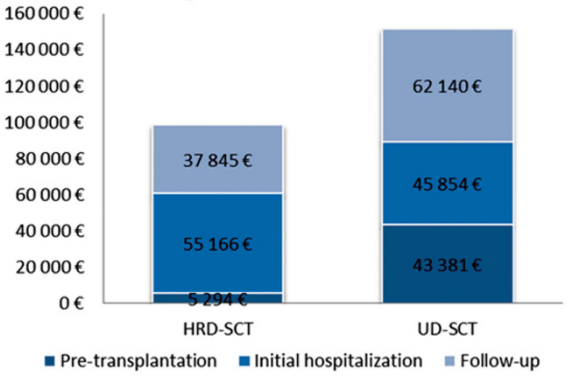
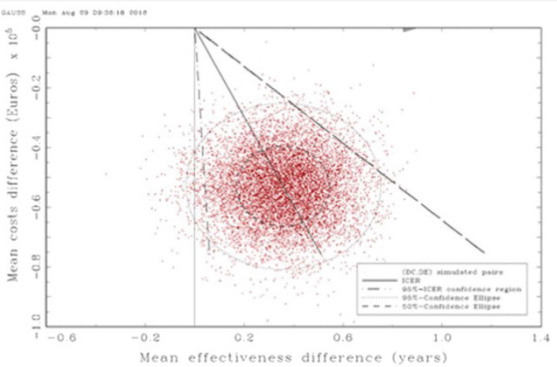


Figure 2: Probabilistic analysis of cost-effectiveness ratio in € per life years gained.



The plain line represents ICER value which is located in south-east of cost effectiveness plan indicating that haploidentical transplant has a lower cost and a higher overall survival. Each point represents a bootstrap simulation taking into account sampling fluctuation uncertainty by Fieller's method. They allow calculation of ICER 95% confidence region represented by dashed lines.

O039
Role of graft cell composition and source in haploidentical transplantation using post-transplant cyclophosphamide

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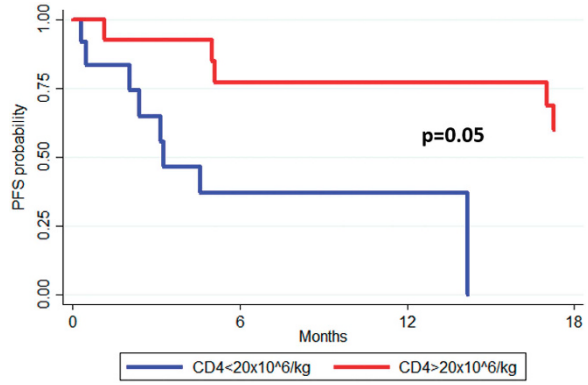
Graft cell composition and source are known to be prognostic in allogeneic hematopoietic cell transplant (HCT). Currently, there are no data in the setting of haploidentical-HCT with post-transplant cyclophosphamide (PT-Cy). One-hundred and fifty-one patients undergoing haplo-HCT with PT-Cy from September 2011 to September 2016 were included in the analysis. Bone marrow (BM) was used as graft source in 29 patients and peripheral blood stem cell (PBSC) in 122 patients. The two groups were similar in terms of age, Disease Risk Index (DRI) and HCT-CI. Differences were reported regarding type of disease

(lymphoid malignancies 66% vs 43%, $P = 0.03$) and conditioning regimen (100% vs 81% myeloablative, $P = 0.01$). Graft cellular subsets analysis was performed by means of flow cytometry (CD34, CD3, CD4, CD8, CD56, CD19, CD38, CD31, CD25, CD45RA, CD95, CD127, CCR4, CCR6, CCR7). Overall Survival (OS) and Progression Free Survival (PFS) were performed with Kaplan–Meier analysis. Acute GVHD (aGVHD), chronic GVHD (cGVHD), Non-Relapse Mortality (NRM) and Relapse Incidence/Progression of disease (RI/POD) were obtained with competing risk analysis. Neutrophil and platelets engraftment cumulative incidences at day +30 were 92% (95% CI: 86–95) and 63% (95% CI: 54–70), with no differences between BM and PBSC. Grade II–IV and grade III–IV aGVHD cumulative incidences at day +100 were 38% (95% CI: 30–46) and 16% (95%CI:10–23). Grade II–IV aGVHD cumulative incidence was significantly lower for BM grafts (14% (95% CI: 4–29) vs 48% (95% CI: 34–53), p1 was the only factor associated with higher RI/POD (HR 1.90, 95% CI: 1.25–2.89, $P = 0.003$), lower PFS (HR 1.61, 95%CI: 1.21–2.14, p8.5x10^6/kg (median) (CD3+/CD8−/CD4+/CCR7+/CD45RA+/CD95−) and recent thymic emigrants >6.9x10^6/kg (median) (RTEs, CD4+/CD31+/CD45RA+) were the only phenotypes associated with a better PFS and OS ($P = 0.02$ and $P = 0.04$ respectively). For the PBSC group, higher CD3 graft count > 230 x10^6/kg (median) was associated with a higher 18-month cGVHD incidence (14% vs 0%, $P = 0.03$). We did not observe significant differences in survival outcomes based on graft source. Patients receiving BM grafts developed less grade II-IV acute GVHD, but grade III-IV aGVHD and cGVHD incidence was similar between the two groups.For the BM group, a higher CD4 count was predictive of better PFS.A negative effect of CD3 cell count was prognostic of higher cGVHD incidence only in the PBSC group. These results should be confirmed in prospective studies.

Figure 1 [O039]



Disclosure of conflict of interest: None.

O040

Human memory B cells reside in the bone marrow and are equipped with an α-defensin weapon–the bone marrow as a source for immunocompetent memory cells for transplantation

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The bone marrow (BM) microenvironment provides specialized niches that support the hematopoiesis but also memory and plasma cell survival. Memory B cells recirculate through the peripheral blood (PB). Few studies further suggest the BM as a niche for them. Little is known about functional properties of BM memory B cells compared to PB and if they get mobilized with G-CSF treatment. We compared with flow cytometry functional properties of memory B cells in paired BM and PB samples. Microarray analysis on sorted memory B-cell subsets was performed to identify their tissue-specific transcriptome characteristics. Paired PB samples of stem cell donors before/after G-CSF treatment and of allogeneic hematopoietic stem cell transplantation (alloHSCT) patients were analyzed for memory B cell subsets. We observed an altered B-cell subset distribution in BM and found that BM CD27+ memory B cells expressed significantly less HLA-DR (MFI ± s.e.m: 8065 ± 2172 BM, 11907 ± 2499 PB; $P \leqslant 0.05$) and CXCR3 (3.9% ± 1.0 BM, 25.8% ± 2.1 PB; $P \leqslant 0.01$), but more Fas-L (24.2% ± 2.8 BM, 6.0% ± 1.6 PB; $P \leqslant 0.05$) than their circulating counterparts. Upon *in vitro* re-activation with SAC/CpG/PWM BM memory B cells exhibited a more resting phenotype than PB memory B cells characterized by decreased proliferation (% Ki67+ cells: 21.0 ± 3.5 BM, 50.1 ± 9.5 PB; $P \leqslant 0.05$), apoptosis (% Annexin V+ cells: 13.5 ± 3.1 BM, 29.2 ± 7.6 PB) and reduced secretion of the inflammatory cytokines TNFa (% TNFα+ cells: 21.6 ± 3.3 BM, 33.3 ± 4.9 PB; $P \leqslant 0.01$) and IL-6 (% IL-6+ cells: 11.6 ± 2.7 BM, 20.6 ± 3.5 PB; $P \leqslant 0.05$). Transcriptome analysis revealed a significant amount of α-defensin mRNA only in BM but not in PB memory B cells, which encode antimicrobial peptides mainly produced by neutrophils as part of the innate immunity (log2FC BM vs PB: 6.21 DEFA1, 7.18 DEFA3, 3.0 DEFA4, Figure 1A). Accordingly, we could detect an increased expression of α-defensins 1–3 (DEFA1–3) at protein level in BM memory B cells (% DEFA1–3 cells ± SEM: 79.9 ± 8.3 BM, 21.8 ± 4.4 PB; $^*P \leqslant 0.05$; Figure 1B; MFI DEFA1–3 ± SEM: 8125 ± 2043 BM, 2345 ± 891 PB; data not shown). Co-culture experiments of sorted CD3+/CD19+ cells with BM serum, containing high amounts of DEFA1–3 RNA and protein carrying exosomes, or with PB and BM-derived DEFA1–3high granulocytes resulted in the induction of DEFA1–3high memory cells from PB (Figure 1C). In the setting of alloHSCT, we could detect increased numbers of DEFA1–3high memory cells in PB of stem cell donors upon G-CSF treatment as well as in the transplant recipients 2–3 weeks after alloHSCT. Importantly, BM mononuclear cells turned out to be significantly more bactericidal than those from PB. Taken together our results suggest that BM-residing memory B cells functionally differ to those from PB. They harbor high amounts of DEFA1–3 and might play a role in BM niche protection from invading pathogens, thus linking adaptive with innate defense mechanisms. DEFA1–3high exosomes and granulocytes within the BM niche seem to mediate the equipment of memory cells with DEFA1–3. G-CSF treatment results in increase of DEFA1–3high memory cells in PB of stem cell donors, which seem to be transferred with the graft into the alloHSCT patient. Future studies should address their contribution to immune reconstitution and protection in recipients.

Disclosure of conflict of interest: None.

O041

Previously published

O042

Outcome of children with acute leukemia given allogeneic HSCT either from an unrelated donor (UD-HSCT) or from an HLA-partially matched relative after αβ-T cell/B-cell depletion (αβhaplo-HSCT)

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Figure 1 [O040]

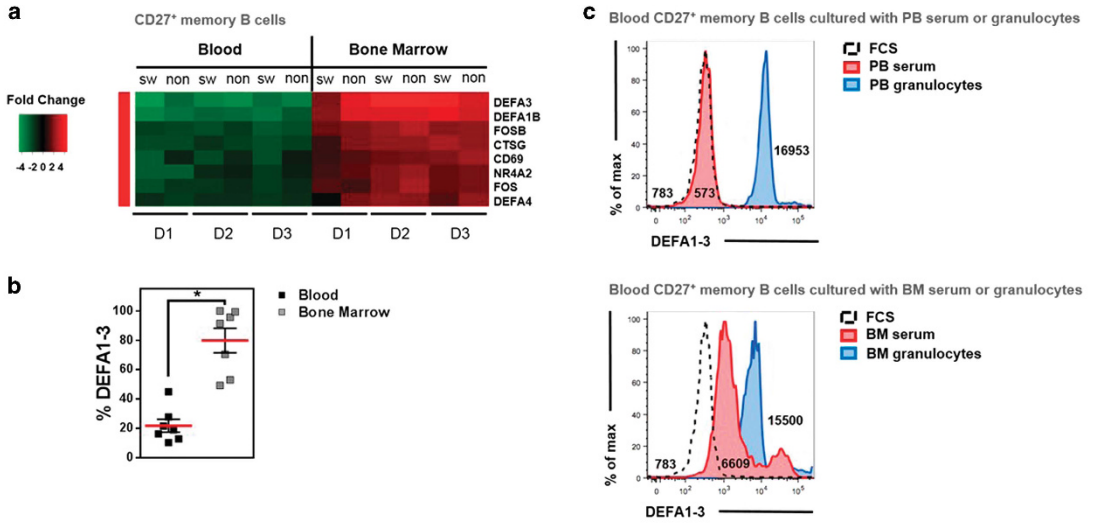

Figure 1: Increased DEFA1-3 expression by BM memory B cells induced by the BM microenvironment. **A)** Switched (sw) and non-switched (non) memory B cells sorted paired PB and BM samples from three different donors (D1-D3) were analyzed for differentially expressed genes using microarray analysis. Shown is an excerpt of 8 of the highest up-regulated genes in BM. **B)** Intracellular DEFA1-3 expression in PB and BM memory B cells were validated with flow cytometry. The graph shows the percentage of CD19+CD27+ memory B cells from PB (black) and BM (grey) expressing DEFA1-3. Mean values±SEM are given; Wilcoxon matched-pair signed-rank test *p≤0.05. **C)** Flow cytometrically sorted CD3+/CD19+ lymphocytes from PB were co-cultured with 20% FCS (negative control), with 5% FCS + 15% serum derived from BM (lower graph) or PB (upper graph) and with 20% FCS + sorted CD45+CD15+ granulocytes (1:1 cultured with lymphocytes) derived from BM or PB. The intracellular DEFA1-3 expression in CD19+CD27+ memory B cells was determined by flow cytometry. The representative histograms represent the DEFA1-3 as % of maximum (MFI).

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Allogeneic hematopoietic stem cell transplantation either from an unrelated donor (UD-HSCT) or from an HLA-partially matched relative after αβ-T cell/B-cell depletion (αβhaplo-HSCT) are both suitable options for children with acute leukemia (AL) in need of an allograft. With the aim of analyzing the outcomes of AL children given one of the 2 options, we evaluated 97 αβhaplo-HSCT recipients and 244 patients receiving UD-HSCT in the same time period, namely October 2010 to December 2015, in one of the 13 centers affiliated with the AIEOP-HSCT network. Six centers performed both αβhaplo-HSCT and UD-HSCT, while only this latter procedure was performed in the remaining 7 centers. All children were transplanted in morphological complete remission (CR) after a fully myeloablative conditioning regimen. The UD was selected using high-resolution HLA typing. Details on patient characteristics of the 2 groups are shown in the Table 1; recipients of αβhaplo-HSCT were transplanted in more advanced phase and received more frequently a TBI-based regimen than UD-HSCT patients. Patients given αβhaplo-HSCT did not receive any post-transplantation pharmacological prophylaxis of graft-versus-host disease (GvHD), while the combination of anti-T lymphocyte globulin (ATLG), cyclosporine-A and short-term methotrexate was employed for preventing GvHD occurrence in UD-HSCT recipients. ATLG was also infused before transplantation in all children treated with αβhaplo-HSCT to prevent both graft rejection and GvHD. Two (2%) and 4 (2%) patients experienced graft failure in the αβhaplo-HSCT and UD-HSCT groups, respectively. Median time to neutrophil and platelet recovery was shorter in children given αβhaplo-HSCT (13 and 11 days vs 19 and 23 days, respectively, $P < 0.001$ in both cases). The cumulative incidence (CI) of grade II-IV and grade III-IV acute GvHD in patients given αβhaplo-HSCT was 16% and 0%, as compared to 39% and 12% in UD-HSCT recipients, $P < 0.001$ and < 0.0005, respectively). Children treated with αβhaplo-HSCT benefited also from a lower incidence of both overall and extensive chronic GvHD (6% and 1%, respectively, vs 20% and 7% in UD-HSCT recipients, $P < 0.01$ and < 0.05, respectively). Forty-eight patients died for transplant-related complications: 9 (9%) and 39 (16%) in the αβhaplo-HSCT and UD-HSCT group, respectively, the CI of transplantation-related mortality being 9% and 16% (P = N.S.). Seventy-three children relapsed at a median time of 190 days (range 40–1603) after the allograft; no statistically significant difference for the CI of disease recurrence was observed between the 2 groups (25% vs 20%, respectively). With a median follow-up of 3.3 years (range 0.5–5 years for surviving patients) the 3-year probability of overall survival for patients given either αβhaplo-HSCT or UD-HSCT is 68% and 64%, respectively (P = N.S.), while the probability of event-free survival in the 2 groups is 63% and 62%, respectively (P = N.S.). The chronic GvHD-free/relapse-free probability of survival in the 2 groups is 59% and 48%, respectively ($P = 0.03$). Altogether, these data indicate that both αβhaplo-HSCT and UD have the same efficacy in children with AL, the former option being, however, associated with a lower incidence of both acute and chronic GvHD.

Table 1 [O042]

	αβHaplo-HSCT		UD-HSCT		P
Gender: M / F	65 / 32	(67% / 33%)	145 / 99	(59% / 41%)	N.S.
Median age at HSCT (range)	9	(0.9-18)	10	(0.4-18)	N.S.
Diagnosis					
ALL	66	(68%)	170	(70%)	N.S.
AML	31	(32%)	74	(30%)	
Median year of HSCT (range)	2013	(2010-2015)	2012	(2010-2015)	N.S.
Disease status at HSCT					
CR1	42	(43%)	132	(54%)	0.001
CR2	47	(49%)	111	(45%)	
Other CR	8	(8%)	1	(1%)	
ALL 2nd CR patients (BFM classification)					N.S.
S1-S2	22	(55%)	63	(66%)	
S3-S4	18	(45%)	33	(34%)	
Stem cell source					
BM	0	(0%)	186	(76%)	0.0001
PBSC	97	(100%)	58	(24%)	
Conditioning regimen					
TBI-based	72	(74%)	132	(54%)	0.001
Chemo-based	25	(26%)	112	(46%)	
Interval from diagnosis to HSCT (years)	1.3	(0.4-9)	0.9	(0.4-12)	N.S.

Disclosure of conflict of interest: None

Donor type

O043

Anti GvHD prophylaxis shape the effect of HLA mismatches on the unshared haplotype in T-cell repleted haploidentical stem cell transplantation: a study from the Acute Leukemia Working Party of European Society for Blood and Marrow Transplantation (EBMT)

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Haploidentical hematopoietic cell transplantation (haploSCT) is an option for patients (pts) who lack a matched donor, with acute GvHD prophylaxis based on anti-thymocyte globulin (ATG) or post-transplant cyclophosphamide (PTCy) as main platforms. No consensus exists on the selection criteria over several haploidentical donors. Here explored associations between antigenic and allelic HLA-A, -B, - C and -DRB1 mismatches (mm) on the unshared HLA haplotype (UH) with outcome of haploSCT on the two platforms. 509 adult acute myeloid and lymphoid leukemia pts who received a T-repleted haplo-HCT as 1st allograft in 2007–2014 as reported to EBMT, for whom HLA-A, -B, -C and –DRB1 typing was available at low (66%) or high (34%) resolution were included. A validated HLA high-resolution imputation algorithm, developed by the German National Donor Registry, was used to impute allele-level matching in 418 pairs. HLA matching status was considered both for individual loci and as cumulative number of mm. The association between this and other variables and 100 day grade 2–4 aGvHD as primary endpoint, and relapse, leukemia-free-survival (LFS) and transplant-related-mortality as secondary endpoints, was explored separately in 313 PTCy and 196 ATG haploSCT in univariate and multivariate analysis. Both GvHD-prophylaxis platforms were comparable for major variable except for reduced intensity conditioning (RIC) and bone marrow as stem cell source, both more applied in PTCy than in ATG regimens (59% Vs 36%, respectively, $P < .01$ for RIC and 47% Vs 28%, respectively, $P < .01$ for BM). In PTCy transplants, the cumulative incidence (CI) of aGvHD was significantly associated with matching for HLA-DRB1 on the UH at the antigenic ($34 \pm 5\%$ Vs $17 \pm 8\%$, $P = .02$) but not the allelic level ($30 \pm 6\%$ Vs $19 \pm 10\%$, $P = 0.33$). The CI of aGvHD was higher in bidirectional or GvH-directed antigenic DRB1 mm compared to others ($34 \pm 5\%$ and $21 \pm 8\%$ respectively, $P = .05$) in PTCy regimens. This association was not present in ATG transplants ($35 \pm 8\%$ VS $30 \pm 15\%$, $P = 0.54$ for antigenic and $33 \pm 7\%$ Vs $58 \pm 23\%$ for allelic DRB1 mm). Also in adjusted multivariate analysis, antigenic DRB1 mm was an independent risk factor for aGvHD in PTCy (HR 2.0; 95% CI 1.2–4.0, $P = .02$) but not in ATG regimens (HR 1.3; 95% CI 0.4–3.4, $P = 0.6$). The association with DRB1 matching was not reflective of the total number of HLA mm since no association was found between the CI of aGvHD and the cumulative number of antigenic or allelic mm on the UH. The GvHD prophylaxis regimen also modulated the influence of other variables affecting T cell alloreactivity: the hazards of aGvHD were significantly associated with peripheral blood as stem cell source (HR 2.2, 95% CI 1.4–3, $P < 0.01$), RIC (HR 0.6, 95% CI 0.4–0.9, $P = .04$) and female donors (HR 1.8, 95% CI 1–3.2, $P = .05$), in PTCy but not in ATG regimens. The use of female donors also reduced the hazards of relapse (HR 0.6, 95% CI 0.4–0.9, $P = .04$) and LFS (HR 0.7, 95% CI 0.5–0.9, $P = .03$) in the PTCy but not the ATG group. The hazards of aGvHD after haplo-HCT were found to be sensitive to different variables influencing T cell alloreactivity including HLA-DRB1 matching status on the UH, use of PB stem cells and female donors, in PTCy but not ATG regimen. The role of HLA matching in haplo-HSCT appears thus to be modulated by the adopted GvHD prophylaxis, calling for further investigations in this increasingly relevant field.

Disclosure of conflict of interest: None.

O044

Previously published

O045

Outcomes after matched unrelated donor and non-T-cell depleted haploidentical stem cell transplantation in patients $\geqslant$ 60 years with acute myeloid leukemia: A comparative study on behalf of the ALWP of the EBMT

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AML is both more common and with more biologically aggressive phenotype in the elderly, thus outcome with conventional chemotherapy are poor. Reduced intensity conditioning (RIC) regimens have allowed older patients (pts) with low comorbidities to undergo HSCT from matched unrelated donors (MUD). HSCT from haploidentical donors (Haplo) are recently emerging as valid alternative with the advantage of fast allocation and availability to most of the pts that are in need of HSCT. With the aim to better define the role of alternative donors in the elderly, we retrospectively compared the results of 10/10 MUD ($n = 2589$, 57% males) and non-T-cell depleted Haplo ($n = 250$, 62% males) transplant (Tx) in pts $\geqslant$ 60 years with de novo or secondary AML. Pts were transplanted between 2007 and 2014 in 210 EBMT centres. None had prior HSCT. Median follow-up was 23 months for both Haplo and MUD. Haplo were performed more recently, 2013 vs 2012 for MUD ($P < 10^{-4}$). Secondary AML was diagnosed in 35% of MUD and 37% of Haplo, de novo AML in 65% of MUD and 63% of Haplo ($P = 0.5$). Disease status at Tx was significantly different between the 2 groups ($P < 10$–4); pts were in CR1 (MUD: 53%; Haplo: 38%), CR2/3 (MUD: 17%; Haplo: 18%) or had active disease (MUD: 30%; Haplo: 44%). Median time from diagnosis to Tx was longer for Haplo (9 vs 6.8 months, $P = 0.001$). Median age at Tx for both MUD and Haplo was 65 years (range 60–78). RIC was administrated in 73% and 77% of the Haplo and MUD Tx, respectively ($P = 0.23$). Stem cell source was bone marrow in 52% of Haplo, and peripheral blood stem cells in 94% of MUD ($P < 10^{-4}$). ATG was most frequently used in MUD (75% vs 26%, $P < 10^{-4}$). Post-Tx cyclophosphamide (PT-Cy) was given in 62% of the Haplo Tx. Neutrophil engraftment was achieved in 90% of Haplo and 97% of MUD ($P < 10^{-4}$). In multivariate analysis, no significant difference was found between MUD vs Haplo Tx in terms of RI (HR: 1.06, $P = 0.69$, 95%CI: 0.76–1.47), NRM (HR: 0.75, $P = 0.09$, 95%CI: 0.54–1.05), LFS (HR: 0.94, $P = 0.63$, 95%CI: 0.76–1.17), GRFS (HR: 1.18, $P = 0.12$, 95%CI: 0.95–1.47), acute GVHD grade II–IV (HR: 1.17, $P = 0.37$, 95%CI: 0.82–1.65), chronic GVHD (HR: 1.21, $P = 0.28$, 95%CI: 0.84–1.75), and OS (HR: 0.87, $P = 0.24$, 95%CI: 0.68–1.1). Extensive chronic GVHD was significantly higher for MUD Tx as compared to Haplo (HR: 2, $P = 0.01$, 95%CI: 1.17–3.47). Overall, 45% of the pts who underwent Tx from MUD and 35% of those transplanted from Haplo donors died of relapse. Main causes of Tx-related death were infections (MUD: 26%, Haplo: 35%), GVHD (MUD: 16%, Haplo: 18%) or others (MUD: 13%, Haplo: 12%). A center effect was found for acute and chronic GVHD and NRM. Using propensity score analysis we were able to match pair 225 Haplo with 450 MUD and to confirm the association of MUD with a higher risk of extensive cGVHD (HR: 2, $P = 0.04$, 95%CI: 1.03–3.95); type of donor was not significantly associated with other outcomes. In our cohort, Haplo and MUD showed similar results. MUD Tx were associated with higher rates of extended chronic GvHD. Results were confirmed in a propensity score analysis. Our findings suggest that Haplo is a suitable and attractive source for pts $\geqslant$60 with AML in need of HSCT. The most effective prophylaxis for prevention of chronic GVHD in unrelated Tx should be addressed.

Disclosure of conflict of interest: None.

O046

Lower incidence of GVHD after haploidentical compared to unrelated donor allogeneic stem cell transplantation for patients younger than 60 years with hematological malignancies: a single center experience of 225 patients

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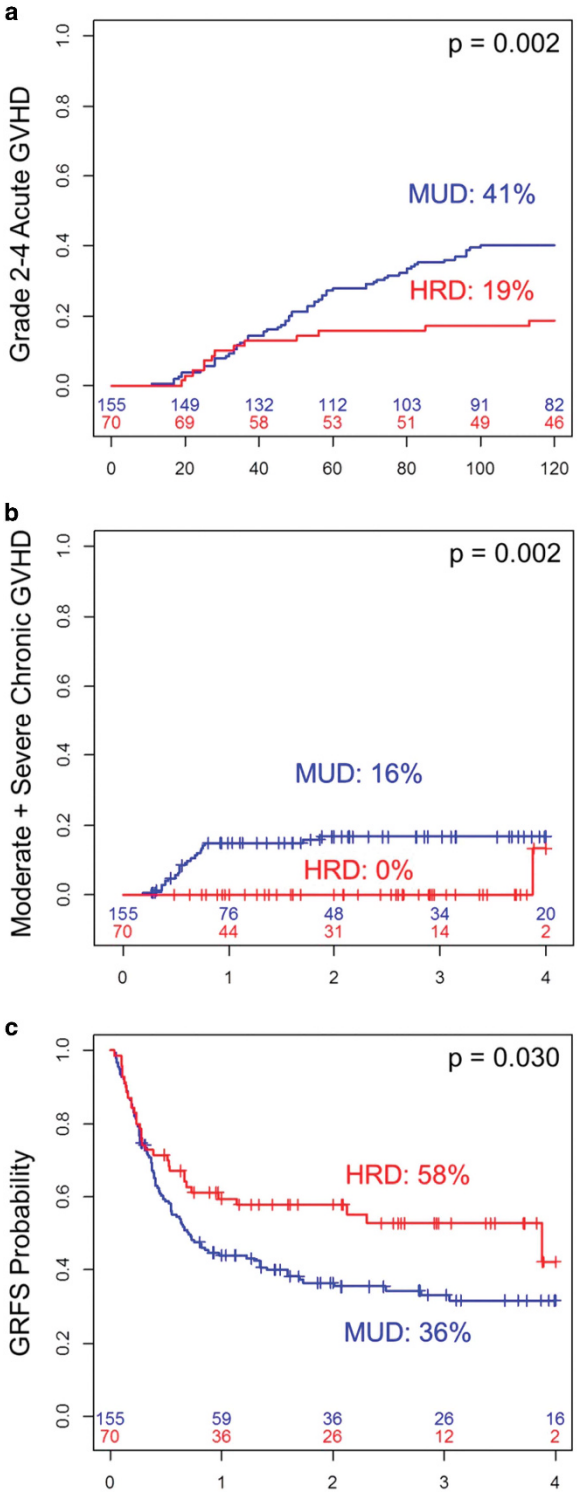
Allogeneic hematopoietic stem cell transplantation (alloHSCT) is limited by the availability of a HLA matched donor. HLA-identical sibling donor is considered as the preferred choice, but is not available for most of patients. For them, unrelated donor (URD) is a valid option, but is currently challenged by the use of haploidentical related donor (HRD). Indeed, large registry database analyses reported similar outcomes between URD and HRD alloHSCT. However, the high variability of transplant procedures across centers makes the interpretation of such results difficult. We previously reported our single center experience showing that outcome after HRD was better than after URD in older patients (Blaise BBMT 2015). We report here a specific monocentric comparison of URD vs HRD alloHSCT for younger patients with hematological malignancies. We collected data from patients <60 years with hematological malignancies who underwent first alloHSCT from URD or HRD between 2010 and 2015 in our center. We compared outcome between URD and HRD groups using univariate analyses. To deal in part with the different baseline characteristics between both groups, we adjusted the impact of donor type by age, disease status at the time of alloHSCT, disease type and conditioning regimens (Multivariate Cox model). We analyzed 225 patients (URD $n = 155$; HRD $n = 70$) with a median age of 50 years (19–60). Compared to HRD group, URD patients were more frequently transplanted for myeloid diseases (55% vs 39%), were more frequently in CR at the time of alloHSCT (74% vs 56%), received more myeloablative conditioning regimens (38% vs 19%) and received more PBSC as graft source (94% vs 64%). GVHD prophylaxis was based on ATG + cyclosporine +/− MMF in URD patients while HRD received post transplantation cyclophosphamide + CSA + MMF. Median follow up was 30 months (3–65). The cumulative incidence of both day+100 acute and 2-year chronic GVHD were significantly higher in the MUD group (grade 2–4: 41% vs 19%, $P = 0.002$, Figure 1A; grade 3–4: 15% vs 3%, $P = 0.008$; moderate + severe chronic: 16% vs 0%, $P = 0.002$, Figure 1B). Relapse incidence (CIR) and NRM at 2 years were similar in both URD and HRD groups (CIR: 27% vs 21%, $P = 0.443$; NRM: 23% vs 19%, $P = 0.558$). This led to similar 2-year PFS and OS (PFS: 51% vs 61%, $P = 0.315$; OS: 59% vs 66%, $P = 0.317$). GVHD-relapse free survival (GRFS) was significantly lower in the URD group (36% vs 58%, $P = 0.030$, Figure 1C). Multivariate analyses confirmed that both acute and chronic GVHD were lower in the HRD group (grade 2–4 acute: HR = 0.44, $P = 0.008$; grade 3–4 acute: HR = 0.19, $P = 0.027$; moderate + severe chronic: HR = 0.09, $P = 0.018$). The decreased incidence of GVHD after HRD alloHSCT was not associated with higher incidence of relapse in multivariate model taking into account the difference in baseline disease characteristics between URD and HRD groups (HR = 0.84, $P = 0.562$). Overall, patients in the HRD group did not reach worse outcome compared to URD group (OS: HR = 0.75, $P = 0.257$, PFS: HR = 0.81, $P = 0.351$; NRM: HR = 0.79, $P = 0.481$). Finally, HRD group had a trend for better GVHD-relapse free survival (HR = 0.66, $P = 0.050$). Our results showed that in the setting of patients $<$ 60 years, the use of a HRD compares favorably with URD by decreasing GVHD without impairing overall outcome. Thus, HRD alloHSCT should be considered as a suitable alternative in the absence of matched related donor.

Figure 1 [O046]



Disclosure of conflict of interest: None.

O047

The older stem cell donor in the Netherlands—a survey on medical assessment, comorbidity and outcome

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As allogeneic stem cell transplantation is increasingly applied in older patients up to the age of 75, subsequently the proportion of older related stem cell donors rises. Safety aspects of G-CSF-induced stem cell mobilization and donation by apheresis have been investigated mostly in healthy young volunteers. The aim of this multicenter survey was to investigate the proportion of 60+ stem cell donors in the Netherlands, the outcome of their medical eligibility assessment and stem cell donation, including donation-related complications and recipient engraftment. All related potential donors 60 years or older from 4 Dutch transplantation centers who were medically assessed between January 2010 and July 2015 were included in the survey. Data were collected retrospectively from donor files and included information on the medical assessment, reasons for deferral, mobilization- and donation-related complications and donor follow-up. In addition, stem cell harvest (amount of CD34 cells) and corresponding engraftment data of recipients were collected and compared with younger donors. 186 potential donors were included (median age 65.2, range 60–77.2 years), of whom 20.4% proved ineligible after medical assessment (in 4 centers ranging from 14.3 to 25%) compared to 9.2% of 359 donors $<$ 60 years (in the same time period in 3 centers). The most common reasons for deferral of older donors were monoclonal gammopathy of unknown significance and malignancies, including 6 hematological malignancies detected at the assessment (3.2%). Remarkably some abnormalities that would have been a reason for deferral according to international guidelines for unrelated donors, did not lead to donor referral, such as ischemic cardiovascular disease and malignancies. From the medically approved donors 89.2 percent proceeded towards donation. The median time to donor approval was 15 days (range 0–97). The target harvest was reached in 79% of donors. However, stem cell harvest was significantly lower than in the younger donors (median total CD34 424.0 and 510.3 $\times$ 10e6 respectively, $P = 0.001$). In two donors an infection, requiring hospitalization occurred within one week after donation. There were no other serious mobilization- and donation-related complications. All recipients transplanted with stem cells from older donors reached neutrophil engraftment (neutrophils $>0.5 \times 10e9/L$, median 18 days) and 95.2% reached platelet engraftment (platelets $>20 \times 10e9/L$, median 12 days). Stem cell donation by related donors 60 years and older is feasible resulting in adequate stem cell numbers and engraftment. From this cohort two serious adverse events were reported, possibly related to the donation. However, data on long-term follow up are missing. As comorbidity increases and 20% of 60+ donors proved ineligible at medical assessment, timely screening and early start of an unrelated donor search are advised to prevent transplant delay for donor reasons.

Disclosure of conflict of interest: None.

O048

KIR-ligand mismatching is associated with inferior survival in patients with acute leukemia following T-cell replete haplo-identical transplantation with post-transplant cyclophosphamide. a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT)

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Haplo-identical stem cell transplantation is increasingly been used in recent years in the treatment of acute leukemia. In particular, the use of T-cell replete grafts with post-transplant cyclophosphamide (PTCy) for prevention of GVHD is becoming a valid treatment option with encouraging outcome. Most patients will have several haplo-identical donors. However, the criteria for selection of the best haplo-identical donor in this type of transplant are not yet well established. NK alloreactivity as predicted by missing KIR ligands in the recipients that are present in the donors has been shown to be an important factor in the outcome of T-cell depleted haplo-identical transplants. NK alloreactivity is associated with reduced relapse risk and improved survival in patients with AML, but not in patients with adult ALL. In addition, pts with donor NK alloreactivity had better engraftment and lower risk of GVHD. The study included 531 patients, median age 46 years (range, 18–78) with AML ($n = 382$) or ALL ($n = 149$) who had T-replete haplo-identical transplant with PTCy between the years 2009–2015. Patients were in CR1 (40%), CR2 (26%) or active disease (34%). Stem cell source was peripheral blood (49%) or bone-marrow (51%). Conditioning was myeloablative (51%) or reduced-intensity (49%). GVHD prevention included cyclosporine or tacrolimus with mycophenolate, in addition to PTCy, in 86%. KIR-ligand mismatching was predicted according to patient and donor HLA typing and correlated with transplantation outcomes. The median follow-up was 14 months (range, 1–70). Ninty-two percent engrafted. The 2-year relapse and non-relapse mortality (NRM) rates in the entire group were 36% (95%CI, 31–41) and 24% (20–28), respectively. The leukemia-free (LFS) and overall survival (OS) rates were 39% (34–44) and 46% (41–51), respectively. Acute GVHD grade II–IV and chronic GVHD occurred in 28% (25–37) and 33% (29–38), respectively. 165 patients (37%) were predicted to have donor NK alloreactivity based on missing expression of C1, C2 or Bw4 ligands that were expressed in their donors. 2-year OS was 47% (38–55) in patients with KIR mismatch and 53% (46–60) in patients with no KIR-ligand mismatching ($P = 0.11$). Multivariate analysis identified AML (compared to ALL) (HR 0.6, $P = 0.002$), advanced age (HR 1.1, $P = 0.04$), active disease (HR 3.4, $P < 0.001$), KIR mismatching (HR 1.4, $P = 0.03$), good performance status (HR 0.7, $P = 0.04$) and female gender (HR 0.7, $P = 0.04$) as factors associated with 2-year OS. KIR mismatching was associated with a trend for higher incidence of relapse (HR 1.4, $P = 0.1$) and of NRM (HR 1.3, $P = 0.28$), but not with increased rate of acute GVHD (HR 0.7, $P = 0.12$) or chronic GVHD (HR 0.9, $P = 0.58$). The same trends were seen when the analysis was limited to patients with AML and to a lesser extent in patients with ALL. Haplo-identical transplant with PTCy is associated with relatively favorable outcome in patients with acute leukemia. KIR ligand mismatching may be associated with worse outcome in these patients. Donors with KIR mismatching should not be preferred and may even be avoided when possible in this setting.

Disclosure of conflict of interest: None.

O049

Comparison of matched- unrelated donors versus alternative donor (9/10) unrelated donor, cord blob unit and haplo-identical donor) in allogeneic stem cell transplantation (allo-SCT) for acute lymphoblastic leukemia (ALL) in CR2: a report of 841 patients from the EBMT Acute Leukemia Working Party

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For the past years, indication of allo-SCT in ALL in CR1 is under debate. However, allo-SCT in ALL in CR2 is well established. At the same time, unmanipulated grafts are increasingly used in the haplo-setting, and innovative regimens for GvHD prophylaxis have been adopted with encouraging results. The current study aimed to compare the outcomes of ALL patients who received allo-SCT in CR2 from a matched unrelated donor 10/10 (MUD) versus alternative donors: unrelated donor 9/10 (UD), cord blood unit (CBU) and haploidentical donor (HD) and reported between 2005 and 2015 to the registry of the EBMT ALWP. 841 patients were included: 428 patients received a MUD, 171 patients an UD, 148 patients a CBU and 94 a HD. They was a higher proportion of patients who underwent allo-SCT in less than 18 months since the diagnosis in the HD group (42.5% vs 36.9% in MUD 10/10 vs 28% in UD 9/10 and 24% in CBU group, $P = 0.005$). The median time to relapse to transplant was similar in the 4 groups ($P = 0.68$). The number of Philadelphia chromosome positive ALL patients and of positive minimal residual disease at transplant were comparable in the 4 groups ($P = 0.60$ and $P = 0.74$, respectively). At 2 year, for overall population, LFS was 36.9%, OS was 42.6%, RI was 32.4%, NRM was 30.7% and GRFS was 30%. In univariate analysis, no difference was found between the 4 groups. In multivariate analysis, 3 predictive factors were associated with better LFS: the time between diagnostic and transplant $>$18months (DxTx$>$18m)(HR = 0.661, 95%CI, 0.54–0.808, $P < 10^{-4}$), a Karnofsky status at transplant $\geqslant$90% (KS) (HR = 0.775, 95%CI, 0.62–0.97, $P = 0.02$),and the year of transplant (HR = 0.955, 95%CI: 0.91–0.99, $P = 0.02$) whereas increase year per 10 y was associated with a lower LFS (HR = 1.103, 95%CI:1.023–1.19, $P = 0.01$).For OS, an HD compared to MUD 10/10, the age of the patient and the positive CMV status of the patient were associated with lower OS, whereas 3 predictive factors were associated with better OS: DxTx$>$18m, KS $\geqslant$90% and the year of transplant. In

multivariate analysis for RI, only DxTx > 18m was a protective factor (HR = 0.49, 95%CI, 0.0.37–0.65, $P < 10^{-4}$). In multivariate analysis, a HD was associated with higher risk of aGVHD II–IV compare to MUD 10/10 (HR = 0.028, 95%CI: 1.049–2.3, $P = 0.03$). At 2 years, in univariate analysis, the cumulative incidence of chronic GVHD was not statistically different between the 4 groups and no factors de risk were identified in multivariate analysis. Concerning NRM at 2 years,in multivariate analysis, patient age and CMV positive status were factors associated with higher NRM (HR = 1.143, 95%CI, 1.026–1.273, $P = 0.015$; HR = 1.49, 95%CI, 1.09–2.04, $P = 0.011$), while year of transplant was the only factor associated with lower NRM (HR = 0.94, 95% CI, 0.88–0.99, $P = 0.027$). Finally, considering GRFS at 2 years, DxTx > 18m and the year of transplant were associated with better GRFS (HR = 0.69, 95%CI, 0.57–0.84, $P < 10^{-3}$ and HR = 0.96, 95%CI, 0.924–0.998, $P = 0.04$). Allo-SCT may rescue more than one third of patients with ALL in CR2. Importantly, the donor type did not have any impact on patients' LFS, RI, NRM and GRFS. However an HD compare to a MUD 10/10 was associated with lower OS and higher aGVHD II–IV. In contrast, DxTx > 18m was a major prognostic factor for LFS and RI. Therefore, a UD 9/10, CBU but also HD with improvement of GVHD prophylaxis as compared to a MUD 10/10, could be considered as a valid option in adult patients with ALL in CR2.

Disclosure of conflict of interest: None.

O050

Bendamustine-Based (BeEAM) conditioning before autologous stem cell transplantation: results of a multicenter study of 474 patients

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Unavailability of Carmustine has led, based on very few literature data, to an increase use of Bendamustine-based (BeEAM) conditioning regimen before autologous stem cell transplantation for lymphoma. The aim of this study was to evaluate the safety of the BeEAM regimen in a large cohort of patients treated in several centers. Patients 16 years or older with histologically confirmed diagnosis of NHL or HL and treated with BeEAM regimen prior to ASCT were retrieved from the database of several participating centers. Toxicities were recorded retrospectively according to CTCAE v4. Acute kidney injury was defined according to KDIGO guidelines as an increase of creatininemia $\geqslant$ 26.5 µmol/L or a creatininemia/initial creatininemia ratio $\geqslant$ 1.5 or dialysis requirement. A total of 474 patients with median age of 56 years were registered. The majority of patients had diffuse large B-cell lymphoma. Acute kidney injury was defined according to KDIGO guidelines as an increase of creatininemia $\geqslant$ 26.5 µmol/L or a creatininemia/initial creatininemia ratio $\geqslant$ 1.5 or dialysis requirement. Bendamustine was administered at a median dose of 197 mg/m^2/day (50-250) on day − 7 and − 6. Grade 1-4 toxicities were mucositis (83.5%), gastroenteritis (53%), skin toxicity (34%), colitis (29%), liver toxicity (19%), pneumonitis (5%) and cardiac rhythm disorders (4%). Stage 1-3 acute renal failure (ARF) according to KDIGO classification was reported in 132 cases (27.9%) (stage $\geqslant$ 2; 12.3 %) and appeared after a median time of 6 days (range: 1–35) after conditioning start. In comparison with the group of patient without renal failure, the group of patients with ARF had older age, higher rate of male gender, higher rate of pre-transplant chronic renal failure, higher day1 creatinine level, lower hyperhydration volume and received higher median bendamustine dose. Colitis, pneumonitis, cardiac arrhythmia, intensive care admission, need for blood transfusion, hospital stay duration, and death were more frequent in patients with post conditioning renal failure. In multivariate analysis, pre-transplant chronic renal failure, bendamustine dose > 160mg/m^2 and age were independent prognostic factors for ARF. A four-point clinical predictor score for acute renal failure stage > 1 was identified and included pre-transplant chronic renal failure (2 points), bendamustine dose > 160mg/m^2/d (1 point) and age > 55 years (1 point). Risk of ARF stratified by score, was 1.5%, 9.6%, 17.4%, 23.1% and 46.1% with score 0 to 4, respectively. BeEAM induced 3.3% non-relapse mortality with high rate of renal toxicity. Pre-transplant chronic renal failure, hyperhydration volume, duration of hyperhydration, and etoposide dose were predictive factor of mortality. BeEAM conditioning induced a high rate of ARF and 3.3% early death. A simple, four-point scoring system can stratify patients by levels of risk for ARF and may allow a reduction of the bendamustine dose to improve clinical outcomes. Prospective comparative studies are needed to confirm toxicity extents of this conditioning as compared with other type of high dose therapy.

Disclosure of conflict of interest: None.

Autoimmune diseases and solid tumors

O051

Outcome of autologous non-myeloablative hematopoietic stem cell transplantation in patients with refractory chronic inflammatory demyelinating polyneuropathy (CIDP)

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Approximately 20% of patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) are refractory to IVIG and or plasmapheresis. In this group of patients we accessed the safety and efficacy of autologous hematopoietic stem cell transplant using a non-myeloablative regimen. Sixty three patients refractory to IVIG and or plasmapheresis who met EFNS/PNS "definite" CIDP electrodiagnostic criteria and either "typical" or "atypical" EFNS/PNS clinical criteria underwent stem cell collection with cyclophosphamide (2.0 g/m^2) and filgrastim. The conditioning regimen was cyclophosphamide (200 mg/kg) divided as 50 mg/kg on day -5 to day -2, rATG (Thymoglobulin) dosed at 0.5 mg/kg/IV on day -5, 1.0 mg/kg on days -4, and -3, and 1.5 mg/kg/IV on days -2, and -1 (total dose 5.5 mg/kg), and rituximab 500 mg on days -6 and +1. Unselected peripheral blood stem cells were infused on day 0. There were no treatment related deaths. After a mean follow-up of 2.5 years, overall survival was 97%. Post transplant medication free remission is 71% (6 month), 77% (1 year), 84% (2 year), 90% (3 year), 83% (4 year), and 85% (5 year). Physical assessment (MRC), disability outcomes (Rankin score, Barthel index, and INCAT scale), and quality of life (SF-36) all improved significantly ($P < 0.01$). Electrophysiologic parameters (average conduction velocity, average conduction block (CB), number of nerves with > 50% CB, and average compound motor action potential) also demonstrated significant post transplant improvement ($P < 0.01$). Non-myeloablative HSCT is a one-time intervention that is associated with improvement in quality of life, increased conduction velocity and nerve CMAP amplitude, decreased CB, reversal of disability, and in most cases long-term independence from conventional therapies.

Disclosure of conflict of interest: None.

O052

Evaluating the cost-effectiveness of autologous haematopoietic stem cell transplantation (aHSCT) versus disease-modifying therapy in multiple sclerosis using a matching-adjusted indirect comparison (MAIC)

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Large published head-to-head trials of autologous haematopoietic stem cell transplantation (aHSCT) versus standard disease-modifying therapy (DMT) in relapsing-remitting multiple sclerosis (RRMS) are awaited. We therefore performed a study to estimate the clinical effectiveness of aHSCT compared with DMT for RRMS using clinical outcomes data from four European transplant programmes active in treating RRMS with aHSCT. A retrospective cohort of aHSCT patients was constructed including individual patient data (IPD) for 75 patients (follow-up ranging from 3 to 521 weeks). The relative efficacy of aHSCT versus natalizumab was estimated using a matching-adjusted indirect comparison (MAIC), an approach which is similar to propensity scoring, whereby IPD from the aHSCT cohort were matched to the mean baseline characteristics of the 300mg q4w natalizumab arm of the AFFIRM trial ($n = 627$). The MAIC logistic regression model included covariates for disease duration, annual relapse rate, and baseline Expanded Disability Status Scale (EDSS). Disease progression was defined as an increase of $\geqslant 1$ EDSS points; sustained disease progression was defined as progression which was sustained at the next clinical assessment (irrespective of the interval between consecutive assessments). The hazard ratio (HR) for progression was estimated using a Cox model. Post-matching, the aHSCT group closely reflected the natalizumab group from the AFFIRM trial (mean disease duration 5-years; 1.5 relapses in previous year; baseline EDSS score 2.3). The HR for sustained EDSS progression for aHSCT versus natalizumab was estimated to be 0.11 (95% confidence interval 0.02, 0.76), whilst the relative risk of relapse for aHSCT versus natalizumab was 0.22. For unconfirmed progression, the proportional hazards assumption was violated, therefore the estimated hazard ratio was uninterpretable. Importantly, most of the weighting in this model was given to two aHSCT patients, thereby suggesting considerable heterogeneity between study populations. Notably, few patients in the aHSCT dataset had sustained progression; this may reflect either high efficacy for aHSCT or insufficient follow-up in the transplant cohort. On the basis of this covariate-adjusted indirect comparison, aHSCT may be highly clinically effective in the treatment of RRMS, although the data available for comparison are limited by known heterogeneity and potentially the presence of other unknown confounders. Given the once-only nature of aHSCT and the high ongoing costs of DMTs for RRMS, there is potential for aHSCT to represent a cost-effective use of health care resources. The ongoing Phase III MIST trial will be pivotal in clarifying the effectiveness of aHSCT versus DMTs; upon completion, this evidence should be considered within a broader economic evaluation framework in order to formally address questions about whether HSCT represents good value for money.

Disclosure of conflict of interest: None.

O053

Screening for NY-ESO-1 expression as a cancer immunotherapy target in soft-tissue sarcoma

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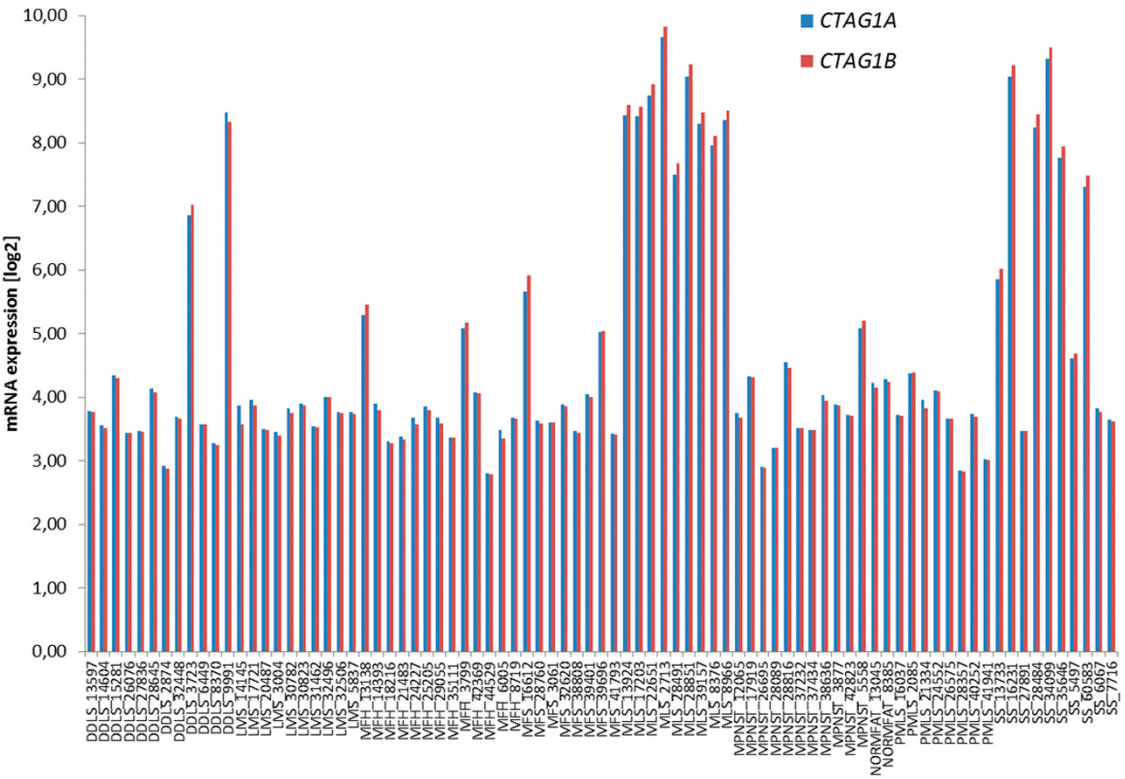
NY-ESO-1 is a cancer testis antigen expressed by several solid tumors. In particular, certain sarcoma subentities, such as

Figure 1 [O053]



synovial sarcoma and myxoid round-cell liposarcoma are known to have high rates of NY-ESO-1 expression. Adoptive immunotherapy with T cells harboring genetically modified T-cell receptors specific for NY-ESO-1 has resulted in remarkable responses and long-term remissions without severe side effects in synovial sarcoma (Robbins *et al*. 2011 and 2015). To identify patients eligible for this promising immunotherapy approach, reliable screening methods are mandatory. We are currently evaluating gene expression profiling and immunohistochemistry data to determine the expression of NY-ESO-1 in soft-tissue sarcoma patients and prepare the ground for a clinical immunotherapy trial with genetically modified T cells specifically recognizing NY-ESO-1 at our institution. Samples were collected at the Institute of Pathology, University Hospital Heidelberg, Germany. Gene expression profiling was performed using Illumina HumanHT-12 arrays. The two genes encoding NY-ESO-1 were covered by three (CTAG1A) and two (CTAG1B) probes, respectively, and mean expression was calculated. Log2 expression values >5, 4-5, and 5: DDLS (1/12 cases), UPS/MFH (2/13), MFS (2/8), MLS (9/9), MPNST (1/11), SS (6/10). Borderline expression was seen in DDLS (2/12), LMS (1/10), UPS/MFH (1/13), MFS (1/8), MPNST (3/11), PMLS (2/8), SS 1/10 as well as in two non-malignant fat samples. The frequency of NY-ESO-1 expression is in line with previously reported results involving DDLS, UPS/MFH, MFS, MLS and MPNST. Comparison of gene expression with immunohistochemistry is ongoing and will help confirm NY-ESO-1 expression especially in patients with borderline expression. Transcriptomic profiling is a valuable tool for the identification of cancer immunotherapy targets. We have implemented NY-ESO-1 as a new candidate therapeutic target in soft-tissue sarcoma patients analyzed within the MASTER (Molecularly Aided Stratification for Tumor Eradication Research) precision oncology program of the National Center of Tumor Diseases Heidelberg, which aims to identify targets for therapeutic intervention in individual patients based on whole-exome/genome and RNA sequencing. Prospective screening for NY-ESO-1 expression will help identify patients who are eligible for NY-ESO-1-directed treatment approaches.

Disclosure of conflict of interest: None.

O054

Allogeneic HSCT for autoimmune diseases: a retrospective study from the EBMT autoimmune diseases, inborn errors and paediatric working parties

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Allogeneic HSCT offers the potential replacement of an aberrant immune system. We used the EBMT registry to identify patients treated with allogeneic HSCT for severe autoimmune diseases (ADs). Long-term outcomes of allogeneic HSCT on the AD was analysed where available. This is a retrospective multicenter study analyzing available EBMT registry data and additional information requested in a specifically designed questionnaire. Between 1997 and 2014 inclusive, a total of 126 patients received allogeneic HSCT for various hematological ($n=49$) and non-hematological ($n=77$) refractory AD. The patients were treated at 62 centers in 20 European countries. The median age of patients at HSCT was 12.9 years (range 0.22–62.16). Ten patients received a previous transplant, mainly autologous HSCT. Donors were MRD for 44 patients, MUD for 61, MMRD for 14 and syngeneic for 7 patients. The graft source was PBSC in 67, BM in 50, and cord blood in 9 patients. Conditioning was myeloablative in 62 and reduced-intensity in 56 patients. Ex-vivo TCD was performed in 13 cases. Serotherapy with ATG was given in 36 patients and alemtuzumab in 23 patients. Post-transplant GvHD prophylaxis was given in 111 patients, mainly ciclosporin-based. Multivariate analysis included AD diagnosis, age at HSCT (cut-off 18 years), donor type (UD versus others), year of HSCT (before or after 2010), conditioning regimen (MAC versus RIC) and GvHD prophylaxis (ex-vivo or in-vivo TCD). Median follow-up was 36 months (range 3.4–189 months). All except 6 patients experienced sustained donor cell engraftment. The median time to a neutrophil count of $\geqslant 500/\mu L$ was 15 days. The following side effects were reported: 6 secondary autoimmune disease, 19 viral reactivations (CMV in 7 and EBV in 10 cases), and 2 cases of secondary malignancy. In all, 47 patients developed acute GVHD, with the incidence of grades II-IV acute GvHD of 13.4% (95% CI: 7.7–20.7) at 100 days. Cumulative incidence of chronic GvHD was 24.5% (95% CI: 16.4–33.5). Response to transplant was available for 38 patients. At 100 days, response was achieved in 59% for immune cytopenia, and 56% for other AD. At the last follow-up complete clinical response of refractory AD was obtained in 70.7% of patients. Relapse incidence was 18.9% (95% CI: 11.8–27.3). Progression-free survival (PFS) was 60.6% at 3-year (95% CI: 51.0–70.1). At the time of this analysis, 72% of patients were alive. Non-relapse mortality (NRM) was 11.3% (95% CI: 6.5–17.6) at 100-day, and 20.5% at 3-year (95% CI: 13.6–28.4). The overall survival (OS) was 71.3% (95% CI: 62.9–79.8) at 3-year. Two factors were found to be significantly associated with improved outcome by multivariate analysis. Age less than 18y was associated with a lower RI (HR: 0.29; $P=0.02$), lower cGVHD (HR: 0.18; $P=0.0002$) and better LFS (HR: 0.50; $P=0.04$); more recent year of transplant was associated with a lower NRM (HR: 0.86; $P=0.003$); a better PFS (HR: 0.89; $P=0.003$) and OS (HR: 0.89; $P=0.004$). There were no statistically significant differences in relation to conditioning regimens, AD diagnosis and donor type. This large retrospective survey of the EBMT registry confirms the potential of allogeneic HSCT to produce long-term disease remission in a large proportion of refractory ADs, with acceptable toxicities and NRM, especially in younger patients. Outcomes have improved in recent years.

Disclosure of conflict of interest: The authors declare no competing financial interests.

O055

Previously Published

O056

Extended analysis of HLA-G polymorphisms and outcome in metastatic renal cell carcinoma patients undergoing allografting

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Graft-versus-tumor (GvT) activity mediated by alloreactive donor T cells has been exploited for the treatment of advanced renal cell carcinoma, a cancer particularly sensitive to immune intervention (Childs *et al*, NEJM 2000; Barkholt *et al*, Ann Oncol 2006). HLA-G, a non-classical HLA molecule with immunomodulatory properties including a tolerogenic effect on T, NK and dendritic cells, has been studied with regard to outcome after transplantation, in particular the 14bp insertion/deletion polymorphism in the 3′ untranslated region has shown to have an impact on GvHD after allogeneic hematopoietic stem cell transplantation (HSCT) for beta-thalassemia (La Nasa *et al*., BJH 2007; Sizzano *et al*., Tissue Antigens 2012). We analyzed $n = 55$ patients affected by advanced stage renal cell carcinoma who received HSCT from a HLA-sibling or a matched unrelated donor between 1998 and 2006 at Milano, Marseille, Clermont-Ferrand and Stockholm. The follow-up was updated in September 2016. The 14bp polymorphism was analyzed in correlation with OS, PFS, acute and chronic GvHD; adjustement for main patient and donor characteristics was performed. Furthermore, exploratory analyses were done on polymorphisms at positions 2988, 2995, 3012, 3020, 3127, 3172, 3181 and 3106. Whenever a different polymorphism was disclosed between patient and donor, the one from the donor was used in the analysis with the exception of those patients who suffered from graft rejection. With a median follow-up of 13 years, three patients were alive at last follow-up, at +12y, +13.5y and +14y after HSCT. Median OS and PFS were 11 months (range 1–168) and 6 months (range 1–102, respectively. For the $n = 51$ patients available for 14 bp analysis, a trend toward better outcome was observed when homozygosity for the 14bp-del allele was present: the median OS of 14bp-del vs others was 29m vs 10m ($P = 0.20$), and PFS was 15m vs 6m ($P = 0.22$), respectively (Figure 1). After adjustment, HR was 0.50 (95% CI 0.23–1.13; $P = 0.10$) and 0.57 (95% CI 0.26–1.26; $P = 0.17$) for OS and PFS respectively, when 14bp-del/del were compared with 14bp-ins/del + ins/ins. No significant associations were observed with acute (any grade) or chronic GvHD. Exploratory analyses on the eight further polymorphisms showed a significant association between T/C at position 2988 and improved OS ($P = 0.06$) and PFS ($P = 0.008$), compared with T/T. To our knowledge, this is the first analysis on the impact of the 14bp-allele polymorphisms of HLA-G and outcome after HSCT for a solid malignancy. After a coordinated multicenter study, we found that the less tolerogenic polymorphisms (14bp-del/del) is associated with better PFS and OS, possibly suggesting more GvT within this group. The exploratory finding on the polymorphism at position 2988, that is associated with a better OS and a significantly better PFS, deserves to be further investigated.

Disclosure of conflict of interest: None

O057
Previously Published

O058
Autologous stem cell transplantation (ASCT) in relapse remitting (RR-MS) and secondary progressive multiple sclerosis (SP-MS): an Australian-based prospective phase II trial

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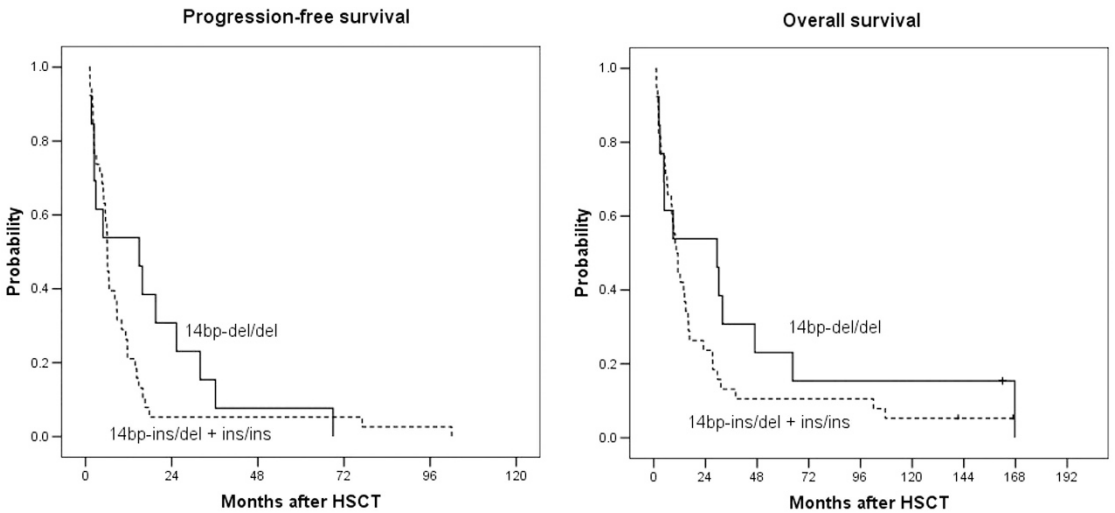
ASCT is a promising strategy for the management of patients with MS who do not respond to conventional measures (1-3). We report the prospective outcomes of ASCT in patients with RR-MS and SP-MS in a single centre. From 2010 to 2016, patients with RR-MS or SP-MS who were fit to undergo ASCT were recruited. Patients were conditioned with Carmustine, Etoposide, Cytarabine and Melphalan (BEAM) before autologous stem cell infusion, followed by anti-thymocyte globulin (Atgam) on days 1 and 2 post-infusion. Outcome measures include safety of ASCT, and efficacy, as measured by Expanded Disability Status Scale (EDSS) and serial magnetic resonance imaging (MRI) studies, and MS quality of life measurements (MSQOL). 33 patients were recruited and underwent ASCT (Table 1), with a median follow up period of 12.8 months (range 3–57 months). ASCT was performed at a median of 96 months after onset of MS (range 12–252 months). Patients had a median EDSS score of 6.0 (range 2.0–7.0), and received 4 lines of treatment (range 2–7 lines of treatment) prior to ASCT. There was no transplant related mortality in this cohort, and the 1 year relapse-free survival was 86%. Infectious complications were noted in 3 patients, which required hospitalisation, with 1 patient requiring ICU admission. After ASCT, the EDSS score improved to a median of 5.00 at 6 months ($P = 0.004$) and 5.25 at 12 months ($P = 0.02$) (Figure 1). 7 patients (25%)

Figure 1 [O056]

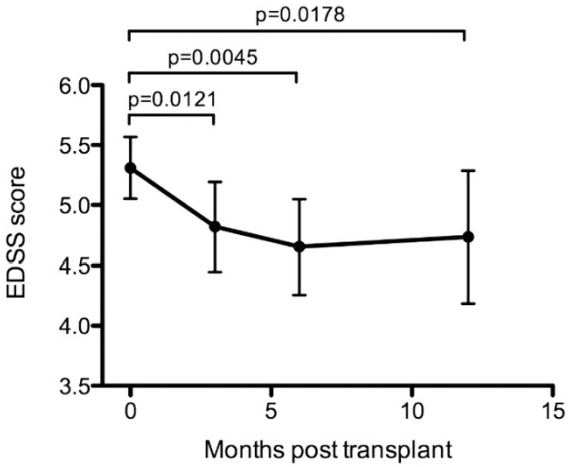


experienced relapse – 5 experienced deterioration of clinical function, and 2 had increased lesions in MRI. Significant improvement of quality of life was noted after ASCT, with MSQOL-54 physical health composite improved from 33 to 59 twelve months post ASCT ($P < 0.01$), and mental health composite improved from 52 to 71 ($P < 0.01$). Subgroup analysis revealed an improvement of EDSS in the RR-MS cohort ($P = 0.0187$) but not SP-MS (p = ns), and while MSQOL-54 physical health composite was improved in both cohorts ($P < 0.01$), improvement of mental health composite was only observed in patients in the RR-MS cohort.

Keywords: multiple sclerosis, autologous transplant, autoimmune disease, prospective trial

[O058]

Figure 1. EDSS before and after ASCT



[O058]

Table 1. Characteristics of patient cohort

		Number	Percentage
Gender	Male/female	11/22	
Age (range)		37 (21-55)	
MS subtype	*RRMS*	20	61
	SPMS	13	39
No. of prior therapy	*2 to 3*	11	33
	4 to 5	19	58
	More than 5	3	9
Baseline disability score	*less than 4*	4	12
	4 to 6	16	48
	more than 6	12	36

ASCT is safe and effective in improving disability and quality of life in heavily pretreated MS patients. Major improvement was seen particularly in the RR-MS patients.

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Disclosure of conflict of interest: None.

GVHD (preclinical)

O059

Impact of HLA disparity on GvHD and relapse rate in haploidentical transplants followed by high dose post-transplant cyclophosphamide

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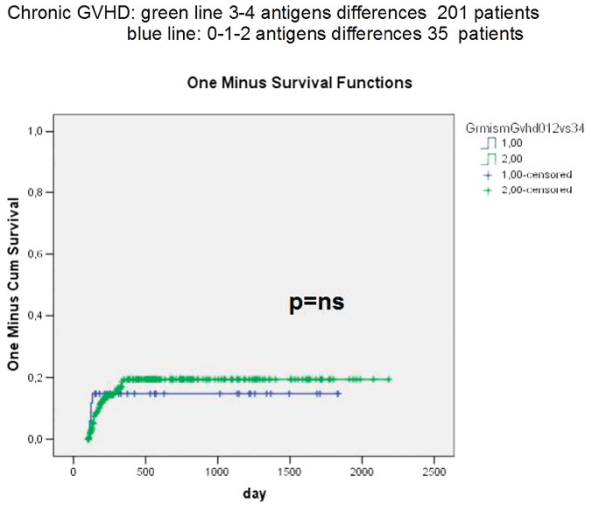
By definition ''haplo-identical'' donor shares genotipically 4/8 antigens with recipient. However because of casual phenotypical homozygosity in the not shared-haplotype in a few couples donor/recipient the degree of disparity is less than standard 4/8 antigens. In Genoa patients without a HLA identical donor were transplanted from a haplo-identical donor since 2011.This large, single center series offered the opportunity to verify: (1) the effective numbers of antigen disparity between donor and recipient (2) the impact of inferior HLA disparity on outcome parameters. All haplotransplants performed from august 2010 ($n = 282$) were included in the study. All patients received a myeloablative regimen (MA) followed by unmanipulated BM, and high dose post-transplant cyclophosphamide (PT-CY), combined with cyclosporine and mycophenolate. Donors and recipients were typed, until 31 December 2015, using DNA method (SSO and SBT) for HLA A, B, C, DRB1, DQ and DPB at a high resolution level, as defined by EFI standards and by NGS at allelic level in 2016 for the same loci. When applicable (72.3% of patients) members of the immediate family where typed to definitively establish HLA genotype and haplotype identity. Parameters analyzed were: cumulative incidence of grade II-IV acute GvHD, moderate-severe chronic GvHD, relapse rate and their statistical correlation with real degree of HLA disparity. For this purpose differences for locus A, B, C DRB1 in GvHD "vector" were evaluated. Acute GvHD incidence was calculated at day 100, the other parameters were calculated at the third year of follow up, all by the method of Kaplan and Meier. Differences were analyzed with the log-rank test. Median age of the 283 patient was 48 years (17-74). Diseases were: acute myeloid leukemia: 111, acute lymphoblastic leukemia: 56, lymphproliferative disorders: 41, chronic myeloproliferative diseases: 43 and myelodisplastic syndrome: 31. At transplant time 137 patients were (49%) in advanced phase of disease. With regards to real numbers of mismatched in GVHD ''vector'' differences (donor versus recipient), among 282 couples: 145 (51%) showed as expected 4 over 8 antigens difference, 86 (30%): 3/8, 33 (11%): 2/8, 9 (3%): 1/8, and no difference: 9 (3%), respectively. For analyses patient population was divided into two groups: 0-1-2 antigens difference ($n = 49$) versus 3-4 antigens difference ($n = 233$).With the same criteria 236 chronic GVHD evaluable patients were evaluated: 35 (0,1,2 differences) and 201 (3,4 differences). With median follow up of 562 days (range 6–2241 days) overall survival and disease free survival were 55.7% and 47% respectively. The cumulative incidence of grade II-IV aGVHD was 17% ($n = 49$). Cumulative incidence of moderate – severe cGVHD was 13% ($n = 39$). Ninety-one patients (32%) relapsed. No significant association was found between the number of HLA mismatches and risk of aGVHD grade II-IV (p = ns) and c GVHD (p = ns) (Fig 1). More mismatching also had no effect on relapse rate (p = ns) (Fig 2). Same results are obtained if the analysis is performed only on patients in complete remission at transplant. This study shows: 1) about half of HAPLO donor recipient pairs, differ for less than 4 /8 HLA antigens. 2) In the setting of a MA conditioning, with PT-CY HLA matching or mismatching had no effect on aGvHD, cGvHD and relapse rate.

Figure 1 [O059]



Disclosure of conflict of interest: None

O060

IL-22+γδT17 as the core of cellular crosstalk networks in intestinal acute graft-versus-host disease

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Acute graft-versus-host disease (aGVHD) is the major complication and cause of mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT), in which the intestine is a particularly serious organ leading to significant morbidity and poor prognosis. Interleukin-17(IL-17) producing γδT (γδT17) cells plays an important role in intestinal regeneration during injury, while it has both protective and inflammatory properties and its mechanism is unclear. The aim of this study is to explore the role of γδT17 cells in the intestine during aGVHD. Lethally irradiated host BALB/c(H-2kb) mouse were injected with T cell depleted bone marrow (non-aGVHD group) plus splenic T cells (aGVHD group) from C57BL/6 mice(H-2kd). The intestine were cut and digested into single cells and mononuclear cells from lamina propria were isolated by centrifugation on a Percoll gradient. γδT cells were sorted by Microbeads and then single-cell gene profiling was performed using BioMark 96.96 Dynamic Arrays (Fluidigm) as described in the manufacturer's protocol. Phenotypic analysis was performed by Flow Cytometry. Single-cell gene profiling reveals higher expression of epithelium-reconstruction-related genes, including Il17a, Il17ra, Il17rc and Ocln (Figure 1). In the early phrase the proportion of γδT17 cells in the intestine from aGVHD group is lower than that from non-aGVHD group (5.9% v.s. 35.3%, $P=0.0001$), while in the late phrase γδT17 cells proportion from aGVHD group is higher than that from non-aGVHD group (44.5% v.s. 33.6%, $P=0.0068$). Interestingly, there are more IL-22+ γδT17 cells in non-GVHD group than in aGVHD group. After improving the ratio of IL-22+ cells in donor γδT cells in transplantation, we observed greater survival in the higher IL-22 group compared with normal aGVHD group (Figure 2). Moreover, Myeloid-Derived Suppressor Cells(MDSCs) changes in consistent with IL-22+γδT17 cells and Innate Lymphoid Cells (ILCs) decrease during aGVHD, and IL-22+γδT17 can also secret GM-CSF to recruit MDSCs. IL-22+γδT17 cells is the key and specific cellular group contributing to the protective property in intestinal aGVHD. IL-22+γδT17 cells may support the survival of Intestinal Stem Cells (ISCs) and promote epithelial regeneration via secreting IL-22 in place of ILC3. Meanwhile, they can also recruit MDSCs to negatively regulate the immune system and reducing intestinal damage.

Disclosure of conflict of interest: None.

Figure 2 [O060]

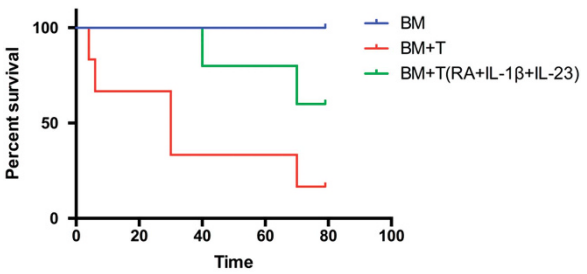

Figure 2 Survival proportions

Figure 1 [O060]

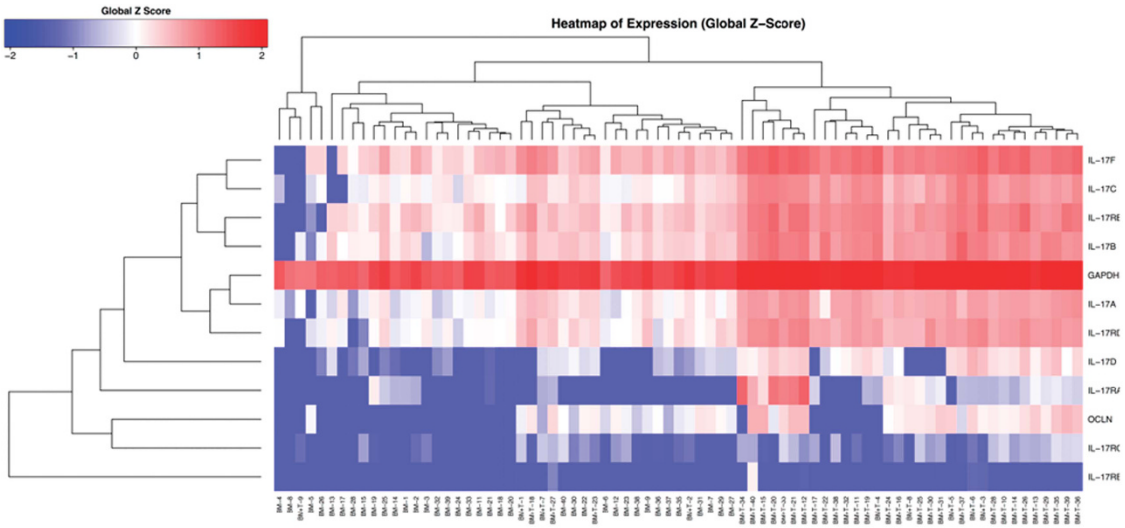

Figure 1 Heatmap of intestinal γδT cells

O061

Oral Syk inhibitor, Entospletinib (GS-9973), controls disease and enhances survival in a mouse model of chronic graft-versus host disease (cGVHD)

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Chronic graft-versus host disease (cGVHD) is a major complication of hematopoietic stem cell transplantation (HCT). The tyrosine kinase Syk is required for B cell hyper-responsiveness in cGVHD patients (1, 2) and for cGVHD development in mice (2). Syk inhibition *in vivo* also reduces established lung pathology in a cGVHD model of bronchiolitis obliterans (2). Whether Syk blockade early after HCT attenuates cGVHD development and affords immune recovery is unknown. In this study entospletinib (ENTO), a specific oral Syk inhibitor (3), was administered early after HCT in a mouse model of cGVHD to test these possibilities. Lethally-irradiated (8.5 Gy) BALB/c recipient mice ($n = 10$ per treatment group) were transplanted i.v. with 1×107 T cell-depleted C57BL/6 bone marrow cells alone (Control), or with 1×107 T cell-depleted C57BL/6 bone marrow cells plus 1×106 C57BL/6 splenocytes (cGVHD). 12 days post-transplant, recipient mice were started on chow formulated with ENTO at a concentration of 0.06% or 0.02%, or with placebo. Pharmacokinetic (PK) studies to assess plasma ENTO concentrations were performed 7 days after ENTO initiation to estimate Syk target coverage. Mice were evaluated over time for weight loss, eye pathology†, alopecia†, lymphocyte reconstitution (by flow cytometry), immunohistochemistry, and survival. †Measurements were performed by a masked investigator. *P*-values were determined by unpaired, two-tailed Mann-Whitney test. Duke University IACUC approved all studies. PK analysis revealed dose-dependent plasma ENTO concentrations based on diet, with Syk target pharmacodynamics (PD) coverage of PDhigh/PDave = 85%/66% for the 0.06% dose and 62%/32% for the 0.02% dose. cGVHD mice receiving ENTO at either dose developed dramatically reduced clinical eye symptoms (Figure 1 and data to be shown), including chemosis ($P < 0.001$), conjunctiva redness ($P < 0.001$), eyelid edema ($P < 0.001$) blepharitis ($P < 0.001$), and mucoid discharge ($P < 0.001$). cGVHD mice receiving placebo developed severe total body alopecia, while alopecia was nearly absent in the ENTO cGVHD groups ($P < 0.001$). Survival of cGVHD mice in both ENTO groups was significantly improved vs placebo (70% alive in each ENTO group through day 72, compared to 20% alive in the placebo group). Lymphocytes reconstituted to a greater degree in each ENTO cGVHD group relative to the placebo cGVHD group ($P < 0.01$ for B cells, $P < 0.05$ for T cells), supporting the hypothesis that specific inhibition of Syk activity affords recovery of immune homeostasis after HCT.

Figure 1 [O061]

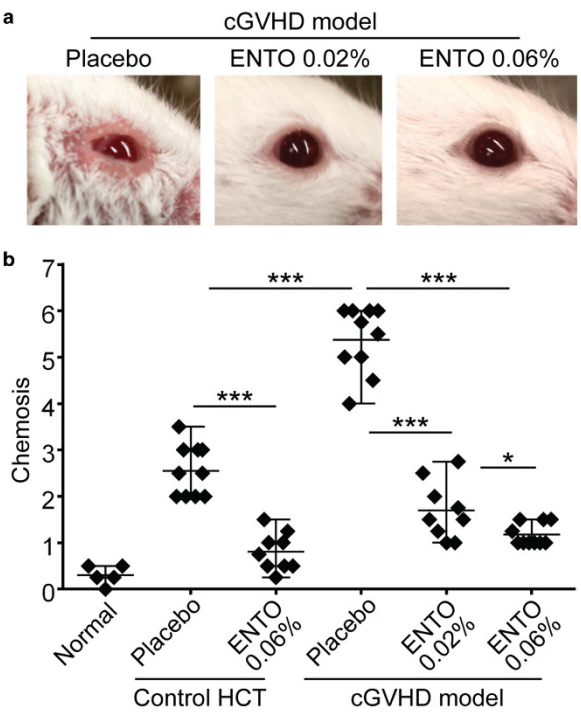

Figure 1. ENTO improves clinical eye scores in cGVHD mice. (A) Representative mice from the cGVHD groups on day 33 post-HCT. (B) Eye chemosis scores for all HCT groups 4 weeks post-HCT performed in a masked fashion by Duke Eye Center investigators. Age-matched normal BALB/c mice were included as reference healthy controls. ***, $P < 0.001$; *, $P < 0.05$. Oral ENTO administration early after HCT in mice ameliorated clinical manifestations of cGVHD, enhanced survival, and improved immune cell recovery. These data support the potential for oral ENTO in the treatment of cGVHD patients. Phase II clinical trials are currently underway.

Clinical Trial Registry: NCT02701634 ClinicalTrials.gov.

Disclosure of conflict of interest: JDP: Gilead Sciences: Employment, Equity Ownership; JYK: Gilead Sciences: Employment, Equity Ownership; A. MM: Gilead Sciences: Employment, Equity Ownership. The remaining authors declare no conflict of interest.

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O062

Previously published

O063

Safety and efficacy of placenta derived decidua stroma cells in experimental studies and in clinical settings

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We introduced bone marrow derived mesenchymal stromal cells (BM-MSCs) as novel therapy for acute GVHD. Not all patients responded to MSC therapy and some of them died due to invasive fungal infection. Decidua stromal cells (DSCs) are isolated from the fetal membrane and showed stronger immunosuppression compared to other MSCs. Toxicity was investigated in Balb/c mice. Human DSCs were infused IV in doses of 4, 20 and $40x10^6$/kg. None of the animals died or showed acute toxicity or adverse reaction related to cell infusion both in short (+3 day) and long (+30 day) follow up. Blood biochemistry profiles related to liver, kidney, heart and blood were not influenced by DSC infusion. Coagulation factors as well as inflammatory indices were not affected. We also applied DSCs to treat GVHD in a full MHC mismatched model (B6 to Balb/c). Recipient mice were conditioned with 950cGy TBI and received DSCs. All mice receiving 40x10^6 DSC/kg died from pulmonary embolism. However, those receiving lower doses had a lower GVHD score and a better weight compared to controls. We also evaluated stromal cell

infusion on fungal infection in a pig model of septicemia. Pigs tolerated 1x10^6/kg DSCs or BM-MSCs well with no side effects and no enhanced risk of candida septicemia. In clinical settings, patients were treated with DSCs for severe acute GVHD ($n = 40$), hemorrhagic cystitis (11), chronic GVHD (4), polyneuropathies (2), ARDS (1). Median dose was 1,5 (0,7-2,8) X10^6/kg, given from 1 up to 15 doses. DSCs were well tolerated and only three patients had transient infusion related toxicity. Adverse events using DSC were similar to retrospective controls, but with less death from acute GVHD. One-year survival for severe acute GVHD using DSCs was 76%, which was similar to 78% in all patients ($n = 453$) undergoing HSCT during 2010-2015. We conclude that DSCs is a promising therapy for acute GVHD and toxicity/inflammation after allogeneic stem cell transplantation with almost no side effects.
Disclosure of conflict of interest: None.

O064
Metabolic serum profiles and chronic graft versus host disease among patients receiving allogeneic stem cell transplantation

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Metabolic regulation is important for immune reconstitution, and the aims of the present study were to investigate serum metabolic profile among patients one year after transplantation, and comparing patients with and without cGVHD. The study included 51 consecutively allotransplanted adult patients (29 men and 22 women; median age 44 years, range 16–69) transplanted with peripheral blood stem cells derived from HLA-matched family donors. Majority of patients received GVHD prophylaxis with cyclosporine A and methotrexate. All samples were collected one year after the allo-HSCT (median 358 days), and global metabolomic profiling analysis in serum were investigated. 31 of the 51 patients (61%) had signs of cGVHD at the one year post-allo-HSCT control. The affected organ systems were (number of patients); liver/bile duct (23), eyes (15), gastrointestinal tract (14), skin (13), mouth (10), lungs (3) and urogenital tract (1). 67% of the patients used cyclosporine A either as a prophylaxis or treatment for GVHD, and 11 patients (22%) used systemic steroid therapy as treatment for GVHD. Using the primary groupings of cGVHD and no cGVHD subjects, Random Forrest classification analysis of serum metabolites resulted in 75% accuracy in differentiating the two groups. This indicating difference in serum biochemical profiles between the two groups was quite evident, and cGVHD appeared to have profound impact on the serum metabolome. (i) First, bile acid metabolites contained four of the top 30 ranked metabolites; including glycochenodeoxycholate sulfate, taurocholate, hyocholate and glycohyocholate. All these potential markers of bile acid metabolism were increased among cGVHD patients. (ii) The metabolic signatures of inflammation associated with cGVHD were evident. A significant increase in lipid mediators such as 1-linoleoyl-GPC (18:2), 1-oleoyl-GPC (18:1), 1-palmitoleoyl-GPC (16:1)*, 12-HETE and sphingosine was exhibited by cGVHD patients. (iii) Changes in phenylalanine and tyrosine metabolism were prominent in cGVHD subjects. A significant increase in microbial flora-derived phenyllactate, phenylacetate, 3-(4-hydroxyphenyl) lactate and phenylalanine in serum of cGVHD patients could indicate alterations in microbial composition and/or activity in response to cGVHD. (iv) We detected potential evidence of proteolysis and oxidative stress in cGVHD subjects. A profound increase in proteolysis markers including was noted in the serum of cGVHD patients, indicating accelerated protein catabolism in cGVHD patients. Consistent with an oxidative stress phenotype, increased activity of γ-glutamyl cycle, was apparent in cGVHD subjects as evidenced by elevations in γ-glutamyl amino acids; e.g. gamma-glutamylglutamate, gamma-glutamylvaline, gamma-glutamylphenylalanine, gamma-glutamyltryptophan and gamma-glutamylthreonine. Similarly, a significant increase in other oxidative stress markers including 2-hydroxypalmitate, alpha-tocopherol, cysteine sulfinic acid and methionine sulfoxide was also observed. (v) Finally we detected an altered complex lipid composition in cGVHD subjects. Serum levels of several phospholipids, plasmalogens, lysolipids, lysoplasmologen and sphingolipids were elevated in cGVHD subjects, reflecting elevated membrane breakdown and remodeling activity in cGVHD subjects. The findings in this study suggest cGVHD patients may exhibit a unique metabolic signature following allo-HSCT.
Disclosure of conflict of interest: None.

O065
Lymphangiogenesis as therapeutic target during acute GVHD

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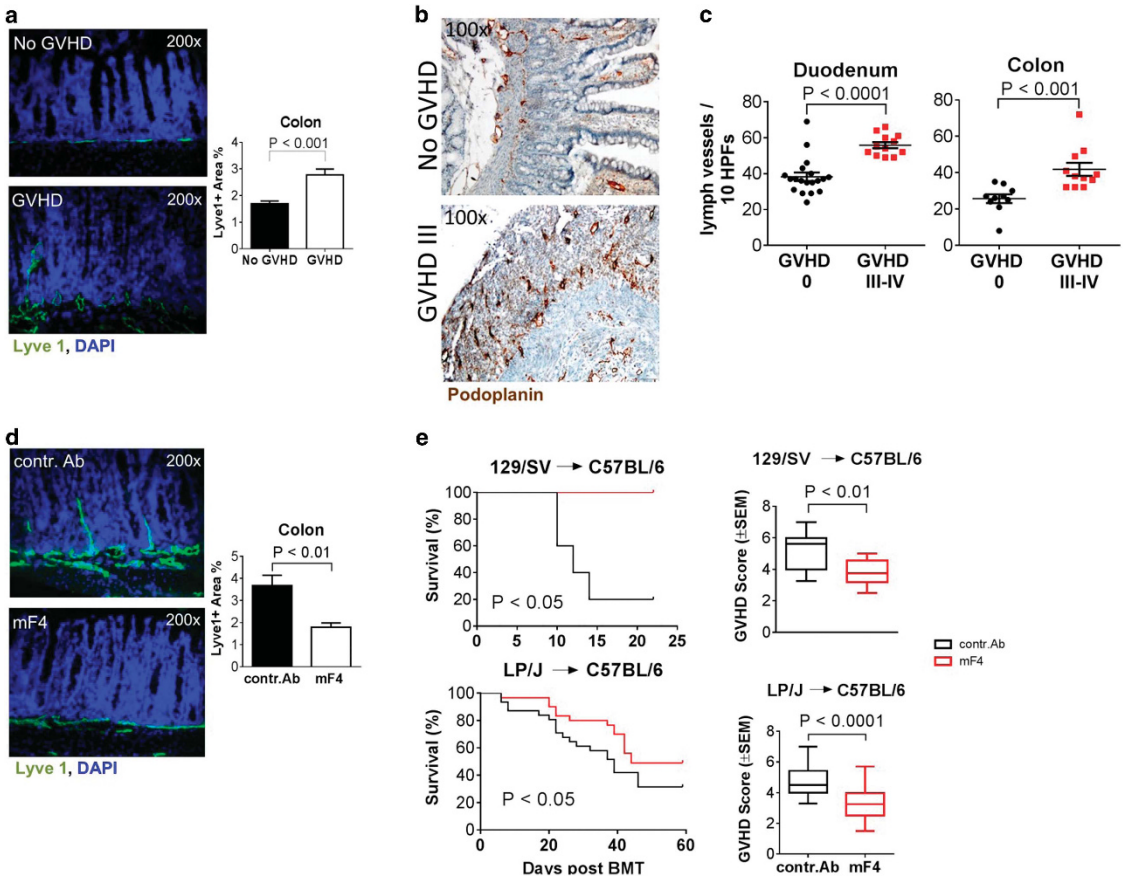
Lymph vessels play a crucial role for immune reactions in health and disease. The inhibition of lymphangiogenesis has been used to reduce tumor metastasis and to prevent graft rejections after solid organ transplantation. The role of lymphangiogenesis during allo-HSCT is unknown. We performed HSCTs in different well characterized murine acute GVHD (aGVHD) models using chemotherapy (Bu/Cy) or radiation conditioning. Target organs were immunohistologically stained and analysed for lymph vessel density and T-cell infiltration. Human duodenal biopsies ($n = 31$) and colon biopsies ($n = 21$) without GVHD vs aGVHD grade III-IV were stained against podoplanin and lymph vessels were counted. To inhibit lymphangiogenesis, allo-HSCT recipients received i.p. injections of anti-VEGFR-3 antibody or control antibody every second day from day 0 until day +16 or till organ harvesting. Target organs were analysed by immunostaining and FACS measurement. For tumor experiments, allo-HSCT recipients were injected with 5x105 tumor cells along with the bone marrow transplant in different models. Quantification was performed with Image J analysis of microscopic image data. The severity of aGVHD was quantified by histology, clinical scoring and mortality. Tumor growth was monitored by bioluminescence imaging and mortality. Our results demonstrate that in experimental mouse models aGVHD is associated to increased lymphangiogenesis in colon (Fig. 1a), the mesentery and lymph nodes. Next, we checked human colon and duodenum biopsies by histological analyses. Fig. 1b shows representative pictures of duodenum biopsies without GVHD and aGVHD grade III. Lymph vessel density was significantly increased in biopsies with aGVHD grade III-IV compared to biopsies without GVHD (Fig. 1c). We used the anti-VEGFR-3 antibody mF4-31c1 to inhibit lymphangiogenesis and found that antibody treatment was successful in reducing lymph vessel density in colon (Fig. 1d), the mesentery and peripheral lymph nodes. Further, allo-HSCT recipients treated with mF4-31c1 had significantly lower organ damage, clinical scores and mortality during aGVHD (Fig. 1e). Another effect of anti-VEGFR3 antibody treatment was improved immune reconstitution after allo-HSCT, which is most likely due to reduced bone marrow aGVHD. Finally, we checked the impact of anti-VEGFR-3 treatment on the GVT effect. We found no significant differences in tumor growth and tumor-related mortality after anti-VEGFR3 treatment vs control antibody treatment indicating preserved GVT activity. In summary, we present novel evidence that aGVHD is associated to lymphangiogenesis in intestinal lesions and in lymph nodes. Our data show that anti-VEGFR-3 treatment ameliorates lethal GVHD

Figure 1 [O065]



and identifies the lymphatic vasculature as novel therapeutic target in the setting of allo-HSCT.
Disclosure of conflict of interest: None.

O066
Regulatory B cells promote graft-versus-host disease prevention and maintain graft-versus-leukemia activity following allogeneic bone marrow transplantation

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Prophylaxis and treatment of graft-versus-host disease (GVHD) have been restricted to either functional inactivation of donor T cells using immunosuppressive drugs, or depletion of donor T cells. These strategies might lead to significant toxicities of the immunosuppressants, delayed immune reconstitution, a high rate of opportunistic infections, and increased risk of hematological malignant relapse. Regulatory B cells (Bregs) are involved in the pathogenesis of GVHD. However, whether Bregs can alleviate acute GVHD without compromising graft-versus-leukemia (GVL) effects remains unclear. Here, we evaluated the role of Bregs in acute GVHD and GVL activity in both a mouse model and a clinical cohort study including 74 patients who underwent an allogeneic stem cell transplantation. In the acute GVHD mouse model, cotransplantation of Bregs prevents onset through inhibiting Th1 and Th17 differentiation and expanding regulatory T cells. In the GVL mouse model, Bregs contributed to the suppression of acute GVHD but had no adverse effect on GVL activity. In the clinical cohort study, a higher dose of Bregs in allografts was associated with a lower cumulative incidence of acute GVHD but not with increased risk of relapse. Our data demonstrate that Bregs can prevent acute GVHD and maintain GVL effects and suggest that Bregs have potential as a novel strategy for acute GVHD alleviation.

Lethally irradiated BALB/c recipients (8 Gy) were transplanted with 5×10^6 TCD-BM derived from B6 mice ($n = 11$) or with TCD-BM plus spleen T cells ($n = 14$). Breg (3×10^6) was injected i.p. into T cell recipients at the time of transplantation ($n = 15$). (A) The survival of BMT recipients was monitored over time. (B) Recipient mice were assessed every 2 d for clinical severity of GVHD; clinical scores are shown. (C) Histopathology of skin, liver, intestine and colon of BMT recipients 14 d after transplantation (original magnification $\times 200$). Upper panel is TCD-BM + T cells + Breg group, middle panel is TCD-BM + T cells group, and lower panel is TCD-BM group. (D) Pathologic damage in the intestine and colon was assessed using a semiquantitative scoring system, as described in Materials and Methods. Results are representative of three independent experiments. The data are mean ± SEM. $^*P < 0.05$, $^{**}P < 0.01$.
Disclosure of conflict of interest: None.

Figure 1 [O066]

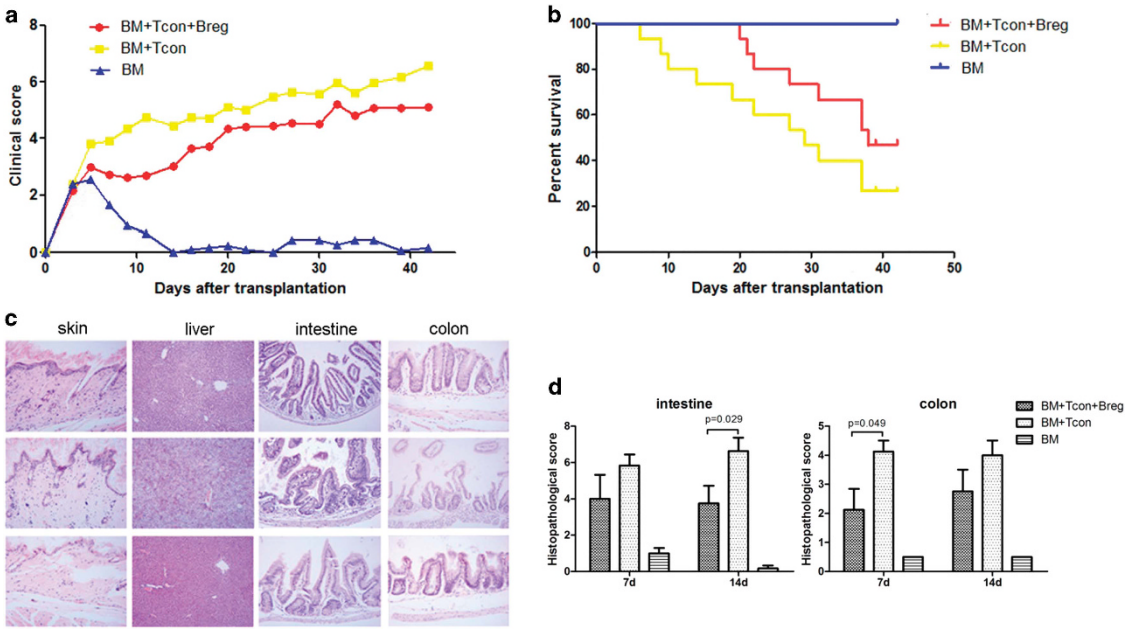

FIGURE 1. Injection of Breg ameliorates GVHD

Cellular therapies

O067

Significant association of IgG glycan structures with intensity of immunosuppression among chronic graft-versus-host disease patients: results of the NIH cohort study

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Chronic graft-*versus*-host disease (cGVHD) is a systemic allo-/auto- immune disorder and a major late complication after allogeneic hematopoietic stem cell transplantation (alloHSCT). The disease is characterized by an altered homeostasis of the humoral immune response and the production of allo-/auto-antibodies. Changes in glycosylation of immunoglobulin G (IgG), the main effector molecule of the humoral immune system, are associated with a number of autoimmune and hematological diseases. Plasma samples and clinical data were collected from patients enrolled in a cross-sectional natural history cGVHD study at the National Cancer Institute, National Institutes of Health, USA (NCT00092235) from 2004 to 2014. cGVHD was diagnosed according to the NIH Consensus criteria. IgG was isolated, deglycosylated and analyzed by hydrophilic interaction chromatography–ultra-performance liquid chromatography. Glycan chromatographic peaks (24) were directly measured and additional derived traits (57), representing composite traits such as total galactosylation, were calculated. Associations were tested using Wilcoxon test. Upon correction for multiple testing via false discovery rate results with *P*-values below 0.05 were considered significant. IgG glycome composition was analyzed in 242 cGVHD patients (43% female; median age 45 years (range 5–71)). A majority had received myeloablative conditioning (56%), had unrelated donors (58%), peripheral blood hematopoietic stem cells (79%), and history of acute GVHD (67%). cGVHD was characterized as *de novo* in 33%, progressive in 37% and quiescent in 30%, and classified as classic in 85%. Most of the patients had severe (75%) or moderate (23%) global NIH cGVHD score. cGVHD was considered to be active by clinical assessment at the time of evaluation in 50% of patients. Intensity of immunosuppression was classified as none in 19%, mild (prednisone alone < 0.5 mg/kg/day) in 8%, moderate (prednisone alone $\geqslant 0.5$ mg/kg/day, and/or any other single agent or modality) in 34%, and high (two or more agents or modalities ($\pm$ prednisone $\geqslant 0.5$ mg/kg/day) in 39% of patients. In this preliminary analysis results revealed a significant association of IgG glycan structures with different intensities of immunosuppression: none vs moderate: GP1 ($P = 0.002$) and GP3 ($P = 0.027$); and none vs high: GP1 ($P = 0.002$), GP3 ($P = 0.006$), GP18 ($P = 0.018$), GP23 ($P = 0.004$), G2 ($P = 0.044$), IGP26 ($P = 0.027$), IGP57 ($P = 0.037$) and IGP69 ($P = 0.037$). Comparisons none vs mild immunosuppression did not show significant associations with glycans. Elevated levels of agalactosylated structures (GP1 and GP3) and those with bisecting N-acetylglucosamine (GP3, IGP69) with pro-inflammatory functions were associated with increased level of immunosuppression. Sialylated (GP18, GP23, IGP26) and galactosylated (G2, IGP57) IgG glycan structures with anti-inflammatory properties showed the opposite trend; their levels reduce with increased immunosuppression (Image 1). There is a need for qualified biomarkers in cGVHD. Our preliminary study shows an association of IgG glycan structures with different intensities of immunosuppression in cGVHD patients. To clarify if such association is marker of disease activity, or consequence of treatment, or both, will require further continued study, preferentially in longitudinal post-transplant cohorts.

Disclosure of conflict of interest: None.

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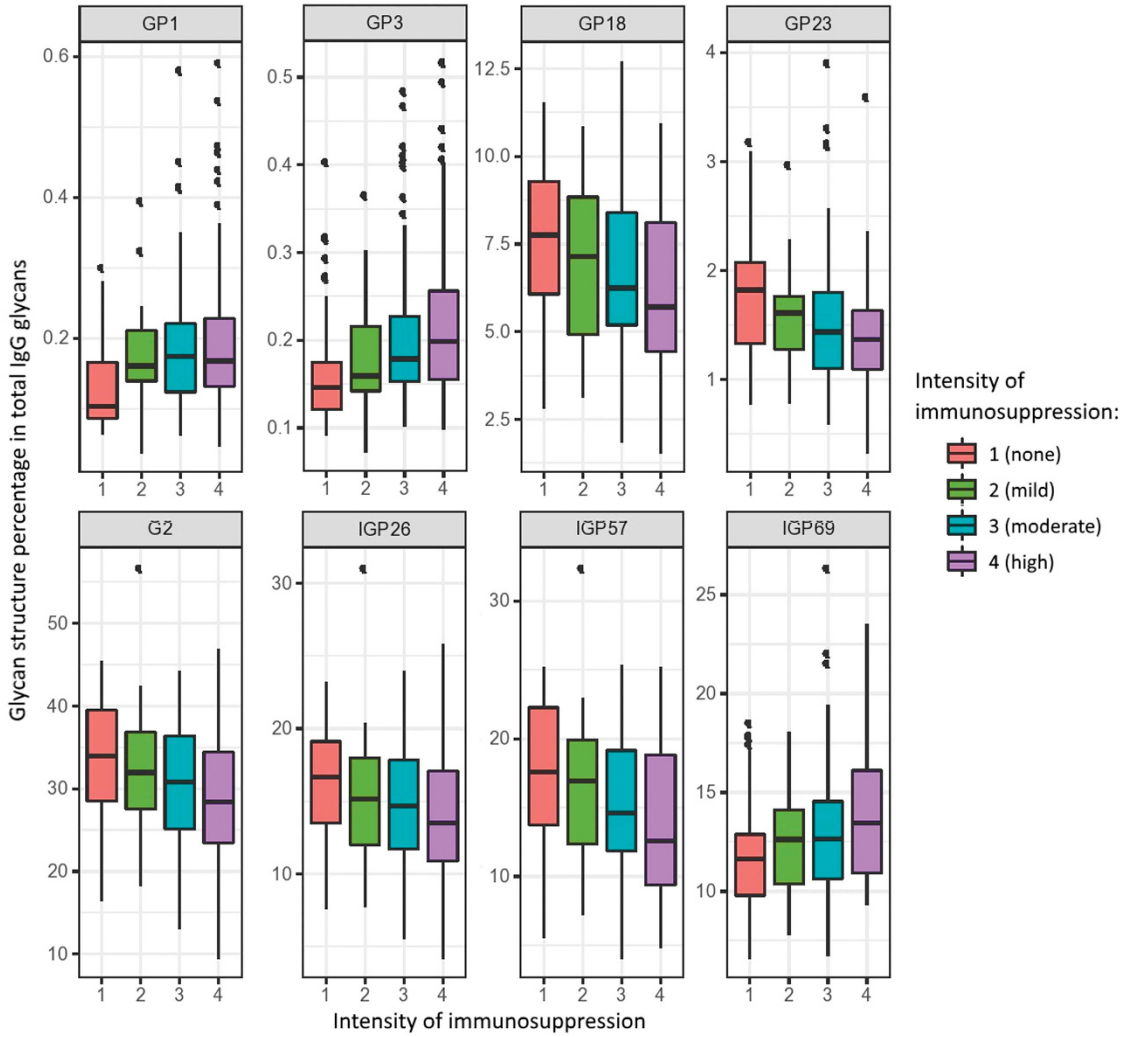
Ann NY Acad Sci 2012; **1253**: 170–80.

Figure 1 [O067]



O068
Previously published

O069
Chronic graft-versus-host-disease and B-cell reconstitution after hematopoietic stem cell transplantation in children

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Hematopoetic stem cell transplantation (HSCT) is an established therapy for many pediatric hematological diseases. Chronic GvHD (cGvHD) is the most important determinant of posttransplant morbidity and mortality. Convincing evidence suggests an important contribution of B-cells in cGvHD pathophysiology. Notably, data on B-cell reconstitution and cGvHD in children, who generally show different kinetics of immune reconstitution are lacking so far. First, in a retrospective cohort of 104 pediatric alloHSCT recipients, transplanted between 2005 and 2013, we analyzed 2151 flow cytometric immune profiles. To identify differences in lymphocyte distribution in patients with and without GvHD over time we applied hierarchial linear analysis. Second, in a prospective cohort of 74 children, we investigated more closely the distribution of B-cell subsets, serum cytokine levels including BAFF, autoantibody production and apoptosis resistance of peripheral B-cells. In the first retrospective cohort, median age was 8.9 ± 7.0 years. Incidence of cGvHD was 15%, median time to onset was 132 ± 198days. In a univariate analysis, risk factors for cGvHD were: a history of previous aGvHD, radiation-based conditioning and a donor-host sex mismatch. As expected, relapse rate was significantly lower in cGvHD patients. Hierarchial linear analysis showed that children later experiencing cGvHD had elevated T-cell frequencies during the first 180 days (63 ± 17 vs 45 ± 23% CD3 + in patients with vs without cGvHD, resp.). In contrast, B-cell frequencies were significantly lower in cGvHD patients before the onset of the disease, but elevated during and after cessation of GvHD symptoms. Interestingly, reconstitution of naïve T-cells was delayed but not abrogated in children with cGvHD, reaching a mean of 44 ± 17% of naïve T-cells in the CD4+ compartment after 2 years postHSCT (compared to 58 ± 15% in children without GvHD). A more detailed analysis of B-cell subsets in the prospective cohort revealed that the lower number of B-cells in cGvHD children were due to a defect in naïve B-cell regeneration. Memory and CD24++ CD38++ transitional B cells were expanded. We detected autoantibodies (mainly ANAs) in 88% of cGvHD children, compared to 13% in children without cGvHD. In approx. 50% of cGvHD children these autoantibodies became negative

after 2 years postHSCT. Apoptosis resistance is a mechanism also operational in pediatric cGvHD, as B-cells from cGvHD children showed reduced rates of apoptosis after 48h in culture, a phenomenon that could be induced by exogenous BAFF in a dose dependent way. In contrast to what has been reported in adults, serum BAFF levels were not elevated continuously during cGvHD, but progressively declined over time. A detailed analysis of bone marrow B-cell precursor subsets has been performed, which is currently under biometrical evaluation. Our data represent the first large and comprehensive data set on B-cell reconstitution and cGvHD in a purely pediatric cohort. We confirm patterns of B-cell dysbalance which have been described in adult cGvHD patients before. However, other features such as the preserved thymic reconstitution despite cGvHD and the rapid decline of BAFF and autoantibodies are in contrast to previous reports. Thus, the higher regenerative capacity of children seems to have a significant impact on the disturbed B-cell homeostasis in cGvHD.
Disclosure of conflict of interest: None.

O070
Extended MHC haplotype disparity level is more relevant then the level of HLA mismatch alone for the patients survival and graft versus host disease in T cell-replate HSCT from unrelated donor

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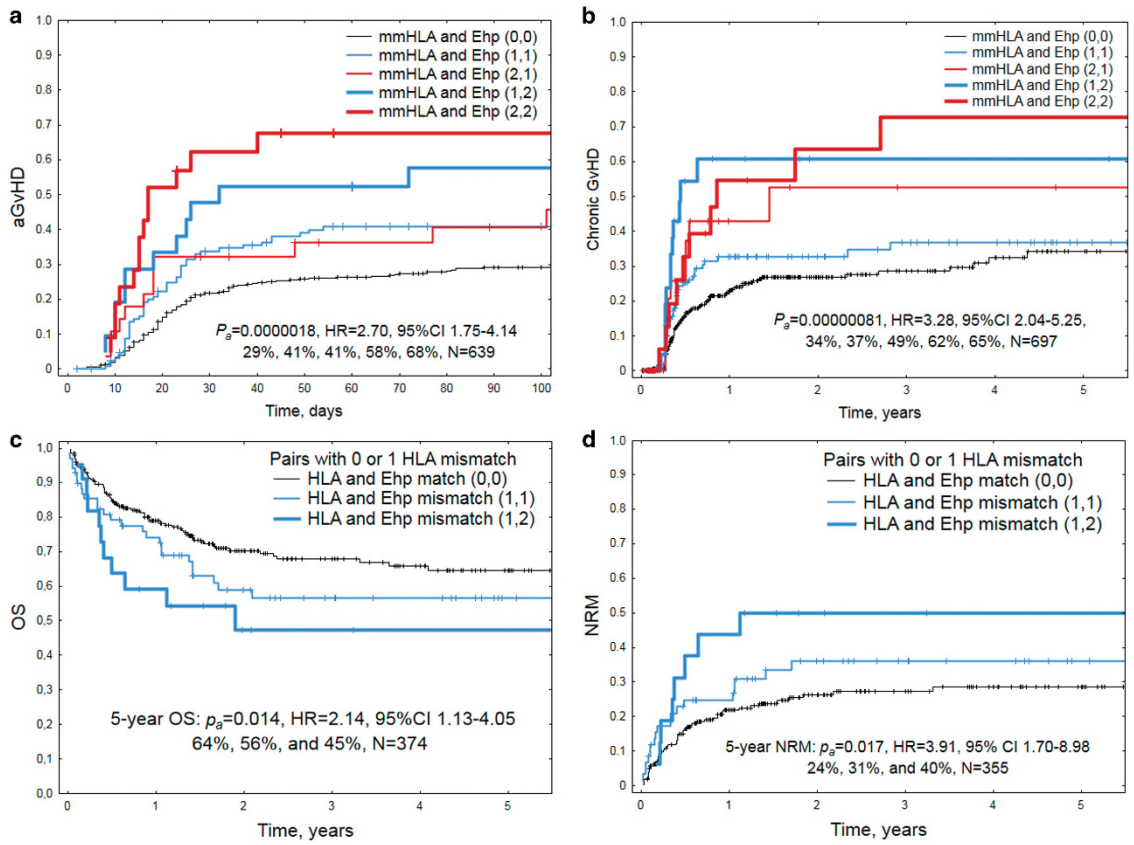
Life-threatening risks in unrelated hematopoietic stem cell transplantation (HSCT) including graft versus host disease (GvHD) and mortality are associated with HLA disparity between donor and recipient.[1] The increased risks might be dependent on disparity in not-routinely-tested multiple polymorphisms in genetically dense MHC region, being organized in two extended MHC haplotypes (Ehp). For modeling we considered that in HLA mismatched donor-recipient pairs increased frequencies of SNP disparities in MHC regions adjacent to mismatched HLA loci were discovered,[2] and extremely strong linkage disequilibrium across MHC is evolutionary selected.[3] Patients ($N = 889$) with myeloproliferative, lymphoproliferative or non-malignant diseases received T cell-replate HSCT from 2001 to 2012. We assessed the clinical role of Ehp disparity levels in donor-recipient pairs by the in silico detection of HLA allele phase mismatch using PHASE 2.1,[4] the algorithm availed for population-based prediction of donor-recipient parity and haplotype phasing. In the final study model we compared cumulative incidences of acute (a) GvHD, chronic (c)GvHD, overall survival (OS) and non-relapse mortality (NRM) in patients given HSCT from unrelated donor with 1 or 2 Ehp mismatch, in strata of unique level of HLA mismatch. In all comparisons the group with matched HLA ($N = 607$) was set as reference. Co-variate adjustments were made in multivariate stepwise Cox proportional hazard analysis with backward elimination for those independent variables correlated with outcome measures in univariate models ($P < 0.1$). We found highly significant increment of

[O070]

Figure 1. Kaplan-Meyer estimates of cumulative incidence frequency in clinical outcomes of unrelated hematopoietic stem cell transplantation depending on HLA and extended MHC haplotype disparity level.



100-day aGvHD (58% vs 41%) and 5-year cGvHD (62% vs 37%) with increasing Ehp mismatch level, even with the same level of 1 (out of 10) HLA mismatch (Figure 1A and B, blue lines). Likewise, significantly increased aGvHD (66% vs 41%) and cGvHD (65% vs 49%) has been found with increasing Ehp mismatch level when donor-recipient pairs were mismatched in 2-3/10 HLA (Figure 1A and B, red lines). In adjusted multivariate models Ehp disparity level remained independent prognostic factor for aGvHD ($p_a = 0.0000018$, HR = 2.70, CI95% 1.75–4.14), cGvHD ($p_a = 0.00000085$, HR = 3.28, CI95% 2.04–5.25), and extended cGvHD ($p_a = 0.000024$, HR = 5.38, CI95% 2.77–10.44) and HLA mismatch level alone has been excluded from these models. In group restricted to single HLA mismatch and low risk phase at transplantation patients with double Ehp disparity had worse 5-year overall survival (45% vs 56%, $p_a = 0.014$, HR = 2.14, CI95% 1.13–4.05) and non-relapse mortality (40% vs 31%, $p_a = 0.017$, HR = 3.91, CI95% 1.70–8.97, Figure 1C and D), as compared to patients with single Ehp disparity. We conclude that routinely available population based haplotype phase modeling is relevant for HSCT biology. HLA-linked factors contribute to the high morbidity and mortality in recipients given HLA-mismatched unrelated hematopoietic stem cell transplant and Ehp matching should be considered in clinical HSCT from HLA mismatched donor.

Disclosure of conflict of interest: None.

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O071

Reg3 alpha serum levels in the course of allogeneic SCT — Synergistic impact of dysbiosis and mucosal damage

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Reg3alpha (Reg3a) serum levels have been reported as biomarkers of intestinal GvHD and correlated with Paneth cell damage and poor prognosis. To further reveal the mechanisms of early Reg3alpha release in the course of allogeneic SCT, we analyzed consecutive Reg3a serum levels at admission, d0-7,14-21 and 28-42 in 75 patients (pts) receiving allogeneic BMT. Serum levels were correlated with occurrence of severe GvHD, mucositis stage2-4, use of broad spectrum antibiotics (Abs) at the time of collection and presence of microbiota damage as indicated by urinary indoxylsulfate levels (UIS). For pretransplant Reg3a levels, only concomitant use of ABs was associated with significantly increased Reg3a levels. In posttransplant samples ($n = 187$), presence of severe mucositis, use of Abs and occurrence of GvHD contributed stepwise to Reg3a release. Pts without Abs and without mucositis and GvHD had continuously low Reg3a levels with a mean of 36 (+/− 4) pg/mL, pts with either Abs or mucositis mean levels of 84 (+/− 9), pts with Abs and either Mucositis or GvHD 244 (+/− 38) ($P < .001$between each cohort). The highest levels were observed in pts on Abs with mucositis progressing to GvHD (429 (+/− 128) pg/mL. An impact of microbiota disruption was suggested by significant upregulation of Reg3alpha in pts with UIS levels below median (196 +/− 41 pg/mL) vs 42 +/− 9 pg/mL in pts with high UIS levels (P 0.009). Multivariate logistic regression revealed, that all factors, severity of mucositis and of GvHD as well as use of Abs independently contributed to increased Reg3a levels. Our data indicate a more complex regulation of Reg3a, which seems to be activated in relation to microbiota disruption and released as a consequence of severe mucosal and Paneth cell damage. Further studies are needed to evaluate the exact causal relation and the initiating role of microbiota disruption.

[O071]

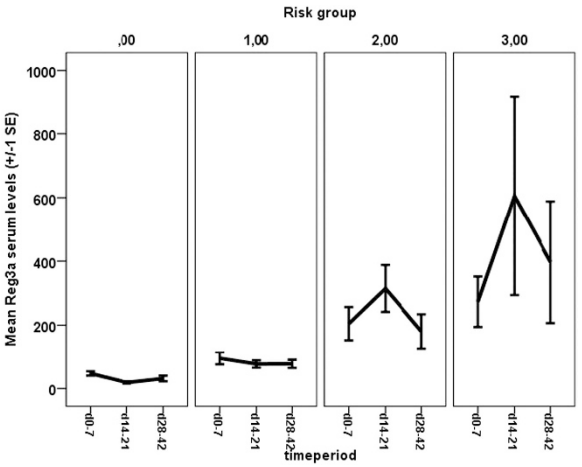

Figure 1: Mean Reg3a levels in different risk groups: 0 = no Abs, no mucositis, no severe GvHD; 1 = either ABs or mucositis, 2 = ABs with either GvHD or mucositis, 3 ABS with GvHD and mucositis. $P < 0.000$ between each group for 0,1,2; P 0.04 for group 2 vs 3.

Disclosure of conflict of interest: None.

O072

Recipient rs17281995 (CD86) and rs2069727 (IFNg) single nucleotide polymorphisms are associated with a lower risk of graft versus host disease in patients receiving an allogeneic stem-cell transplant from a related donor after a reduced intensity conditioning regimen: A multicenter experience

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Graft versus host disease (GVHD) is the main cause of morbidity and non-relapse mortality after allogeneic hematopoietic stem cell transplantation (allo-SCT), even in HLA-identical sibling donors. Many efforts have been made trying to identify particular single nucleotide polymorphisms (SNPs) to elucidate the risk of acute GVHD (aGVHD) before transplant to personalize the procedure and improve results. However, there is little information related to allo-SCT with reduced intensity conditioning (RIC). We included paired recipient-donor samples from 274 RIC allo-SCT patients diagnosed of AML ($n = 88$), NHL ($n = 54$), MDS ($n = 52$), MM ($n = 28$), CLL ($n = 25$), HL ($n = 15$), or others ($n = 12$) in four centers in Spain. Flu-Bu conditioning was used in 56% of the transplants while Flu-Mel in 43%. Clinical characteristics were not significantly different between centers. We analyzed 52 SNP from 44 different gene loci, selected from those previously described related to GVHD in allo-SCT, known to be involved in the immune response and/or autoimmune diseases, or those with a potential role in donor/recipient interaction. SNP Genotyping was carried out by Sequenom Mass ARRAY platform (Sequenom, San Diego, CA). The analyses were carried out taking into

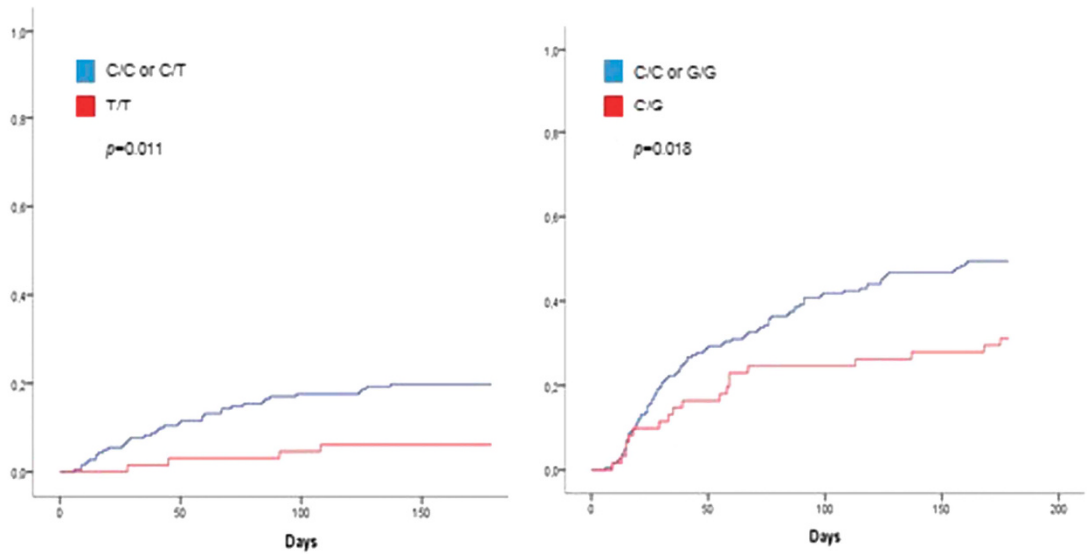
account the receptor, donor and both profiles. Allele frequencies were estimated by direct counting and compared between groups using Fisher's test. *P*-value < 0.05 was considered to be statistically significant. Log-rank analysis was used to compare differences between survival curves. Patients' characteristics are shown in Table 1. Cumulative incidence of aGVHD at day 200 was 56%, grades II-IV in 47% and III-IV in 18% in our series, while cGVHD at 4 years was 63%. With a median follow up for alive patients of 44 months, overall survival was 52.1%, while event free survival at 4 years was 43%. The main cause of death was disease relapse/progression (18.1%). Transplant related mortality (TRM) was 21%, and GVHD related mortality was 11.6%. In the univariate analysis, patients with genotype C/G in rs17281995 (CD86) showed a lower aGVHD (39% vs 60%, $P = 0.01$), and aGVHD grades II-IV (31% vs 51%, $P = 0.007$). Genotype T/T in rs2069727 (IFNg) in recipients was associated with lower aGVHD grade (III-IV 5% vs 22%, $P = 0.008$), and lower TRM (13% vs 25%, $P = 0.036$). Other variable influencing aGVHD grades II-IV was Flu-Mel conditioning (54% vs 40%, 0.028). In the multivariate analysis, rs17281995 (CD86) C/G genotype (HR 0.4, 95% CI: 0.22–0.75), Flu-Mel conditioning (HR 1.7, 95% CI: 1.1–2.7), rs2069727 (IFNg) T/T genotype (HR 0.6, 95% CI: 0.35–0.99) and Tacro+Rapa GVHD prophylaxis (HR 1.7, 95% CI: 1.1–2.7), significantly associated to aGVHD grades II-IV. The rs2069727 (IFNg) T/T genotype (HR 0.31, 95% CI: 0.09–1.0), and the

[O072]

Table 1. Patients basic characteristics and comparison between centers

	Median/%	p value
Age	57 years	0.49
Diagnostic	AML (32%) NHL (20%) MDS (19%) Others (29%)	0.5
Disease status risk	High (21%) Intermediate (39%) Low (40%)	0.3
Conditioning regimen	Fludarabine-Busulfan (56%) Fludarabine-Melphalan (43%) Others (1%)	0.2
GVHD prophylaxis	Cyclosporine -Methotrexate (73%) Tacrolimus-Sirolimus (22%) Others (5%)	0.2
aGVHD location	Skin (29%) Gastrointestinal (38%) Liver (8%)	0.3
cGVHD	63%	0.3

Graphic 1. Left, IFNG rs2069727 aGVHD grades III-IV cumulative incidence. Right, CD86 rs17281995 aGVHD grades II-IV cumulative incidence.



rs17281995 (CD86) C/G genotype (HR 0.32, 95% CI: 0.09–1.1) were the only variables showing a trend to be associated to aGVHD grades III-IV. There was no relation between rs17281995 (CD86) and rs2069727 (IFNg) polymorphisms and incidence/severity of cGVHD or OS. The rs17281995 (CD86) and rs2069727 (IFNg) donor genotypes did not influence allo-SCT outcome. The present data suggest an association between rs1781995 (CD86) and rs2069727 (IFNg) polymorphisms with incidence and severity of aGVHD. Confirmation in larger series is required. FUNDINGS: PI12/02361, RTICC (RD12/0036 grupos 0052, 0069 y 0071), BIO/SA60/13 e Innocampus (CEI-2010- 1-0010).
Disclosure of conflict of interest: None.

O073
Impact of graft-versus-host disease on outcomes after pediatric single cord blood transplantation: a retrospective analysis from the JSHCT GVHD Working Group

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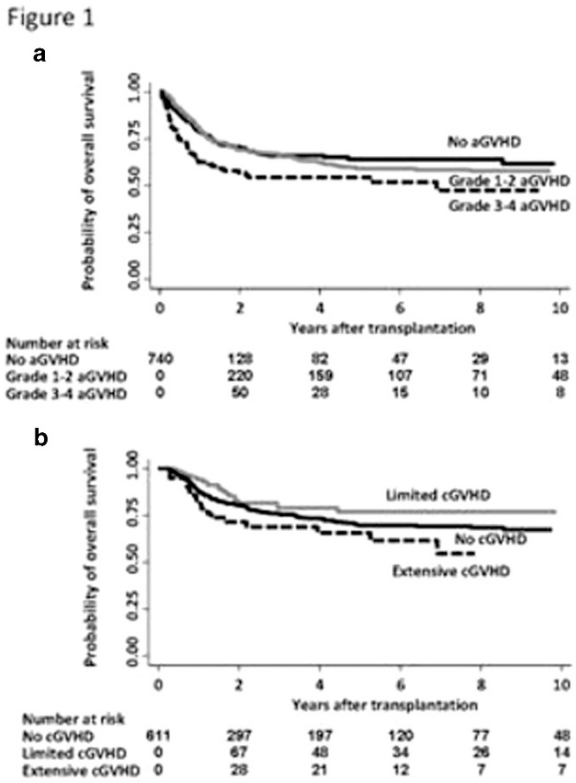
The effect of graft-versus-host disease (GVHD) on transplant outcomes after cord blood transplantation (CBT) is not yet fully understood. We recently reported that mild acute GVHD (aGVHD) or chronic GVHD (cGVHD) was associated with not only a low risk of relapse but also a low risk of non-relapse mortality (NRM) and provides a survival benefit in adult single CBT (Kanda J, *et al*. Leukemia 2016). However, the number of total nucleated cells and T cells per recipient weight in cord blood differs considerably between pediatric and adult patients, which may lead to different effects of GVHD on transplant outcomes. Therefore, using registry data from the Japan Society for Hematopoietic Cell Transplantation (JSHCT), we analyzed the impact of GVHD on outcomes in pediatric single CBT. We included pediatric patients, aged 0 to 15 years, with acute leukemia or myelodysplastic syndrome who underwent their first CBT ($n = 740$) between 2000 and 2014. The effect of aGVHD on outcomes was analyzed after adjusting for other significant variables among all engrafted patients, and the effect of cGVHD was analyzed among the engrafted patients who survived without relapse for at least 100 days. The occurrence of GVHD was treated as a time-dependent covariate. The median age of the recipients at transplant was 5 (range, 0–15) years. Two-thirds of the patients had standard-risk disease. Calcineurin inhibitor and methotrexate were used in 83% of patients. Only single unit grafts were included in the cohort. Fifty percent received a UCB unit containing more than 5.0 × 107/kg TNCs. Acute GVHD of grades I-II (GI-II) and III-IV (GIII-IV) occurred in 56% and 14% of the patients, respectively. The occurrence of GIII-IV aGVHD was associated with a higher risk of NRM (hazard ratio (HR) 4.07, $P < 0.001$) when compared with no aGVHD. GI-II aGVHD was not associated with NRM. The occurrence of GI-II or GIII-IV aGVHD was not associated with a low relapse risk. These resulted in no survival benefit of GI-II aGVHD (HR 1.04, $P = 0.789$) and an adverse effect of GIII-IV aGVHD (HR 1.68, $P = 0.007$; Figure 1a). Limited and extensive chronic GVHD occurred in 16% and 7% of the evaluable patients, respectively. The occurrence of limited cGVHD (HR 0.82, $P = 0.410$) or extensive cGVHD (HR 0.62, $P = 0.199$) was not associated with a low relapse risk as compared to no cGVHD. The occurrence of limited cGVHD was marginally associated with a lower risk of NRM (HR 0.16, $P = 0.077$), whereas the occurrence of extensive cGVHD was associated with a higher risk of NRM (HR 2.69, $P = 0.027$). These resulted in the significant association between limited cGVHD and a low risk of overall mortality (HR 0.60, $P = 0.045$), but no significant association between extensive cGVHD and overall mortality (Figure 1b). Consistent with the observations in adult cohorts, our results indicate that severe aGVHD should be prevented because of its association with high overall mortality and NRM. However, unlike adult cohorts, mild acute GVHD provides no overall benefit for relapse, NRM, and overall mortality. Consistent with adult cohorts, mild cGVHD may be beneficial for survival, probably due to the low risk of NRM when compared to no cGVHD. Severe cGVHD is associated with a higher risk of NRM.
Disclosure of conflict of interest: None.

Figure 1 [O073]



O074
Interleukin-6 is an early biomarker for acute GvHD and survival after allogeneic transplant

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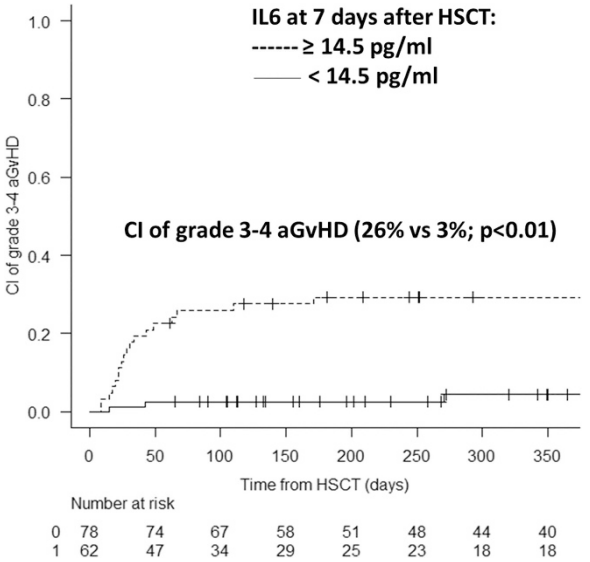
Acute graft-versus-host disease (aGvHD) is a leading cause of transplant-related mortality (TRM) after allogeneic HSCT (allo-HSCT). We conducted a prospective observational study to ascertain the potential of interleukin-6 (IL6), measured in patient blood samples before conditioning and 7 days after allo-HSCT, in predicting aGvHD, TRM and survival after transplant. We collected samples from 151 consecutive patients (93 males; median age 52) who underwent allo-HSCT at our institution between April 2014 and June 2016. Most patients were affected by myeloid malignancies (AML = 50%, MDS = 14%). Revised DRI (Armand *et al.*) was low-intermediate in 48%, high in 45% and very high in 7% of patients. Most patients (88%) received PBSC. Conditioning was myeloablative in 118 patients. Stem cell donors were unrelated ($n = 59$), family haploidentical ($n = 63$), HLA-identical sibling ($n = 29$). Post-transplant GvHD prophylaxis was PT-Cy in 96 patients, ATG in 31 patients, both agents in 17 cases. Sirolimus and MMF were used as additional prophylaxis. All patients included in this analysis were tested for IL6 baseline and at day +7 after HSCT. Median follow-up on survivors was 14 months (range 2–31). The 100-d cumulative incidence (CI) of grade 2-4 aGvHD was 26% (14% grade 3-4 aGvHD). The median day of aGVHD onset was 30 days. The 100-d CI of TRM was of 4% with a 1-year OS of 72%. ROC analysis identified a threshold of 2.5 pg/mL for IL6 baseline levels as predictor for 100-d TRM (AUC 0.83; sens 83%, spec 67%, $P = 0.006$). IL6 concentrations maintained diagnostic utility also in patients experiencing grade 3 or 4 aGvHD, when measured 7 days after HSCT: in this setting, ROC analysis allowed us to identify a threshold of 14.5 pg/mL (AUC 0.75; sens 90%, spec 65%, p 0.001). Moreover, we divided patients into groups according to whether biomarker concentrations were above (high) or below (low) the identified thresholds. At baseline, IL6 levels above 2.5 pg/mL were significantly associated with a higher 100-days CI of TRM (10% vs 1%; $P < 0.01$) and a worse 1-year OS (52% vs 86%; $P < 0.01$). When measured 7 days after HSCT, IL6 levels equal or superior to 14.5 pg/mL identified patients with a higher 100-days CI of grade 2-4 aGvHD (32% vs 18%; p 0.05), and grade 3-4 aGvHD (26% vs 3%; $P < 0.01$). Moreover, higher IL6 concentrations at day +7 correlated with higher TRM (7% vs 1%; p 0.06) and worse 1-year OS (52% vs 87%; $P < 0.01$). Interestingly, IL6 concentrations were able to better stratify OS in patients with the same DRI class. By multivariate analysis (adjusting for age, DRI, Sorror comorbidity index, type of donor, source of stem cells, conditioning regimen and GvHD prophylaxis) pre-transplant IL6 concentrations were significantly associated to grade 2-4 aGvHD (HR 2.2, 95% CI 1–4.8; p 0.03), grade 3-4 aGvHD (HR 3.8, 95% CI 1.1–13; p 0.03), TRM (HR 4.2, 95% CI 1–17.2; *P* 0.04), and OS (HR 2.8, 95% CI 1.3–6.4; p 0.01); post-transplant IL6 levels correlated with grade III-IV aGvHD (HR 9.1, 95% CI 1.7–50; *P* 0.01), and OS (HR 3.5, 95% CI 1.4–8.7; $P < 0.01$). In this prospective observational study, measurement of plasma IL6 resulted a valuable biomarker in predicting the risk of aGVHD and TRM, providing a window for additional prophylactic or preemptive strategies, and potentially improving the final outcome of allo-HSCT. These findings should be validated in a multicenter study.

Figure 1 [O074]



Disclosure of conflict of interest: None.

GVHD (clinical-1)

O075
Nervous system regulates thymic regeneration after immune injuries

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Paradoxical to its importance as the main organ responsible for generating T cells throughout life, the thymus is extremely sensitive to negative insults including cytoreductive chemo- or radiation therapy, infections and GVHD. Insufficient recovery of thymic function has been directly correlated with increased risk of opportunistic infection and poor clinical outcome in transplanted recipients. Therefore, strategies to regenerate thymic function and immune reconstitution represent a significant unmet clinical need. While multiple paracrine and endocrine pathways have been shown to regulate thymic function, the regulatory role of the peripheral nervous system remains largely unknown. Given its previously described role in modulating bone marrow hematopoiesis after damage, we sought to investigate if the sympathetic nervous system (SNS) mediated similar effects on thymic regeneration after immune insults. We observed that thymic concentration of epinephrine and norepinephrine was increased in mice after sub-lethal total body irradiation (SLTBI), reaching a maximum concentration at day 4 and returning to its baseline levels at day 14 post-SLTBI. Daily administration of epinephrine or norepinephrine directly resulted in a significant decrease in thymic regeneration post-SLTBI. We identified that SNS-related negative regulation of thymic recovery occurs specifically through an α1A/D dependent mechanism, given that administration of tamsulosin, an α1A/D specific inhibitor was able to enhance thymic cellularity post-SLTBI, while no effect was observed after the administration of pan-α and pan-β adrenergic antagonists. Besides the autonomic nervous system, sensory nociceptive C-fibers have been shown to pose a strong peripheral input to the immune system, mainly via the

transient receptor cation channels TRPV1 and TRPA1, which among others, serve as receptors for multiple endogenous and exogenous reactive ligands. We obsverved that whithin the thymus TRPA1 was highly expressed in the medulla and sparsely in the cortex, mainly representing intraparenchymal small nerve fibers. Nerve fibers were also found to adjacent to vessels, while interestingly thymic endothelial cells expressed TRPA1 as well. On the other hand, TRPV1 expression was weak and primarily localized at the subcortical area. While thymic cellularity was unimpaired in a TRPV1 KO setting, TRPA1 KO mice exhibited significantly lower thymic cellularity at baseline and after SLTBI, suggesting that TRPA1 represents a critical factor for organ regeneration after insults. Consistenlty, administration of cinnamaldehyde and allyl-isothiocyanate, two potent, exogenous TRPA1 agonists, significantly enhanced thymic regeneration post-SLTBI. Our study attributes for the first time functional roles to distinct peripheral nervous system compartments in the context of endogenous thymic regeneration. Most importantly, the pharmacological modulation of negative SNS-imposed or positive TRPA1/nociceptive-imposed signals represents a novel therapeutic approach to enhance thymic regeneration and immune recovery in immunocompromised patients.
Disclosure of conflict of interest: None.

O076
Prospective multicenter pilot phase II Study of sequential infusion of donor lymphocyte infusion (DLI) and Cytokine Induced Killer (CIK) cells for patients with relapse after allogeneic transplantation

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Disease relapse is a major cause of mortality following allogeneic hematopoietic stem cell transplantation (alloHSCT)

Figure 1 [O076]

Figure 1A. Progression Free Survival by relapse type

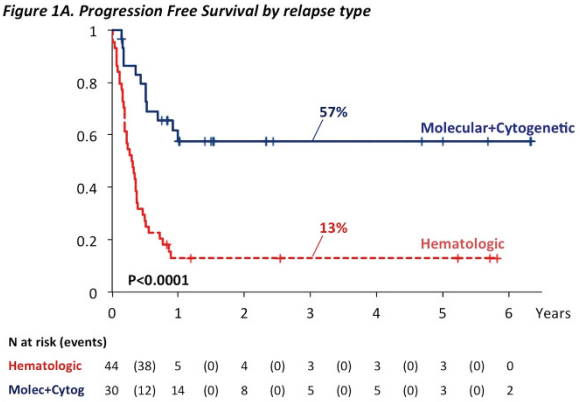
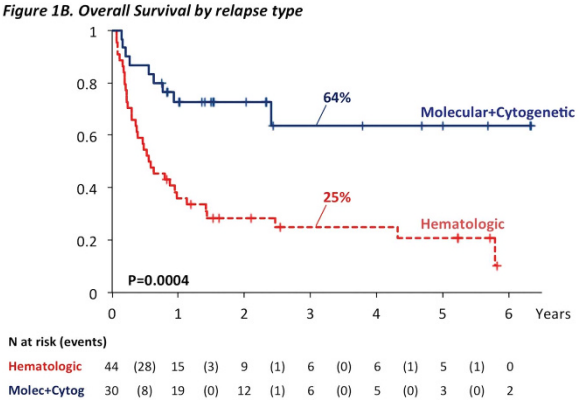


Figure 1B. Overall Survival by relapse type



for hematologic malignancies. When allogeneic transplant fails, donor lymphocyte infusion (DLI) is one of the main clinical option, but this treatment is complicated by a high risk of acute graft-versus-host disease (GvHD). Donor's Cytokine Induced Killer (CIK) cells have shown Graft versus Leukemia (GvL) activity with little GvHD and, therefore, may represent an ideal alternative candidate to treat post-transplant relapse. We report the final results of a phase II multicenter pilot study, whose objective was to evaluate the safety and efficacy of sequential administration of donor derived unmanipulated DLI and CIK cells in patients with recurrent hematologic cancers after alloHSCT. Seventy-four patients relapsed after matched related ($N=42$) or unrelated donor ($n=32$) alloHSCT, were enrolled in the study. This phase II multicenter study was authorized by Istituto Superiore di Sanità, as for Advanced Therapeutic Medicinal Product (ATMP) regulations, and approved by the Agenzia Italiana del Farmaco (AIFA). The trial was registered as EUDRACT number 2008-003185-26; ClinicalTrial.gov: NCT01186809. We evaluated 74 patients (including 16 children and 58 adults) treated with sequential administration of unmanipulated donor lymphocytes infusions (DLI) followed by three infusions of donor derived CIK cells. Two patients died before starting therapy due to disease progression, 9 patients died during the DLI administrations due to disease progression, 1 patient developed aGvHD and was not further treated with CIK cells and 1 patient was withdrawn from the protocol. Therefore, 61 patients received at least one CIK administration and 43 completed study protocol. The first 12 patients were treated with increasing numbers of CIK cells, in groups of three patients per dose level. Since dose limiting toxicity (DLT) was never observed (acute GvHD of grade IV), the highest dose planned (5×10^6/kg, 5×10^6/kg and 10×10^6/kg) was then administered to all patients. As per protocol, clinical response was determined 100 days after the last CIK administration and the study was analyzed on an intent to treat basis. Acute GvHD was observed in a total of 12 patients (16%): grade 1-2 ($n=7$) and 3-4 ($n=5$). During follow up, chronic GvHD was observed in 11 patients (15%) (4 mild, 5 moderate and 2 severe). An early death occurred in 2 (3%) patients, progression of disease was observed in 41 (55%) patients, a stable disease in 8 patient (11%), a complete remission in 20 (27%) and a partial remission in 3 (4%), for an overall response rate of 31%. Progression free survival (PFS) and overall survival (OS) were significantly associated ($P<0.0001$) with the type of relapse since at 3 years it was 13% and 25% vs 57% and 64 % for patients enrolled due to a hematologic vs a molecular/cytogenetic relapses, respectively (Figure 1 A-B). By multivariate analysis, the type of relapse and a short time from alloHSCT to relapse (<6 months) were the significant predictors of survival (HR 3.37, 95%CI 1.59–7.16 and 2.1, 95% CI 1.10–3.90). Our study shows that administration of CIK cells is feasible in patients with recurrent hematologic cancer after alloHSCT with a relatively low toxicity in terms of GvHD. Particularly in the setting of the molecularly relapsed patients, long-term survival can be achieved.
Disclosure of conflict of interest: None.

O077
Rapid process for the generation of functional chimeric antigen receptors against novel targets

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Chimeric antigen receptor (CAR) T cells bind to surface antigens via a single-chain variable fragment (scFv) and elicit potent anti-tumor activity. To our knowledge, no CAR development platform exists that allows the rapid generation, screening, biochemical characterization, and identification of functional CAR constructs against novel targets integrating multiple state-of-the-art high-throughput technologies. We

have established a rapid process for the development of functional CARs against novel targets using fully human antibody phage display, compatible vector systems for bacterial and mammalian expression, as well as high-throughput functional and biochemical characterization assays. The individual steps of our process were validated using different tumor antigens and we here describe the complete workflow for one model antigen expressed on multiple myeloma cells. Using two rounds of panning selections from a large naïve fully-human antibody phage display library we generated a pool of scFvs that bind to the model antigen. After confirming the reactivity of the polyclonal phage population by time-resolved fluorescence assay we generated multiple monoclonal binders in scFv, scFv-Fc and CAR formats. In addition to determining antigen binding of the soluble antibody formats we established a high-throughput flow cytometry assay simultaneously determining CAR surface expression and antigen binding. Furthermore, we adapted protocols for small-scale lentiviral transduction and expansion of primary CAR T cells followed by a sensitive, high-throughput luciferase-based cytotoxicity assay using multiple CAR candidates. Finally, in collaboration with Wasatch Microfluidics we performed high-throughput surface plasmon resonance measurements and epitope binning of candidate binding domains. After two rounds of antibody phage selections we obtained 1,323 scFv binders. The subsequent bacterial expression of 163 soluble scFv clones yielded 23 unique monoclonal binders. Surprisingly, a comparison of these 23 binders in different formats showed that none of the traditional screening formats, including soluble scFv and scFv-Fc fusion constructs, correlated with CAR binding. CARs showing high combined expression and antigen binding were found to have affinities in the low nanomolar range (18.4–22.9nM). They also displayed significant cytotoxicity of myeloma cell lines spontaneously expressing the antigen (53-79% killing at an effector:target-ratio of 10:1), but healthy cells expressing lower levels of the antigen were relatively spared. Importantly, in a murine xenograft model of multiple myeloma we found that our newly generated CAR T cells specifically killed tumor cells without overt toxicities. We show that the process that we have developed allows the rapid generation of multiple candidate scFvs, screening, as well as functional and biochemical characterization of CARs targeting novel antigens within 2 months. Determining key properties of binding domains, which have been shown to shape CAR T cell function and phenotype, during initial screening enables the rational selection of CAR candidates prior to low-throughput downstream analyses. In addition, our data suggest that the common strategy of reformatting existing monoclonal immunoglobulins into CAR binding domains, while fast and usually reliable, may not produce ideal CAR constructs.

Disclosure of conflict of interest: AM is an employee of Wasatch Microfluidics. The remaining authors declare no conflict of interest.

O078

The infusion of multi-antigen specific T-cell products for the prevention of viral infections after T-cell depleted allogeneic stem cell transplantation

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Viral infections and disease relapse are major complications in the interval between T cell depleted allogeneic stem cell transplantation (TCD alloSCT) and donor lymphocyte infusion (DLI). The infusion of selected donor T cells can be an effective method to restore anti-viral and anti-tumor immunity early after TCD alloSCT. In this phase I/II study (EU FP7 T control) the feasibility and safety of the generation and preemptive administration of donor T cells targeting CMV, EBV and AdV to restore viral immunity together with T cells targeting tumor associated antigens (TAA) and minor histocompatibility antigens (MiHA) to boost the graft versus leukemia (GVL) response is evaluated. Efficacy is assessed by in-vivo appearance/expansions of target Ag-specific T cells in the peripheral blood detected with direct tetramer staining, and the effect on viral reactivation and disease relapse until DLI was given 20 weeks later. HLA-A*02+ patients treated for a hematological malignancy with an HLA-matched TCD alloSCT from a CMV+ and/or EBV+ donor were included. 6-8 weeks after alloSCT, T cells directed against HLA-A*02-restricted peptides of CMV, EBV and AdV, and the TAA NY-ESO-1, WT-1, RHAMM, PRAME and proteinase 3 were isolated under GMP conditions in 1 day, using the reversible streptamer-nanobead technology by cliniMACS selection out of the naïve and memory T cell compartment from 2*10^9 donor PBMC. Depending on the patient/donor HLA-typing, additional streptamers targeting viral peptides in HLA-A*01, A*24, B*07, or B*08 were added to the procedure as well as the HLA-A*02/HA-1h streptamer in case of MiHA disparity in the GVL direction. At the moment of the interim-analysis of this trial, 21 multi Ag-specific T cell products have been generated that consisted of 0.4-26*10^6 cells with purities of 46-99% target Ag-specific T cells within the T cell compartment. 19 products were administered without infusion related complications or GHVD; 2 patients experienced GVHD at the day of infusion and did, therefore, not receive their product. 14 patients were analyzed at this stage. All 14 donors were EBV + and AdV+ and 5/14 donors were CMV+. All products consisted for 99% of virus-specific memory T cells, while the remaining 1% included TAA, MiHA and naïve virus-specific T cells. No product-related adverse events were reported. 13 patients completed follow-up; 1 patient died during follow-up. 2 patients showed disease relapse before DLI without obvious coinciding expansion of TAA or MiHA-specific T-cells. More sensitive techniques may be needed to visualize these cells. None of the patients experienced AdV reactivations, although in 1 patient AdV-specific T cells appeared after infusion of our T cell product. In 6 patients CMV reactivations were observed. 2 patients received the product from a CMV+ donor and 4 patients from a CMV- donor. In all 6, CMV-specific T cells were detected and CMV was cleared. 3 patients experienced an EBV reactivation. In 2 patients, the virus was cleared without obvious expansion of EBV-specific T cells. 1 patient required treatment for an EBV-PTLD; ultimately EBV-specific T cells appeared and the virus was cleared. In conclusion, we have shown that the streptamer-nanobead based generation and adoptive transfer of donor-derived multi Ag-specific T cell products is feasible and safe and can be used as a strategy to prevent viral infections between TCD alloSCT and DLI.

Disclosure of conflict of interest: None.

O079

CD19 targeted CAR-T therapy versus chemotherapy in re-induction treatment of refractory/relapsed acute lymphoblastic leukemia: results of a case-controlled study

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CD19 targeted CAR-T cells (CART19s) have potent anti-leukemia activities in patients with refractory/relapsed acute lymphoblastic leukemia (R/R ALL). This case-controlled single center study was designed to determine the safety and efficacy of CART19 therapy for R/R ALL in contrast to chemotherapy. A matched case-controlled study, in which each patient treated with CART19s (CART19 group, 22 patients) was paired with 3 control subjects selected among R/R ALL patients treated with conventional or salvage chemotherapy (chemotherapy group), was performed. Patients relapsed after allogeneic hematopoietic stem cell transplantation (allo-HSCT) received donor lymphocyte infusion after chemotherapy if donor lymphocytes

were available. Patient characteristics were shown in Figure 1A. The complete remission rate was significantly higher in CART19 group than in chemotherapy group (90.5% (95% confidence interval (CI), 76.2–99.9) VS 38.1% (95% CI, 32.0–44.2), $P < 0.001$). For patients relapsed after allo-HSCT and chemotherapy, the CR rates in the 2 groups were 100% VS 48.0% ($P = 0.0099$) and 84.6% VS 30.8% ($P = 0.0432$), respectively. Among patients who had complete remission, a higher percentage in CART19 group had results below the threshold for minimal residual disease (0.01% marrow blasts) (100% vs 25.0%, $P < 0.001$). In the survival analysis, the overall survival rate at 12 months was significantly higher in CART19 group than in chemotherapy group (51.5% vs 12.7% ; hazard ratio, 0.576 (95 % CI, 0.09839 to 0.5865); $P = 0.048$) (Figure 1B). 22.2% and 46.7% post-transplant patients in CART19 group and chemotherapy group complicated with graft versus host disease (GVHD) ($P = 0.241$) but for patients who obtained complete remission, 22.2% and 75.0% patients complicated with GVHD ($P = 0.0348$) in the 2 groups respectively. Pancytopenia was another kind of toxicity. For patients achieved complete remission, the median duration of absolute neutrophil count less than 500/μL and absolute platelet count less than 20000/μL were longer in CART19 group than in chemotherapy group (22.6 days (4-35 days) vs 16.3 days (8-19 days), $P = 0.021$) and (32.1 days (4-39 days) vs 18.8 days (10-23 days), $P = 0.023$), respectively. CART19s induced high complete remission rate both for relapsed patients after allo-HSCT and after chemotherapy in contrast to conventional or salvage chemotherapy. CART19s also induce less incidence of GVHD but longer duration of pancytopenia. Our data suggest that CART19s could provide a novel therapeutic approach for patients with R/R ALL.

Disclosure of conflict of interest: None.

Figure 1 [O079]

a

Characteristics	CART19 group (22)	Chemotherapy group (66)	P value
Age			>0.05
Median (range)	41.3(8-57)	42.8 (15-59)	
Male sex--% (No.)			>0.05
No. of previous induction therapies			
1	4	13	
2	6	18	
More than 2	12	35	
Duration of first remission			>0.05
<12 months	17	49	
>=12 months	5	17	
Previous stem cell transplantation	9	27	>0.05
Bone marrow blasts			>0.05
<50%	5	16	
>=50%	17	50	
Karotype--% (No.)			>0.05
Normal	12	45	
Ph positive	6	10	
T (4,11)	2	5	
Other abnormalities	2	6	

b

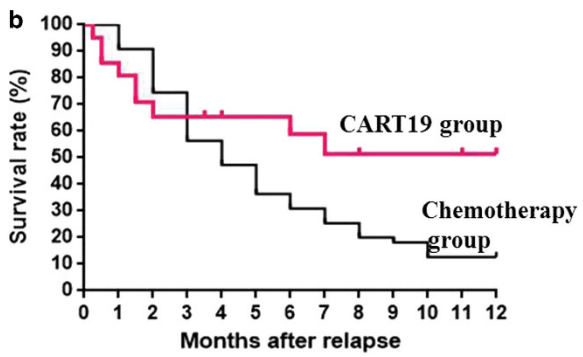

Figure 1 A, Patient baseline characteristics. B, overall survival rate in 2 groups

O080

Five years of therapy with donor and 3rd party derived EBV and CMV specific cytotoxic T cells – safety after more than 1,000 infusions

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At Memorial Sloan Kettering Cancer Center (MSK), GMP grade EBV and CMVpp65 viral specific cytotoxic T lymphocytes (CTLs) have been produced for use on specific protocols since 1994 (EBV) and 2005 (CMV), respectively. Experience with adoptive cellular therapy has accelerated over the last 2 decades and we anticipated that this will result in more appropriate referrals for therapy. Over the 5 year period from January 2011 until December 2015 we have treated 164 patients on 5 distinct protocols; in addition, 12 patients who did not qualify for protocol therapy received CTLs on Single Patient Use Emergency INDs. Indications for CMV-CTL treatment were: CMV after hematopoietic cell transplant (HCT), after solid organ transplant (SOT), and in the setting of HIV infection. In the EBV setting, indications were: EBV viremia, and EBV disease arising after HCT and SOT and in the setting of underlying or acquired immune deficiency. In addition, subsets of patients with EBV positive malignancies without defined immune deficiencies have been treated. A total of 1,054 infusions of EBV-CTLs and CMV-CTLs have been administered. Infusions were administered in the inpatient and outpatient setting of the Medicine and Pediatric Stem Cell Transplant Services at MSK. Cumulative safety data collected over this time period is being reported. Of 80 patients treated with donor derived and/or third party derived CMV-CTLs during this time period, 30 patients had severe adverse events (SAEs) reported with 7 patients experiencing 17 possibly related Grade 3 or higher SAEs (1 mental status changes, 1 with diffuse alveolar hemorrhage (DAH) in a patient with a prior history of DAH, 4 hypoxic events and 1 patient with multiple cytopenias). There were no probably or definitely related SAEs. Of 100 patients treated with donor derived and/or third party derived EBV-CTLs during this time period, 34 patients had SAEs reported with 7 patients experiencing 9 possibly related Grade 3 or higher SAEs (1 patient with mental status changes, 1 seizure, 1 nausea, 2 lymphopenia, 3 electrolyte imbalance, 1 febrile neutropenia). There were no probably or definitely related SAEs. No patients developed Graft versus Host Disease (GvHD) related to EBV or CMV-CTL therapy during this time period. Prior to January 2011 one patient developed GvHD after each type of cell therapy (EBV-CTL: Grade 1 skin responding to topical steroids; CMV-CTL: Grade 3 skin and lower GI occurred in the setting of new onset HHV6 viremia required systemic therapy). No patients developed any manifestations of cytokine release syndrome or hemophagocytic lymphohistiocytosis and no patient who had received prior radiation developed radiation recall. In conclusion, adoptive T cell therapy using both using donor derived viral specific cytotoxic T cell lines therapy and third party derived banked viral specific cytotoxic T cell lines has been well-tolerated without infusion reactions or cytokine release syndrome and is associated with minimal GVHD and a low incidence of SAEs with no probably or definitely related Grade 3, 4 or 5 events related to CTLs.

Disclosure of conflict of interest: HD, GK and RO'R: Atara Biotherapeutics: Consultancy and Research Funding. The remaining authors declare no conflict of interest.

O081

Treatment of post-allogeneic stem cell transplant cytopenias with sequential doses of mesenchymal stromal cells: results of a multicenter Phase II trial

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Post-transplant cytopenias are a complication with remarkable morbidity and mortality for which there is no effective treatment in refractory cases. Mesenchymal stromal cells (MSC) as key regulators of the bone marrow (BM) niche and because of their immunomodulatory properties are a potentially attractive therapeutic tool in this setting. Twelve patients were included in this multicenter phase II clinical trial (EudraCT code: 2013-000534-35). Main inclusion criteria were hemoglobin 100x10^9/L)) to the day 90, adverse effects and survival was analyzed after infusion four doses of 1x10^6 MSC / kg of recipient body weight on days 1, 4, 11 and 18. The primary objective was to analyze the safety and feasibility of MSC infusion in this setting. Secondary objective was to analyze the effectiveness in terms of blood counts recovery and length of the response. Median age of the 12 patients included was 49 years (range 20–66)), and most patients had AML ($n = 8$). Cell source for transplantation included HLA-identical URD ($n = 7$), identical sibling ($n = 3$), UCB ($n = 1$) and haploidentical donors ($n = 1$). Seven patients received RIC regimen. Regarding the type of cytopenia, most patients had isolated thrombocytopenia ($n = 9$), neutropenia ($n = 1$), or both ($n = 2$). Most patients had received one prior treatment for cytopenia (range 1–3), mainly steroids and immunoglobulins. Nine out of the twelve patients (75%) had concomitant GVHD at least a month previous to the first MSC infusion. MSC infusion was performed after a median of 106 days from allo-BMT (range 35–633). There were no adverse effects related to the cell infusions that were performed in the ambulatory setting in some cases. Within the first 90 days, ten out of the twelve patients (83%) responded to cellular therapy and eight of them achieved complete response (CR). On day 90, six patients maintained CR and two maintained partial response (RP), whereas two patients had no response and two were non-evaluable. At the last follow-up, with a median of 213 days (range 769861), seven patients (3 CR, 4 PR) maintained the response, four patients deceased due to the progression of disease ($n = 1$) or sepsis ($n = 3$). One patient achieved CR with an alternative treatment. Patients that achieve response to MSC therapy seemed to have an advantage in terms of long-term survival. Treatment of peripheral cytopenias with MSC is feasible, has no adverse effects and is potentially useful in most patients. Achieving either CR or PR to MSC therapy seems to favor long term survival for those patients.

Disclosure of conflict of interest: None.

O082

Adoptive transfer of CMV-specific T cells for persistent CMV infection after haploidentical stem cell transplantation: association between antiviral immunity and the improving of quantity and quality of CMV-specific T cells

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Adoptive transfer of cytomegalovirus (CMV) specific T cells has been developed as a safe and effective treatment strategy for CMV infection. However, little experiences had been reported about the CMV-specific T cells adoptive therapy post haploidentical stem cell transplantation (halpo-SCT). Meanwhile, the mechanisms in driving sustained antiviral immunity by adoptive transfer remain undetermined. The aims of the study were (i) To evaluate the safety and antiviral activity of donor CMV-specific T cells for persistent CMV infection in haplo-SCT recipients; (ii) To identify the association of CMV-specific immunity reconstitution (including quantity and function of CMV-specific T cell) and CMV infection resolution. There were 40 patients with persistent CMV infection prospectively accepted adoptive CMV-specific T cells therapy after halpo-SCT. Another 40 matched patients with transient CMV infection after haplo-SCT and 10 age-matched health donors were selected as controls. Phenotypical and functional characteristics of CMV-specific T cells were analyzed before and after immunotherapy in the treatment group, as well as in the control group. Single pools of overlapping 15-mer peptides for CMV pp65 and HLA class I CMV pentamer-matching peptides were used. Surface staining was performed with the following antibodies: CD3, CD4, CD8, CD45RA, CCR7 and PD-1. For intracellular staining, fixed cell was incubated with IFN-γ, IL-2, TNFα and Granzyme B. Proliferation was detected with CFSE and cultured for 7 day with CMVpp65 peptide. All of the 40 treated patients cleared CMV viremia by 12 weeks post adoptive T cell transfer, and no infusion-related side effect was observed. In the treatment group, 33 patients (33/40, 82.5%) had CMV viremia clearance within 4 weeks post T cell transfer without recurrence. A massive *in vivo* expansion of CMV-specific CD4+ IFN-γ+ as well as CD8+ IFN-γ+ T cells, especially the effector memory and effector T cell subpopulation, was detected in these patients. With regard to the function of CMV-specific T cells, we observed impairment of CMV-specific T cells in patients with persistent CMV infection after haplo-SCT. To be encouraging, we found that adoptive transfer of CMV-specific T cells could decrease expression of inhibitory molecular PD-1 on CMV-specific T cells and improve cytokine production and proliferation ability of CMV-specific T cells. However, the remaining 7 patients who still had CMV recurrence after 4 weeks post transfer, neither quantity nor function of CMV-specific T cells were reversed. Adoptive transfer of CMV-specific T cells is safe and efficient in

Figure 1 [O082]

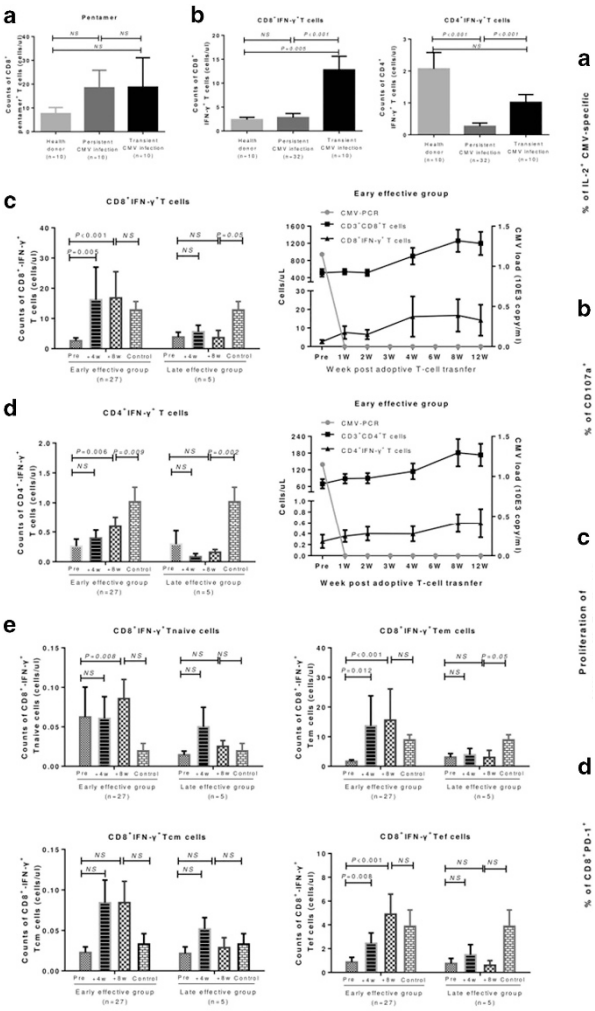

Figure 1

Figure 2 [O082]

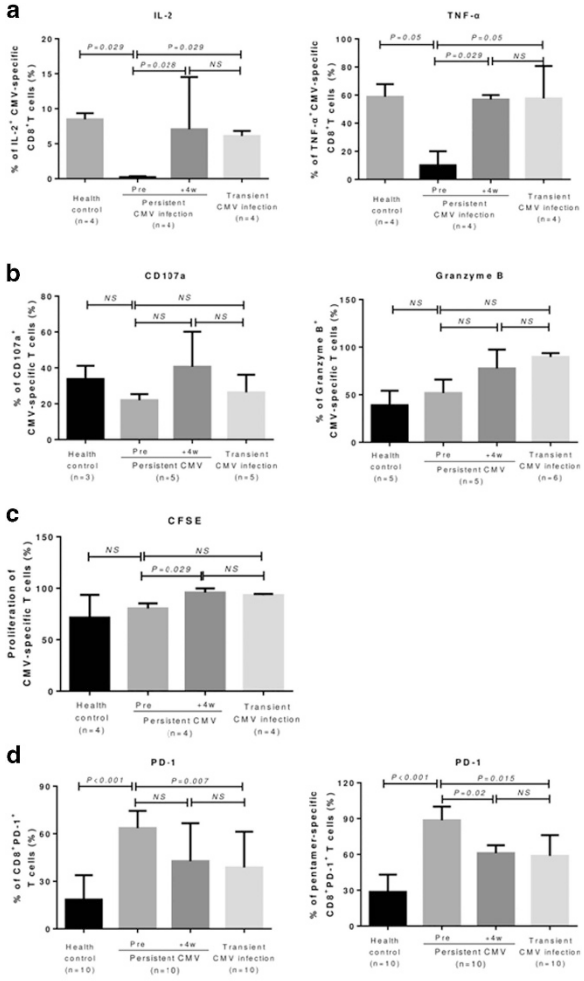

Figure 2

eliminating persistent CMV infection after haplo-SCT. Adoptive transfer of CMV-specific T cells would be help for prompt CMV-specific T cell quantitative and functional recovery against persistent CMV infection after haplo-SCT.

Disclosure of conflict of interest: None.

Transplant complications and QOL

O083

Efficacy and safety of defibrotide in patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) onset diagnosed after day 21: a post *hoc* interim subgroup analysis from an Expanded-Access Program

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Hepatic VOD/SOS is a potentially life-threatening complication of conditioning for hematopoietic stem cell transplant (HSCT). VOD/SOS with multi-organ dysfunction (MOD) may be associated with >80% mortality. Although VOD/SOS typically begins <21 days post-HSCT (per Baltimore/modified Seattle criteria), late-onset VOD/SOS has been reported in 15%-20% of cases, sometimes post hospital discharge (1, 2). EBMT has proposed new criteria to include late-onset VOD/SOS (>21 days post-HSCT) by Baltimore criteria, histological evidence of VOD/SOS, or a version of Baltimore criteria comprising ⩾2 of: bilirubin ⩾2 mg/dL, painful hepatomegaly, weight gain >5%, or ascites—*plus* mandatory hemodynamic/ultrasound evidence of VOD/SOS (3). Defibrotide (DF) is approved to treat severe hepatic VOD/SOS post-HSCT in the European Union, and for hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT in the United States. Interim data for 867 patients (pts) in a DF expanded-access program include 756 pts treated post-HSCT, with 51% observed Day +100 survival and treatment-related adverse events (TRAEs) in 21% of pts. Efficacy and safety data in the subgroup of pts with late-onset VOD/SOS are presented. The original expanded-access protocol required VOD/SOS diagnosis by Baltimore criteria or biopsy by Day+35 post-HSCT, with MOD (renal/pulmonary) by Day+45. The study was amended to include pts with later-onset VOD/SOS, with or without MOD; VOD/SOS diagnosed by modified Seattle criteria; and VOD/SOS after HSCT or chemotherapy alone. All pts received DF 25 mg/kg/d (6.25 mg/kg q6h) for a recommended ⩾21 days. "Late-onset" was defined as diagnosis >21 days post-HSCT; hemodynamic/ultrasound data (EBMT criteria) were not available. Of 756 HSCT pts enrolled by April 18, 2015, and receiving ⩾1 dose of DF, 205 (27%) had late-onset VOD/SOS, 116 (47%) with MOD (Table 1). Observed Day+100 survival was: 47%, total group; 42%, pts with MOD; 53%, pts without MOD. AEs occurred in: 71%, total group; 74%, pts with MOD; 67%, pts without MOD, and 22%, 24%, and 19% had TRAEs, respectively. The most common TRAEs were epistaxis, pulmonary hemorrhage, gastrointestinal hemorrhage, or hypotension (>3% to <5% each). TRAEs leading to study discontinuation ($n = 21$) or death ($n = 7$) were primarily hemorrhage.

[O083]

Table 1. Baseline Demographics

Variable		*All VOD/SOS (N = 205)*	*With MOD (n = 116)*	*Without MOD (n = 89)*
Female, %		49	49	48
Median age (range), years		24 (0.3–74)	24 (0.3–67)	25 (0.3–74)
Age ⩾18 years, %		62	61	64
Primary disease, 15%	Acute myelogenous leukemia	40	45	33
	Acute lymphocytic leukemia	18	19	17
Graft-vs-host disease prophylaxis, >15%; %	Tacrolimus	59	64	54
	Methotrexate	32	32	32
	Sirolimus	16	20	11

In this study, diagnostic criteria requiring onset before day 21 would potentially miss >27% of pts with VOD/SOS, highlighting the importance of including late-onset VOD/SOS in

diagnostic criteria. TRAEs for this subgroup were similar to the overall interim results. Factors contributing to survival in these pts form a potential area for future exploration. Support: Jazz Pharmaceuticals.

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O084

Impact of ATG use on the outcome of patients with hematological malignancies undergoing reduced-intensity conditioning for allogeneic hematopoietic cell transplantation

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During the last years reduced-intensity conditioning (RIC) has been increasingly used for allogeneic hematopoietic cell transplantation (HCT) to minimize transplant-associated morbidity and mortality while exploiting the graft-versus-leukemia effect. Prophylaxis using ATG infused with conditioning for HCT reduces both acute and chronic graft-versus-host disease (GvHD) but does not significantly improve survival. ATG prophylaxis when given at higher doses and with RIC increased the relapse risk in a few reports with small patient numbers. Therefore, we performed this registry-based retrospective study in a large patient cohort to analyze the effect of ATG on outcome of HCT in adults with hematological malignancies. We identified 26139 patients (60% male, 40% female) with a median age of 56 (range, 18–78) years who underwent HCT after RIC in the years 2000 to 2013. In 12788 patients ATG was included for GvHD prophylaxis. Main hematological diseases consisted of acute leukemia (33%), myelodysplastic syndrome/myeloproliferative disorders (20%), lymphoma (19%) and plasma cell disorders (13%) resprectively. Forty-six percent of patients were in complete remission prior to HCT. Forty-eight percent of patients had a related donor and in 92% peripheral blood stem cells were used for HCT. For GvHD prophylaxis mainly cyclosporine A (CSA) in combination with mycophenolate mofetil (45%), CSA and methotrexate (30.5%) or CSA alone (14%) were administered. Survival free from acute GvHD, chronic GvHD and relapse (GRFS) was the primary study endpoint. Median follow-up of survivors was 40 months overall and 43.8 and 37.4 months in the no-ATG and ATG patient cohort, respectively. In both univariate and multivariate analyses, outcomes were weighted by inverse of the propensity score obtained on age, patient gender, cell sources, donor type, year of transplant, diagnosis, disease status at HSCT and CMV mismatch. In a univariate analysis the use of ATG was associated with increased probability of GRFS (45% vs 37.2% at 1 year, $P < 0.0001$) as well as decreased incidence of acute GvHD grades II-IV (8.7% vs 10.4% at 100 days, $P < 0.0001$) and III-IV (2.3% vs 3.3% at 100 days, $P < 0.0001$). Furthermore, incidence of chronic GvHD (35.8% vs 50.5% at 1 year, $P < 0.0001$) and nonrelapse mortality (NRM) (17.3% vs 20.1% at 1 year, $P < 0.0001$) were significantly lower in the ATG cohort. Overall survival was significantly higher (67.4% vs 64.9% at 1 year, $P < 0.0001$) in patients given additional ATG for GvHD prophylaxis. In a multivariate model adjusted for conditioning and prevention of GvHD, the use of ATG was associated with reduced risk of acute GvHD grades II-IV (HR 0.74, $P < 0.0001$) and grades III-IV (HR 0.66, $P < 0.0001$) as well as chronic GvHD (HR 0.64, $P < 0.0001$). Furthermore, GRFS (HR 0.83, $P < 0.0001$) was improved in the ATG cohort. NRM (HR 0.81, $P < 0.0001$) and overall mortality (HR 0.93, $P = 0.003$) were reduced and relapse incidence (R 1.18, $P < 0.0001$) was increased in patients given ATG. Further results on ATG dose and brand will be presented. Adult patients with hematological malignancies treated with allogeneic HCT after RIC benefit from the use of ATG in terms of survival free from GvHD and relapse. However, a prospective clinical study should be performed to allow definite recommendations for clinical application.

Disclosure of conflict of interest: None.

O085

Microbiome-derived markers predict the clinical outcome of allogeneic hematopoietic stem cell transplant recipients: results of a prospective study in 100 adult patients

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Recent advances in supportive care have significantly reduced TRM; nevertheless infections and GvHD represent major complications in allogeneic HSCT (allo-HSCT). Recent studies indicate that patients undergo dramatic alterations of intestinal microbiota during allo-HSCT, potentially affecting the outcome. Between October 2014 and March 2016, we conducted a prospective observational study to examine the intestinal microbiota by NGS in 100 consecutive adult patients, who received allo-HSCT for high-risk hematological malignancies. Stem cell donors were family haploidentical ($n = 45$), sibling ($n = 15$), MUD ($n = 35$), CBU ($n = 5$). Stem cell source was mainly T-cell replete PBSCs. Fecal specimens were collected before conditioning (T0), during aplasia (T10) and after engraftment (T30). The fecal microbiome was analyzed using the 454 GS Junior System, and QIIME software. The transplant procedures markedly impacted the enteric microbiome, with a

Figure 1 [O085]

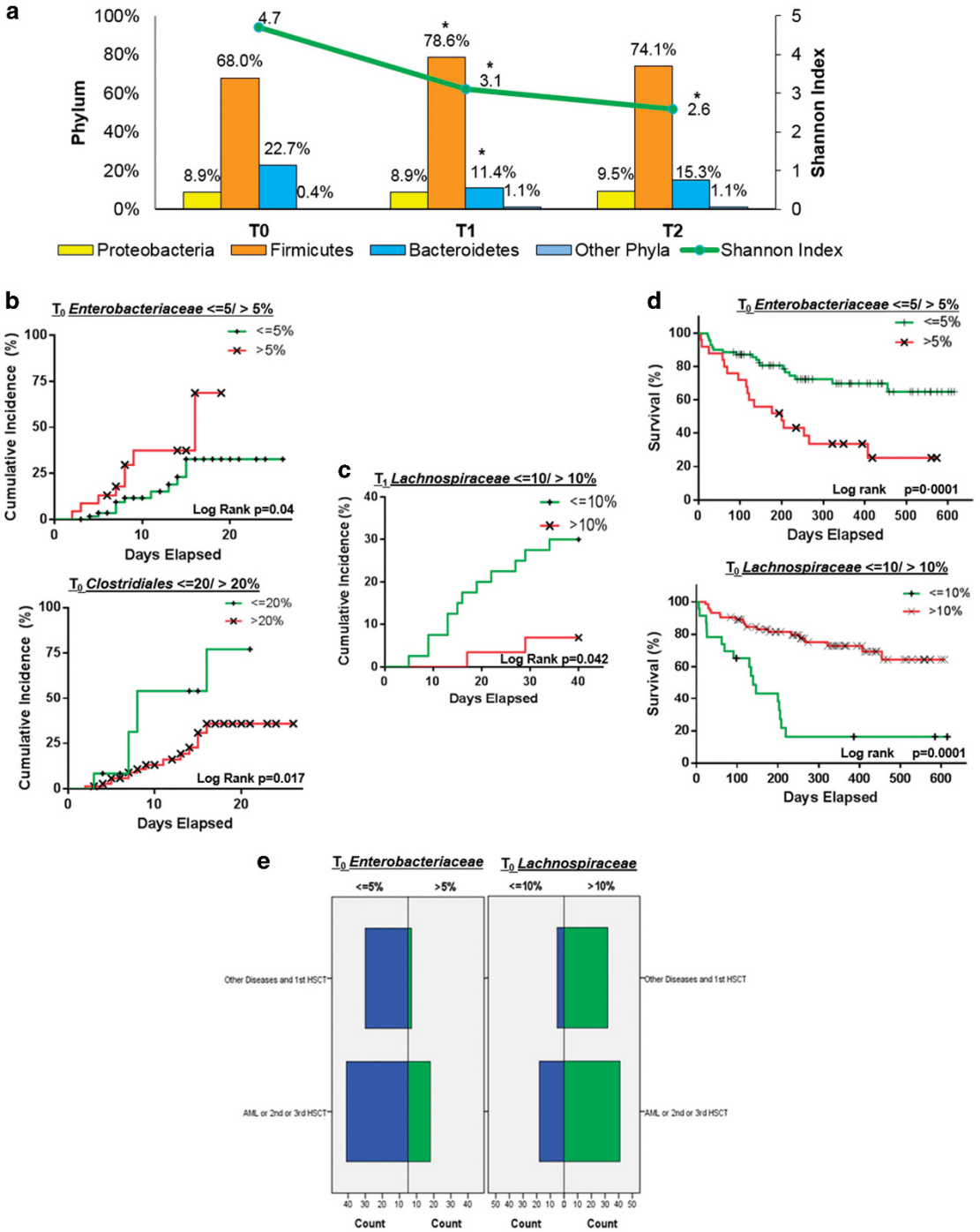

Figure 1 (A) Phylogenetic changes and alpha diversity in allo-HSCT patients across all time points using mean values and paired sample T-test. During the peri-transplant period, patients show extreme shifts in the intestinal microbiota including an overall loss of diversity and richness, as well as alterations in taxonomic domination. An overall loss of Shannon index of 2.10 ($p<0.001$) is observed between T_0 and T_2. Significant shifts between T_0 and T_1 were observed in both *Firmicutes* and *Bacteroidetes*, with a significant average increase in *Firmicutes* by 10.6% (p=0.017) and an average decrease in *Bacteroidetes* by 11.3% (p=0.012). **(B)** Cumulative incidence for severe sepsis or septic shock based on specific cutoffs at T_0: 5% of *Enterobacteriaceae* (RR 2.12; p=0.04) and 20% *Clostridiales*, including *Lachnospiraceae,* RR 2.56; p=0.01). **(C)** Cumulative Incidence for aGVHD for 10% *Lachnospiraceae* at T_1 (RR 4.35; p=0.042). **(D)** Kaplan-Meier mortality curves for *Enterobacteriaceae* (above) and *Lachnospiraceae* (below) at T_0. **(E)** Bacterial domination at T_0 in patients with AML or patients undergoing 2nd or 3rd HSCT.

dramatic decrease of the intestinal microbial diversity (alpha diversity), especially between T0 and T10 ($P < 0.0001$). The loss of diversity was mainly due to the decrease of Bacteroidetes, paralleled by an even more significant decrease of Firmicutes, in particular those belonging to Lachnospiraceae ($P = 0.0004$) and Ruminococacceae ($P < 0.0001$) families. A significantly different distribution in the baseline microbiome was reported in patients who will experience different clinical outcomes. The presence of $\geqslant$ 5% Proteobacteria, and in particular of Enterobacteriaceae, at T0 was the most sensitive and specific risk-stratification marker. Patients who developed a bacteriologically-confirmed sepsis by GN-MDR bacteria show an increase of Enterobacteriaceae (cut-off 5%; $P = 0.001$, RR 5·6). This increase of Enterobacteriaceae was significant also when considering the risk of severe sepsis and septic shock (RR 2·125; $P = 0.0425$). Most importantly these microbiome changes was significantly associated to overall survival (RR 2·541; $P = 0.0001$), confirmed by the multivariate analysis. A low ($< = 10\%$) relative amount of Lachnospiraceae at T0 is associated to an increased risk of GN-MDR sepsis ($P = 0.0261$), whereas a $< = 10\%$ amount of Ruminococcaceae is associated to increased risk of severe sepsis and septic shock ($P = 0.0259$). Both markers were associated to an increased risk of death ($P = 0.0001$ and $P = 0.0404$ respectively). More in details, $< = 10\%$ Lachnospiraceae was associated to an increased risk of death for both infectious and non-infectious causes ($P = 0.0002$). Interestingly, significant microbioma changes were observed at 10 days after transplant, in patients who developed a subsequent acute GvHD, with a predominant role played by gram-positive bacteria belonging to Firmicutes. More in details, the presence of Lachnospiraceae was associated to a decreased risk of acute GvHD ($P = 0.04$ and RR = 4·35), whereas dominance of Enterococcaceae ($P < 0.01$ and RR = 3·23) and Staphylococcaceae ($P < 0.01$ and RR = 3·5) was associated to its increased incidence. Longitudinal study of microbioma profile allows early identification of patients at risk for major transplant-related complications such as sepsis by GN-MDR or acute GvHD, offering a new tool for individualized pre-emptive or therapeutical strategies to improve the outcome of allo-HSCT.

Disclosure of conflict of interest: None.

O086

Outcome of second cancer after hematopoietic stem cell transplantation: On behalf of the complications and quality of life working party of the EBMT

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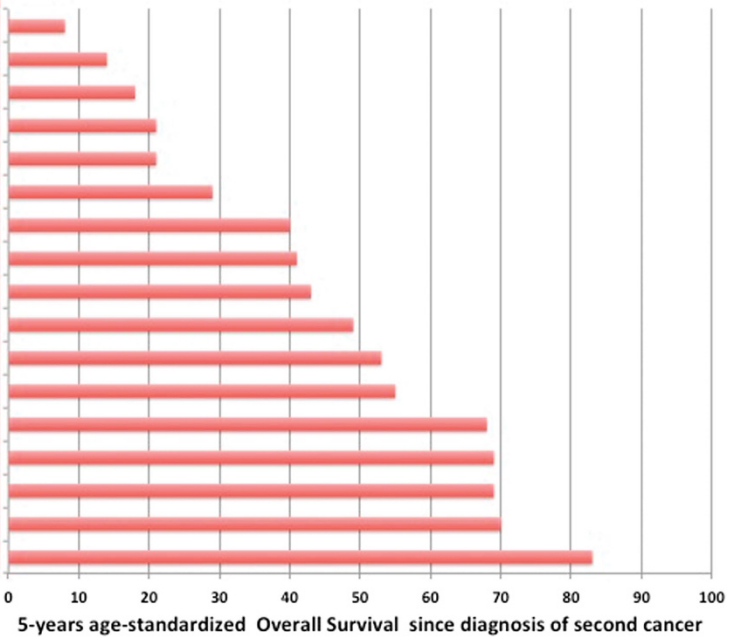
Second cancers (SC) after HSCT are well-known late complications, associated with substantial mortality. Incidence and risk factors for many SC have been established, but there is a paucity of data on their outcome after HSCT. We aimed to estimate the outcome of SC after HSCT. It is a retrospective observational study based on data from the EBMT registry. We identified all patients transplanted in Europe between 1977 and 2015 and developing SC after HSCT (excluding malignant hematopoietic and lymphoid neoplasms; non-melanoma skin cancers). Primary diagnoses were acute leukemia (23%), chronic leukemia (9%), lymphoma (34%), plasma cell disorders (23%), solid tumors (4%), MDS and MPN (6%), and acquired marrow failure syndromes (1%). For 17 frequent SC 5-year age-standardized overall survival (OS) from time of diagnosis of the SC was calculated. For six prevalent SC (breast, lung, melanoma, oropharyngeal, colorectal, prostate), the age-standardized 5-year OS (according to the International Cancer Survival Standard; ICSS) of HSCT patients with SC diagnosed

Figure 1 [O086]

Figure 1: Number of second cancers, median survival and 5-years age-standardized overall survival and 95% CI since diagnosis of 17 different types of second cancers after HSCT

Number	Sec. Cancer	Median Survival	OS	95% CI
145	Pancreas	0.6	8	(3-18)
597	Lung	0.9	14	(11-19)
90	Hepatobiliar	0.9	18	(11-31)
88	Esophageal	0.9	21	(13-36)
156	Brain	0.9	21	(15-30)
158	Gastric	1	29	(21-39)
46	Endometrial	3.4	40	(26-63)
446	Colorectal	3.2	41	(36-48)
77	Ovarian	2.2	43	(32-58)
144	Bladder	4.9	49	(39-62)
207	Oropharyneal	8.2	53	(46-62)
177	Kidney	5.2	55	(47-65)
343	Melanoma	nr	68	(62-74)
547	Breast	10.6	69	(64-74)
410	Prostate	9.8	69	(64-75)
57	Cervix	12.4	70	(57-86)
149	Thyroid	nr	83	(76-92)



nr, not reached;
Median survival in years;

since the year 2000 was compared to data from cancer patients of a general population (EUROCARE, European Cancer Registry, period 2000-2007). From the EBMT registry 3848 SC out of 220'617 HSCT patients were extracted, 1346/80'784 allogeneic and 2502/139'833 autologous HSCT patients. After allogeneic HSCT, there were 707 males (52%); median age 46y (range, 1.2–69) at HSCT and 54y (3.2–76.5) at SC; median follow-up time since HSCT 143 months (12–409), and since SC 36.1 months (0.0–186.6); time interval between HSCT SC was 6.6 years (3.2–76.5). After autologous HSCT, there were 1482 males (59%); median age 56y (1.7–70) at HSCT and 62y (4.5–82) at SC; median follow-up time since HSCT 114 months (5.4–354), and since SC 32.2 months (0.0–180); time interval between HSCT to SC was 5.0 years (0–29). In total 1689 of 3848 (44%) patients with SC died. The main cause of death was SC (72.4%), followed by original disease (24.8%). All other causes of death accounted for $\leqslant$1.1%. The number of the SC, median survival after second cancer, and 5-years age-standardized OS since diagnosis of SC are shown on Figure 1. OS following diagnosis of SC after HSCT depends mostly on the type of cancer. There was no relevant difference between patients treated with allogeneic or autologous HSCT (data not shown). On Table are shown age-standardized 5-year OS from the 6 SC after HSCT diagnosed since 2000, and as comparison, 5-years age-standardized OS from a European general population with the same type of cancers (EUROCARE).

[O086]

Cancer	*Age-standardized 5y OS Percentage (95% CI)*	*EUROCARE Age-standardized 5y OS Percentage (95% CI)*
Breast	70.3 (58.5–84.5)	72.4 (72.3–72.6)
Lung	12.9 (9.2–18)	11.5 (11.4–11.6)
Melanoma	62.6 (54.7–71.7)	76.6 (76.2–76.9)
Oropharyngeal	51.7 (40.6–65.9)	33.7 (32.8–34.6)
Colorectal	40.4 (34.4–47.5)	48.8 (48.6–48.9)
Prostate	72 (63.8–81.4)	69.7 (69.5–69.9)

This large population-based analysis on SC among HSCT survivors showed that the outcome for patients developing a SC after HSCT is mainly dependent on the type of cancer. It seems that for a number of SC OS is comparable to cancer patients from a general population. A systematic comparison is now required for all post HSCT second cancers.

Disclosure of conflict of interest: None.

O087

Final efficacy and safety results from a defibrotide expanded-access program for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome

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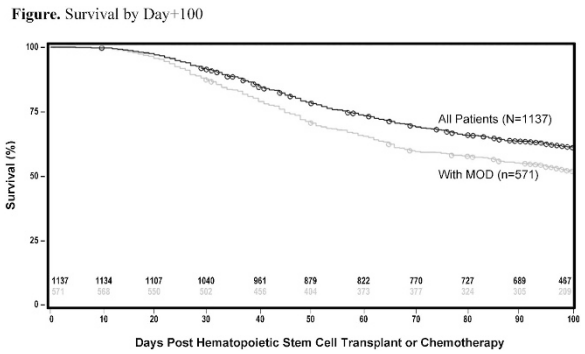
Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a potentially life-threatening complication of conditioning regimens for hematopoietic stem cell transplant (HSCT) but also may occur after chemotherapy alone. VOD/SOS with multi-organ dysfunction (MOD) may be associated with $>$80% mortality. Diagnosis of VOD/SOS has traditionally been based on the Baltimore or modified Seattle criteria, and the EBMT recently proposed new criteria for adults based on the Baltimore criteria. Defibrotide is approved for treating severe hepatic VOD/SOS post-HSCT in the European Union, and for hepatic VOD/SOS with renal or pulmonary dysfunction post-HSCT in the United States. The goal of the defibrotide expanded-access protocol was to provide access to defibrotide prior to approval in the United States and to collect additional data on safety and efficacy in a broader patient population, including those with and without MOD, and following HSCT or chemotherapy. This is the largest prospective evaluation of defibrotide for the treatment of VOD/SOS. Day+100 survival and safety results are provided. The original expanded-access protocol required VOD/SOS diagnosis by Baltimore criteria or biopsy post-HSCT, with evidence of MOD (renal and/or pulmonary dysfunction). The study was amended to also include patients without MOD; with VOD/SOS diagnosed by modified Seattle criteria; and/or with VOD/SOS after chemotherapy alone. All patients received defibrotide 25 mg/kg/d (6.25 mg/kg q6h) for a recommended $\geqslant$21 days. The final analysis is based on 1154 patients enrolled between 2007 and 2016 who received $\geqslant$1 dose of defibrotide. Of these patients, 571 (49.5%) had MOD. Median patient age was 12 years (range 0.0–77.0), with 15.8% aged 16 years. Most common primary diseases were acute leukemias (48.4%). This was the first HSCT for 73.4% of all patients. In 1137 patients with a confirmed VOD/SOS diagnosis, 88% received HSCT (84.3% allograft, 15.5% autograft, 0.2% type unknown) and 12.0% had chemotherapy only. Kaplan-Meier estimated Day +100 survival (Figure 1) was 61.1% (95% CI, 58.2%–63.9%) for all patients; 51.9% (95% CI, 47.6–55.9%) for the subgroup with MOD. Overall, 810 patients (70.2%) reported $\geqslant$1 treatment-emergent adverse event (AE). Of these, 248 patients (21.5%) had AEs that investigators assessed as related (possibly, probably, or definitely) to study medication. Related AEs in $>$2.0% were pulmonary hemorrhage (4.3%), gastrointestinal hemorrhage (3.0%), epistaxis (2.3%), and hypotension (2.1%). Serious AEs were reported by 598 patients (51.8%), of which 133 (22.2%) were assessed as related. Related AEs lead to discontinuation in 12% and death in 2.7% (pulmonary hemorrhage, 1.0%, was most common). Results from this final analysis of the defibrotide expanded-access protocol demonstrate favorable Day+100 survival (61.1%) in a diverse population with VOD/SOS, and 51.9% in the subgroup with MOD, a complication typically associated with dismal outcomes. The observed safety profile for defibrotide was consistent with results from prior studies. These findings, consistent with prior clinical trials, provide supportive evidence for the clinical utility and safety profile of defibrotide for treatment of VOD/SOS in patients with and without MOD.

Figure 1 [O087]



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O088

Prevalence and predictors of cardiovascular risk in patients with moderate and severe chronic graft-versus-host disese

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Advances in allogeneic hematopoietic stem cell transplantation (alloHSCT) have prolonged patient survival leading to the need to study and treat late effects in long-term survivors. Notably, patients (pts) after alloHSCT have 4-fold higher risk of cardiovascular disease (CVD) and 2-4 fold higher risk of CVD-related mortality than the general population. This is likely a result of combined effects of treatment exposures. CVD risk and factors impacting prevalence of classic risk factors (CVRF) have not been studied in patients with chronic graft-versus-host disease (cGVHD), the main late immunological complication of alloHSCT. This study included 312 pts enrolled on the NIH cGVHD natural history protocol (NCT00092235), a cross-sectional study in which patients underwent one-week comprehensive evaluations. We quantified 10-year risk of CVD using the 2013 ACC/AHA Pooled Cohort Risk Assessment Tool for Atherosclerotic Cardiovascular Disease (ASCVD) in 196 pts eligible for the calculation (age 40-79) and compared potential predictors and survival between pts with low ($<7.5\%$) and elevated ($\geqslant 7.5\%$) risk based on the cutoff at which initiation of statin therapy is strongly suggested. Factors included in the ASCVD calculation are listed in Figure 1. Given the lack of inclusion of cancer therapy or alloHSCT-related factors in ASCVD, potential predictors of the tool's component CVRF were assessed separately in all 312 pts. The study population ($n=312$) was fairly evenly split by gender (58% male, 42% female), more often received myeloablative conditioning (54%) and less often total body irradiation (38%). Most patients had severe (72%) followed by moderate (26%) cGVHD, had received a median of 4 (range, 0–11) prior systemic immunosuppressive therapies (IST) for cGVHD, and a median of 5 (range, 1-8) organs affected by cGVHD. 59/196 pts (30%) were found to have elevated ASCVD. Those with elevated risk more frequently received non-myeloablative conditioning for allo-HSCT ($P<0.0001$), weighed more than low-risk pts ($P=0.014$), more frequently had joints and fascia cGVHD ($P=0.039$), and females less frequently had genital cGVHD ($P=0.039$). BMI was not associated with ASCVD. 25/59 pts (42%) with elevated ASCVD were not on statin therapy. Multivariable modeling produced a classification rule in which de novo or quiescent cGVHD onset, high CRP, and high diastolic BP predicted elevated ASCVD. Survival in patients with vs without elevated risk was not statistically different (median follow-up of survivors was 73 months, range: 2-144). The prevalence of CVRFs in all 312 pts ranged from 11-49% and variables most frequently associated with CVRF were 3+ IST for cGVHD, age at alloHSCT, and time from cGVHD diagnosis to consent (Figure 1). Pts with cGVHD have high prevalence of elevated ASCVD (30%) and individual CVRFs. Non-myeloablative conditioning, likely reflecting older age, was most strongly associated with elevated ASCVD while several other factors, most notably: 3+ prior IST for cGVHD, age at alloHSCT, and time since diagnosis of cGVHD; were associated with CVRFs. The consistent association of IST for cGVHD with CVRF is a new observation and indicates that cGVHD severity and therapies contribute to CVD. Further prospective and longitudinal studies including all relevant CVRFs need to be performed to accurately determine real risk of CVD and related mortality after alloHSCT.

Disclosure of conflict of interest: None.

O089

Performance status drives the impact of age on the outcomes of autologous hematopoietic cell transplantation in elderly patients aged 65 and older: A retrospective analysis by the complications and quality of life working party of the EBMT

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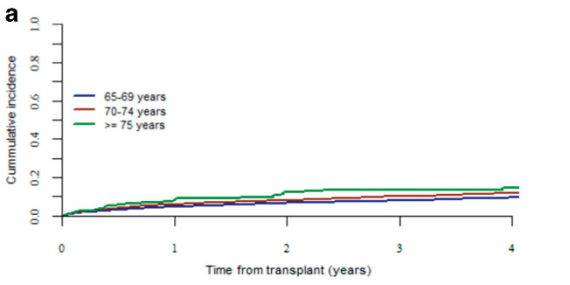
Advanced age may no longer be a barrier to successful autologous hematopoietic cell transplantation (autoHCT), in particular for patients with good functional status. However, reports of autoHCT in elderly patients aged $\geqslant 65$ years-old (yo) are limited, as they are underrepresented in clinical trials and data usually come from relatively small subgroup analyses in the main indications, namely multiple myeloma (MM) and lymphoproliferative disorders (LPD). Here, we sought to evaluate the feasibility and the factors driving the outcomes of autoHCT in a large cohort of elderly patients reported to EBMT. All consecutive autoHCT in recipients $\geqslant 65$ yo reported to EBMT between 2000 and 2014 were included. Data

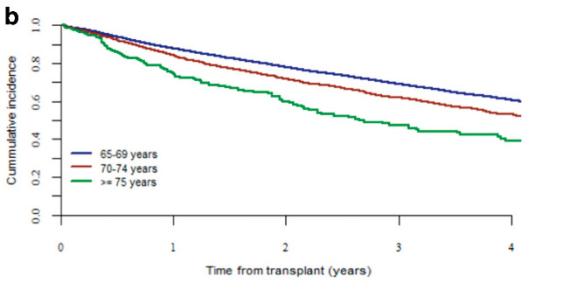
collection and outcome analysis followed EBMT registry and statistical guidelines. A total of 21390 autoHCT, including 3514 second or subsequent procedures, from 515 EBMT centres in 45 countries were identified: median age 67 yo (IQR 66-69; 17531 65-69 yo, 3570 70-74 yo and 289 ⩾ 75 yo); 61% male; 65% MM, 30.5% LPD, 3.4% acute leukemia, 1.1% others; 10.3% received reduced-dose conditioning regimens; 69.5% had a Karnofsky Performance Score (KPS) >80. Median time from diagnosis to autoHCT was 8.9 months (IQR 5.9-23). Median follow up time for survivors was 15.3 months (IQR 4.2-41.7). AutoHCT activity in elderly patients increased from 3.4% (443/13163) in 2000 to 9.8% (2444/23883) in 2014 (p80, the increased HR from increased age is only 1.04 for NRM and 1.2 for OS. Our study, in a large series of elderly recipients of auto-HCT, shows that NRM and OS at 1 and 3 years are acceptable and identifies factors with an independent impact on their outcome. Of note, despite significantly poorer outcomes in older patients, the impact of age depends on patients' performance status, and it becomes marginal in those with KPS >80. In spite of this being a highly selected population and the caveats of any retrospective study, these data confirm that age per se is no longer a barrier to successful autoHCT. They further endorse the need to assess comorbidity and frailty beyond age in older auto-HCT candidates to improve outcomes further. Specific studies in particular diseases and indications are warranted.

Figure 1 [O089]

Figure 1. Non-relapse mortality (NRM, A) and overall survival (OS, B) after autologous HCT in patients ≥65 years old.



NRM	All ≥65 yo	65-69 yo	70-74 yo	≥75 yo	p
1 year	**4.9%** [4.6-5.2]	**4.6%** [4.3-5.0]	**5.7%** [5.0-6.6]	**8.3** [5.1-12.4]	*0.001*
3 years	**8.3%** [7.8-8.7]	**7.8%** [7.4-8.3]	**10.1%** [9.0-11.4]	**13.4** [9.0-18.7]	



OS	All ≥65 yo	65-69 yo	70-74 yo	≥75 yo	p
1 year	**87.0%** [86.5-87.5]	**87.7%** [87.2-88.3]	**84.0%** [82.7-85.4]	**74.6%** [68.9-80.8]	*<0.0001*
3 years	**67.6%** [66.8-68.5]	**69.1%** [68.2-70.0]	**61.8%** [59.7-63.9]	**47.5%** [40.2-56.0]	

Disclosure of conflict of interest: None.

O090
Early cardiotoxicity associated with post-transplant cyclophosphamide in haploidentical stem cell transplantation

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High-dose (HD) Cyclophosphamide (Cy)-induced cardiotoxicity is a rare but often lethal complication following allogeneic stem cell transplantation (HSCT). Only few studies have assessed the incidence of fatal and severe cardiac event (CE) following HD Cy in conditioning regimen. Recently, the use of HD post-transplant (PT)-Cy in the Haploidentical (Haplo)-SCT setting has become popular, but risk factors, clinical manifestations and incidence of early cardiac event (ECE) are still poorly assessed. We analyzed all CE occurring within 3 months after PT-Cy in 56 pts undergoing Haplo in a single center. Median age was 47 yrs (range 15.5–72.5) and 54% of pts were males. Pts were Caucasians ($n=32$, 57%), Afro-Caribbeans ($n=7$, 13%), Polynesians ($n=4$, 7%), North-Africans ($n=9$, 16%) or Asian ($n=4$, 7%). Prior to transplant, 31 pts (55%) had cardiovascular disease (CVD) risk factors. Diseases were AML ($n=31$, 55%), ALL ($n=8$, 14%), MDS/MPN ($n=6$, 11%) and lymphoma ($n=11$, 20%). Haplo was performed after a median of 2 prior treatments (range 0-6). Nine pts (16%) had a history of previous HSCT and 6 (11%) received a previous autologous-SCT. Only 6 pts had never received anthracyclines prior to transplant. Stem cell source was PBSCs ($n=42$, 75%) and bone marrow ($n=14$, 25%). Conditioning was thiotepa-busulfan-fludarabine ($n=31$, 55%), sequential conditioning combining thiotepa-etoposide-cyclophosphamide ($n=22$, 40%) or clorabine-cytarabine followed by fludarabine-based RIC ($n=3$, 5%). Thymoglobuline was administrated to 46 pts (82%). PT-Cy 50 mg/kg/day was administrated on day+3 ($n=56$) and day+5 ($n=42$). GVHD prophylaxis was cyclosporine and mycophenolate mofetil in all pts. Transthoracic echocardiography and EKG were performed before and after HSCT. ECE occurred in 10 pts (18%) within 3 months after PT-Cy. The main complication was left ventricular systolic dysfunction (LVSD) (defined by an LEVF < 50%) in 6 pts (11%) at a median of 7 days (range 1-20) after PT-Cy first dose. One pt developed junctional tachycardia associated with LVSD on day+1 after PT-Cy first dose and did not receive the second dose. LVSD led to death in 3 pts (50%). Other ECE were myopericarditis without LVSD in 1 pt (2%), acute coronary syndrome in 1 pt (2%) and supra ventricular arrhythmia in 2 pts (4%) at day+23, +5, +35 and +85 after PT-Cy first dose, respectively. As expected, NRM was significantly higher in pts who developed ECE compared to pts who did not (50% vs 19.6%, $P=0.009$). Age, gender, BMI, CVD risk factors, disease status, previous treatments or transplants or anthracycline administration, stem cell source and conditioning did not seem to be associated with the occurrence of ECE. Half of the pts with ECE had no CVD risk factors and 60% had no history of CE. Out of the 6 pts who developed LVSD, only 1 had a history of low LEVF at 46% and 1 had controlled arrhythmia. Interestingly, 6 of the 7 pts with post PT-Cy LVSD or myopericarditis were non-Caucasian (1 Afro-Caribbean, 2 Polynesian, 2 North Africans, 1 Asian). Occurrence of serious ECE appears to be a relatively frequent complication after Haplo-SCT with PT-Cy compared to literaure in traditional HSCT practice without HD PT-Cy. Such serious events developed even in pts without history of CVD risk factors and were associated with high NRM. Thus close cardiac monitoring is warranted after PT-Cy, especially in non-Caucasian pts.

Disclosure of conflict of interest: None.

Myeloma

O091
Impact of extramedullary disease in newly diagnosed multiple myeloma patients undergoing autologous stem cell transplantation: A study from the Chronic Malignancies Working Party of the EBMT

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X Leleu[14], M Delforge[15], P Pioltelli[16], M Schipperus[17], JA Snowden[18], M Itälä-Remes[19], M Musso[20], L Garderet[21] and N Kröger[1]

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We investigated the characteristics and effects of extramedullary disease (EMD) in newly diagnosed multiple myeloma (MM) patients after upfront autologous stem cell transplantation (ASCT). Within the EBMT registry, 3744 patients (female $n=1576$, male $n=2168$) received upfront single (3391) or tandem ASCT (353) and were reported between January 2005 and December 2014 with available data on extramedullary involvement at time of diagnosis. The overall incidence of EMD was 18.2%. Within EMD, 543 patients (14.5%) had paraskeletal (PS group) and 139 (3.7%) extramedullary involvement (EM group), while 3062 (81.8%) had no EMD (MM group). Involved sites in EM patients were: kidney ($n=38$), skin (32), lymph nodes (24), CNS (14), lung/respiratory tract (9), gastrointestinal tract (GI)/liver (8), pleura/heart and spleen/ovaries/testes (7, respectively). Number of involvements were one (93.5%) or $\geqslant 2$ (6.5%). Primary end point was five year progression-free survival (PFS). At ASCT, 21.2% of PS patients reached complete remission (CR) compared to the MM (18.9%) and the EM group (11.5%; $P=0.24$). In the univariate analysis, the MM and PS group showed similar PFS of 32.9% (95% CI, 30.5–35.3) versus 37.2% (30.7–43.7), with a median PFS of 33.3 versus 34.9 months ($P=0.85$), and similar five year overall survival (OS) of 67.1% (64.7–69.5) versus 64.0% (57.5–70.5; $P=0.10$). In contrast, EM patients had significant worse PFS of 25.9% (15.7–36.1), with a median PFS of 24.7 months compared to MM ($P=0.001$) and PS patients ($P=0.003$), and significantly worse OS 49.7% (38.3–61.6) compared to MM ($P<0.001$) and PS patients ($P=0.001$). Within the EM group, median PFS of involved sites was: kidney (48.5 months), skin (21.6), lymph nodes (15.4), CNS (25.2), lung/respiratory tract (18.6), GI/liver (6.1), pleura/heart (10.0) and spleen/ovaries/testes (not reached). Patients without EMD (MM group) and EMD patients with one involved site showed similar PFS of 32.9% (30.5–35.3) versus 36.2% (30.5–41.9), with a median PFS of 33.3 versus 34.7 months ($P=0.67$), while $\geqslant 2$ involved sites showed worse PFS of 11.3%, with a median PFS of 21.6 months compared to one involved site ($P=0.003$) and the MM group ($P<0.001$). Comparing ASCT strategies, MM patients showed significantly higher PFS of 41.4% (34.1–48.7) after tandem compared to single ASCT with 31.8% (29.3–34.3), with a median PFS of 38.4 versus 33.1 months ($P=0.02$), while OS was 72.8% (65.9–79.7) versus 66.4% (63.9–68.9; $P=0.09$). In EMD patients, tandem ASCT showed non-significantly higher PFS of 41.2% (26.1–56.3) compared to single ASCT with 33.7% (27.8–39.6), with a median PFS of 45.1 versus 31.4 months ($P=0.07$), while OS was 58.8% (41.9–75.7) versus 61.3% (55.4–67.2; $P=0.65$). Cox proportional hazards regression considering independent risk factors for worse PFS yielded: EM with one involved site (HR 1.77; 95% CI, 1.22–2-57; $P=0.003$), EM with $\geqslant 2$ sites (HR 3.46; 1.62–7.41; $P=0.001$) and no CR (HR 1.78; 1.33–2.13; $P<0.001$), while tandem ASCT resulted in improved PFS (HR 0.75; 0.59–0.95; $P=0.02$). This large EBMT study showed that EM involvement, no CR at ASCT and $\geqslant 2$ involved sites are independent risk factors for worse PFS and OS. One involved site and PS involvement resulted in similar PFS and OS compared to patients without EMD, while tandem ASCT improved PFS compared to single ASCT.

Disclosure of conflict of interest: None.

O092
Previously published

O093
Outcome of the rare myeloma subtypes: An analysis of the collaboration to collect autologous transplant outcomes in lymphoma and myeloma (CALM) data

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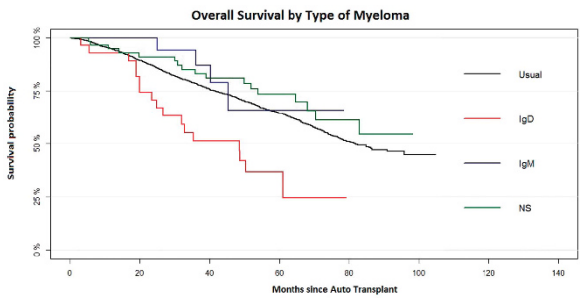
Rare subtypes of myeloma remain challenging to treat and due to their infrequent incidence there is limited data on their outcome. The Collaboration to collect Autologous transplant outcomes in Lymphoma and Myeloma (CALM) study has provided an opportunity to compare the real world outcomes of patients with myeloma. The aim of this study was to compare the outcome different subtypes of "rare" myeloma using CALM data. The CALM database identified 2802 patients with newly diagnosed myeloma undergoing first autologous stem cell transplantation (ASCT). Patients were divided in to "usual" myeloma (IgG, IgA and light chain myeloma) and "rare" myeloma (IgD, IgM, IgE and non-secretory (NS)). Only one patient with IgE myeloma was identified, and was therefore excluded from analysis. This study compared the overall survival (OS) and progression free survival (PFS) of these patients and also the impact of novel versus non-novel drug containing induction regimens prior to ASCT. 2,695 patients had "usual" myeloma, while 108 had "rare" myeloma (29 IgD, 17 IgM, 1 IgE and 61 NS). IgD myeloma was found to be associated with the worst OS and PFS. With a follow up time of 72 months the OS for "usual", IgD, IgM and NS myeloma was 56.4%, 24.5%, 65.8% and 61.2% respectively ($P=0.002$; Figure 1). Similarly at 36 months the PFS was 39.5%, 29.8%, 51.5% and 50.2% respectively ($P=0.0374$). PFS with a non-novel agent was shown to be inferior to induction with a novel agent (p0.0088) but the difference in OS was not statistically

significant ($P = 0.3758$). We postulate that patients receiving non-novel induction received a novel agent at the time of relapse which may have impacted on OS results. Four different combinations of novel based induction regimens were compared: velcade based induction, lenalidomide based induction, thalidomide based induction or combination novel induction with velcade and either lenalidomide or thalidomide. All were compared with non-novel induction. Again no difference in OS was seen ($P = 0.3764$). PFS was best in the Thalidomide group and worst in the non-novel group ($P = 0.0207$). When non-novel drugs were excluded from the analysis of OS and PFS results similar to the whole group were observed. It was not possible to perform a sub-analysis comparing the novel agents within the rare myeloma subtypes as the numbers were too small. Multivariate analysis was carried out to evaluate the impact of both the subtype of myeloma and treatment on outcomes. Using "usual" myeloma as a baseline multivariate analysis confirmed that IgD myeloma had the worst OS with HR 2.53 (p0.001). There was no OS advantage in the novel induction agent group. With regards to PFS there is a trend towards superiority in the novel induction agent group hazard ratio (HR 0.89, $P = 0.070$). PFS in NS myeloma was confirmed to be superior (HR 0.62, $P = 0.011$). Rare subtypes of myeloma have been associated with inferior outcomes and an aggressive clinical course. This study confirms that IgD myeloma is associated with a poorer outcome as expected; however, NS and IgM myelomas have superior PFS and OS.

Figure 1 [O093]



Disclosure of conflict of interest: None.

O094

WT1 heteroclitic epitope immunization following autologous stem cell transplantation induces WT1-specific immune responses and improves survival in patients with high-risk multiple myeloma

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The Wilms tumor 1 (WT1) protein is a tumor associated antigen that is a target for anticancer immunotherapy. We demonstrated overexpression of WT1 in multiple myeloma (MM) cells by IHC, as well as formation of a WT1 peptide fragment (RMFPNAPYL)/HLA-A*0201 complex on the engagement interface between malignant plasma cells and T-cells in HLA-A*0201+ MM pts using the high-affinity fully human IgG1 mAb ESK1. We report initial results from MM immunized with the WT1 heteroclitic peptide mixture galinpepimut-S (GPS) following autoSCT. We report results of a phase I/II trial of 18 pts with MM undergoing autoSCT with melphalan conditioning (200 mg/m2). All pts were placed on lenalidomide maintenance (10 mg daily) starting 3 months post autoSCT. 15/18 pts had high-risk cytogenetics at diagnosis (t(4;14), t (14;16), del17p, 1q21/25 gain by FISH and/or del13q by karyotyping). GPS was administered with montanide adjuvant s.c. starting 2 wks post autoSCT and biweekly thereafter, for a total of 6 doses initially. Pts continued thereafter with booster GPS administrations every 4 weeks for an additional set of 6 doses. GM-CSF (70 µg) was administered on day -2 and day 0 of each GPS administration. The GPS mixture consisted of 4 peptides at a dose of 200 µg each: 1. WT1-A1: Y*MFPNAPYL, 2. 427-L (long): RSDELVRHHNMHQRNMTKL, 3. 331-L: PGCNKRYFKLSHLQMHSRKHTG, and 4. 122A1-L: SGQAY*MFPNAPYLPSCLES. Two of the 4 peptides were mutated at a single residue (*) (R to Y) to induce stronger HLA-binding and avoid tolerance, aiming for enhanced immune responses. WT1-specific immune responses were assessed by intracellular IFN-g analyses upon stimulation with PBMC's pulsed with i. a total pool of overlapping 15mers spanning the entire WT1 protein or ii. each of the 4 WT1 peptides contained in GPS, or iii. the non-mutated (native) WT1 peptides corresponding to the 2 heteroclitic sequences within GPS (WT1-A and 122A-L). 18 pts with a median follow up of 14 mo (range: 6–25 mo) -for survivors- are reported, median age 61.6 y (range 46–72). The rates for OS and PFS (with 95% CI) at 18mos were 0.86 (0.70–0.99) and 0.62 (0.40–0.97), respectively. The 2 pts that died had extramedullary disease prior to autoSCT and developed rapid progression. All pts tolerated GPS administration without systemic side effects; however, all pts local nodularity at injection sites that resolved over 2-6 weeks. Importantly, CD8+ and CD4+ immune responses could be detected at various levels in all pts following GPS administration. These immune responses were induced not only by the mutated, heteroclitic peptides contained within the GPS mixture, but were also detected against the native WT1 peptide sequences that are expressed on the malignant plasma cells. Administration of the novel WT1 heteroclitic peptide immunizer GPS post autoSCT demonstrates remarkable safety. This 'off-the-shelf' immunotherapeutic has been specifically designed to elicit responses across most common HLA Class I and II alleles. Impressive WT1-specific CD8+ and CD4+ immune responses were seen, along with a promising 18mos PFS and a median PFS that has not been reached in this high-risk MM population. Based on these results, a larger phase II trial is being planned to optimally integrate post-transplant immunotherapeutic strategies to meaningfully delay or reduce risk of relapse in this challenging clinical setting.

Disclosure of conflict of interest: None.

O095

Long follow-up of upfront tandem auto-allo transplant in multiple myeloma and impact of "new drugs" at relapse

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We report an update on long term clinical outcomes of a multicenter trial, designed in the late 1990s prior to the introduction of new drugs, where treatment of newly diagnosed multiple myeloma (MM) patients with an autograft followed by a nonmyeloablative allograft or with double autografts was exclusively based on the presence or absence of a HLA identical sibling (Bruno B *et al*. N Engl J Med 2007). Of 162 consecutive newly diagnosed MM patients, 80 were assigned to tandem autograft - nonmyeloablative allograft (donor group) and 82 to tandem autografts (no donor group). Fifty-eight patients in the allograft-arm and 46 in the tandem autograft-arm completed their protocol. After a median follow-up of 12.2 years (range 7.7–15.4+), median overall survival (OS)

was 11.4 (CI 95% 11.4-not reached) in the allograft-arm and 3.9 years (CI 95% 2.1–7.6+) in the tandem autograft-arm (HR 0.51, CI 95% 0.31–0.83; $P = 0.007$), whereas progression-free survival was 3.6 and 1.5 years (HR 0.46, CI 95% 0.29, 0.74; $P < 0.001$), respectively. Five-year cumulative incidence of non-relapse mortality was 17.2% (95%CI: 7.4—27.1) in the allograft-arm and 4.3% (95%CI: 0–10.3) in the autograft-arm. One of the main physician's concerns of allografting is chronic graft-versus-host disease (cGVHD). In our study, its 2-year cumulative incidence was 67.2% (95%CI: 54.9—79.5). We also evaluated the cumulative incidence of immunosuppression discontinuation in patients with cGVHD, considering both death and relapse as competing events: 26.8% of cGVHD patients (95%CI: 13—40.6) at 24 months and 39% (95%CI: 23.6—54.4) at 60 months were alive, in response and off immunosuppression. In both arms, main reason for treatment failure remained disease recurrence. Thirty-three/58 patients in the allograft-arm relapsed at least once. At first relapse treatments were as follows: 13 received donor lymphocyte infusion (DLI, 1/13 alone, 4 with chemotherapy, 8/13 with new drugs), 10 new drugs, 4 radiotherapy, 2 conventional chemotherapy (CC), 2 palliative care (PC). At second relapse ($N = 22$), 1 received DLI, 17 new drugs, 2 CC, 1 a second allograft, 1 unknown. Of note, 2 patients in the allograft-arm had a biochemical relapse without reaching clinical criteria for treatment and were alive at 11 and 13 years from diagnosis. In the autograft-arm 39/46 relapsed, and received: 25 new agents, 3 CC, 6 a third autograft, 1 allograft, 2 PC, 2 unknown; whereas at second relapse ($N = 20$) they received: 15 new agents, 1 CC, 1 allograft and 3 a third autograft. Overall, 28/30 (93%) and 35/37 (95%) treated patients in the allograft- and autograft-arm, respectively, received new agents at disease relapse. Interestingly, median OS from 1st relapse was 7.5 years in the allograft-arm vs 2.0 years in the autograft-arm (HR 0.47, CI 95% 0.26–0.84; $P = 0.01$). Our update showed that many patients developing cGVHD were cGVHD-free at 5-years post-transplant, and that a synergism between graft-versus-myeloma and new agents exists. Given that MM remains an incurable disease, the combination of new drugs and allografting should be prospectively explored in high risk patients.

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O096
Previously published

O097
Comprehensive analysis of 212 donor lymphoycte infusions after allograft in multiple myeloma provides evidence for a strong graft versus myeloma (GvM) effect

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The major reason for treatment failure after allografting in multiple myeloma (MM) is relapse. Donor Lymphocyte Infusions (DLI) are considered to harness T cell mediated GvM effect either by prevention or treatment of relapse. Here, we evaluated the efficacy of 212 DLI after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in 85 patients with MM. Between 1998 and 2016, 151 escalating DLI procedures were given in 73 patients in order to increase remission status or prevent relapse ("preemptive" DLI = pDLI), while 41 patients with relapsed myeloma received a total of 61 DLI-procedures ("therapeutic" DLI = tDLI). pDLI and tDLI were performed median 334 (r.,57-4192) and 1015 (r.,124-3953) days after allo-HSCT. Median starting dose was 1×106 CD3/kg for pDLI and 5×106 CD3/kg for tDLI. Half-log dose escalation was performed in 43 pDLI- and 17 tDLI-patients if no sign of GvHD or response was seen after 6 weeks. Concomitant anti-myeloma active medication at the time of pDLI or tDLI with IMiDs or proteasome inhibitors were applied in 39 (53%) and 30 (73%) patients, respectively. Overall, 57% of the patients received only G-CSF stimulated DLI, while 43% received at least one unstimulated DLI. Acute Graft-versus-Host-Disease (aGvHD) grade II-IV and III/IV occurred in 15% and 5% respectively and chronic GvHD in 26% of the patients. None of the patients died from treatment-related mortality (TRM). Overall response rate (ORR) to pDLI was 71% (molecular CR: $n = 18$; CR: $n = 12$, VGPR: $n = 5$ and continuous mCR in $n = 2$ and cCR in $n = 15$). ORR to tDLI was 37% (CR: $n = 3$, VGPR: $n = 6$, PR: $n = 5$ and MR: $n = 1$). Overall response rate tended to be higher if DLI were not applied in combination with IMiDs or proteasome inhibitor (56% vs 41%, $P = 0.06$). Furthermore, cGvHD resulted in a higher ORR: 71% vs 42% ($P = 0{,}003$). Interestingly, unstimulated DLI did not induce higher remission rate (50% vs 46%; $P = 0.3$), but resulted in a higher cGvHD incidence (28% vs 15%, $P = 0.03$). After a median follow-up of 69 months (r., 30-118.9) from pDLI the median PFS was 38 months (r., 1.4-164.7) and median OS after pDLI has not been reached resulting in a 3-year-PFS and OS of 51% and 71%, respectively. 3-year PFS and OS was higher if a CR was achieved after pDLI: 65% vs 14% and 81% vs 48% ($P < 0.0001$ and $P = 0.001$). After a median follow-up of 32 months (r., 16.7-90.7) after tDLI the median OS was 24 months (r., 11.8-115.5) and the 3-year PFS and OS were 7% and 32%, respectively. In contrast to non-responder tDLI responders (CR/VGPR/PR/MR) had better PFS (median 15 months vs 1.4 months) and OS (median 37 vs 17 months), resulting in a better 3-year PFS and OS of 20% vs 0% and 53% vs 19% ($P < 0.0001$ and $P = 0.043$). DLI are an effective adoptive immunotherapy post allografting in multiple myeloma in prevention and treatment of relapse. Response is strongly correlated with occurrence of GvHD, but response can also be seen without GvHD. Patients who achieved CR after DLI have best outcome.

Disclosure of conflict of interest: None.

O098
Achievement of stringent CR at day 100 after allogeneic SCT as salvage therapy for first relapse after autografting in multiple myeloma patients is associated with improved survival outcomes

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Registry data from the EBMT suggest an increasing use of allo-SCT as salvage therapy after failure to auto-SCT. The prognostic role of "stringent" CR (sCR) is still controversial also there are no data in allogeneic setting. In present single center study we provide data on the use of allo-SCT in patients (pts) with first relapse/progressive disease after autograft focusing on the achieving of sCR, MRD detection and maintenance. A total of 89 pts (m, 62%) with median age of 53y (24-73) relapsed after an autograft (single, 64%; tandem, 36%) and received an allo-SCT during 2000–2015 yrs at University of Hamburg were included. A total of 77% of pts received a reinduction therapy. 13 pts (34%) had high risk cytogenetics (del17p and/or t(4;14) by FISH). 12 pts experienced extramedullary relapses. At time of allo-SCT pts were in

CR (11%), vgPR (20%), PR (34%), SD (29%) or PD (6%). Allo-SCTs were performed mostly with peripheral stem cell (92%) and from unrelated (matched, 40%; mismatched, 32%) donors. Myeloablative conditioning was used in 70%. A total of 33 pts (37%) received a maintenance therapy ± DLIs (lenalidomide, 79%) starting at median 6 mo (4-8) post-transplant. The cumulative incidence (CI) of acute GvHD (grade II-IV) at d100 was 43% (32-55%). The CI of chronic GvHD at 5y was 51% (39-63%; mild, $n = 19$, moderate, $n = 12$, severe, $n = 5$). Of the 19 pts receiving DLIs (positive immunofixation, $n = 15$; prophylaxis, $n = 4$), 5 (26%) developed GvHD (grade II-IV); six (40%) of 15 pts responded (CR). The CI of TRM at d100 and at 5y were 8% (4-16%) and 19% (12-28%), respectively. The use of radiation was associated with higher TRM (28% vs 9%; $P = 0.03$). The CI of relapses at 5y was 61% (49-72%). The pts with longer remission duration (> 24 mo) had lower relapse incidence (31% vs 65%, $P = 0.07$). The 5y EFS was 28% (19-39%). The median EFS was 29 mo (22-36). In univariate analysis, we observed decreased survival probability for pts with high risk cytogenetics ($P = 0.012$), remission duration $\leqslant 24$ mo ($P = 0.04$) and for those without maintenance ($P = 0.002$). In multivariate analysis the significant impacts of remission duration $\leqslant 24$ mo (HR 3.0, 1.4-6.6; $P = 0.007$), no maintenance after allograft (HR 2.2, 1.2-4.0, $P = 0.01$) and MRD (FACS) negativity (HR 0.4, 0.2-0.7, $P = 0.002$) were observed. In landmark analysis at d100 we observed improved survival for pts in sCR compared to those in CR/vgPR (68% vs 35%; $P = 0.023$) as well as those with negative MRD (79% vs 52%; $P = 0.037$). After a median follow up of 48 mo (6-170), the 5y OS was 57% (46-78%). The median OS was 76 mo (42-110). In univariate analysis, we observed decreased survival probability for pts with extramedullary relapse ($P = 0.039$), high risk cytogenetics ($P = 0.006$) and those who received reduced intensity conditioning ($P = 0.022$) and remission status at allo-SCT (CR/vgPR vs others, $P = 0.02$). In multivariate analysis the significant impact of no maintenance after allograft (HR 2.4, 1.1-5.4, $P = 0.033$) and MRD (FACS) negativity (HR 0.3, 0.1-0.6, $P = 0.001$) was observed. In landmark analysis at d100 we observed improved survival for pts in sCR compared to those in CR/vgPR (74% vs 45%; $P = 0.032$). Allo-SCT being performed as salvage therapy after autograft failure resulted 30% 5y EFS. The achievement of sCR on d100 post-transplant, augmented by the MRD detection, seems to be prognostic important. The use of DLIs and maintenance therapy post-transplant represent a possible approach to further improve survival.
Disclosure of conflict of interest: None.

Acute leukemia

O099

Thiotepa-busulfan-fludarabine compared to busulfan-fludarabine as conditioning regimen for matched sibling and unrelated donor transplant in patients with acute myeloid leukemia in fist complete remission. A study from the Acute Leukemia Working Party (ALWP) of the European society for Blood and Marrow Transplantation (EBMT)

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Intravenous (iv) Busulfan plus fludarabine (BF) is a widely used conditioning regimen for matched sibling (MSD) and unrelated donor (URD) transplant (SCT) in AML. Thiotepa, busulfan and fludarabine (TBF) regimen was initially developed for cord blood and subsequently employed in haplo-SCT; however, there is limited evidence about its value in MSD and URD SCT in AML. We included adult AML patients (pts) who had received TBF or BF as conditioning regimen for MSD or URD SCT in CR1 between 2007 and 2015, reported to the EBMT. Pts who received oral busulfan, T-depleted grafts, or transplant from 8/10 or inferior HLA-matched donor were excluded. Myeloablative conditioning regimen (MAC) was defined by iv Busulfan dose $> = 9.6$ mg/kg (TBF-MAC and BF-MAC), while reduced-intensity conditioning (RIC) by iv Busulfan dose of 6.4 mg/kg (TBF-RIC and BF-RIC). A total of 2910 pts met the inclusion criteria (212 TBF and 2698 BF). 147 pts received TBF-MAC and 65 TBF-RIC, while 1459 received BF-MAC and 1239 BF-RIC regimen, respectively. Fifty-seven percent of the pts were transplanted from MSD, 34% from 10/10 URD and 9% from 9/10 URD, respectively. As compared to BF-MAC, TBF-MAC group included significantly younger pts (45 vs 50 years), which were transplanted more recently (2014 vs 2013), received more frequently URD transplant (49% vs 35%) from a male donor (69% vs 59%) and BM as stem cell source (34% vs 17%). Engraftment rate was 98% following both regimens. The 2-year NRM was significantly higher after TBF-MAC compared to BF-MAC (27% vs 16%, $P = 0.006$), respectively. Incidence of grade II-IV aGVHD was 25% vs 24% ($P = 0.8$), respectively. The 2-year cumulative incidence of cGVHD was similar following TBF-MAC (35%) compared to BF-MAC (40%, $P = 0.5$). The 2-year RI was significantly lower in TBF-MAC (14%) compared to BF-MAC (27%, $P = 0.002$), while LFS and OS were 59% vs 57% ($P = 0.5$) and 62% vs 61% ($P = 0.9$) in TBF-MAC vs BF-MAC, respectively. The 2-year refined GVHD-free, relapse-free survival (GRFS) was 52% in TBF-MAC and 41% in BF-MAC ($P = 0.2$). Multivariate analysis confirmed significantly higher NRM (HR 2.7, $P < 10^{-4}$) and lower RI (HR 0.47, $P = 0.005$) for TBF-MAC, thus leading to similar LFS ($P = 0.6$) and OS ($P = 0.3$) as compared to BF-MAC. A propensity score (PS)-matched pair analysis conducted on 138 TBF-MAC vs 262 BF-MAC pts confirmed those results. Among pts who received a RIC regimen, TBF group (TBF-RIC) included significantly more pts receiving BM graft (17% vs 5%), transplanted more recently (2014 vs 2012), with a combination of CMV positive donor (71% vs 53%) and recipient (87% vs 66%), as compared to BF-RIC. Engraftment rate was 96% following TBF-RIC and 99% after BF-RIC ($P = 0.063$).Incidence of 2-year NRM was 15% and 18% for TBF-RIC and BF-RIC, respectively ($P = 0.6$). Incidence of grade II-IV aGVHD was 22% in both protocols. Cumulative incidence of cGVHD at 2 years was 40% in TBF-RIC and 34% in BF-RIC ($P = 0.95$), while RI was 39% vs 30% ($P = 0.6$), respectively. Similarly, no difference was observed in terms of LFS (47% vs 52%, $P = 0.4$) and OS (60% vs 57%, $P = 0.8$). The 2-year refined GRFS was 38% in both groups. Multivariate analysis and PS-matched pair analysis on 61 TBF-RIC vs 118 BF-RIC pts confirmed those results. These data suggest that in AML pts transplanted from MSD or URD-SCT in CR1, TBF-MAC provides better leukemia control but significantly higher NRM, thus leading to similar survival as compared to BF-MAC. RIC doses of TBF and BF resulted in analogous outcome.
Disclosure of conflict of interest: None.

O100

Outcomes after single cord blood and unmanipulated haploidentical stem cell transplantation using thiotepa-busulfan-fludarabine (TBF) as myeloablative conditioning in adult patients with acute myeloid leukemia in complete remission: a comparative study on behalf of EUROCORD and the ALWP of the EBMT

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Unrelated cord blood transplantation (UCBT) and unmanipulated haploidentical stem cell transplantation (Haplo) are valid alternative options to treat patients (pts) with AML in need of HSCT. TBF as myeloablative conditioning (MAC) in single UCBT (SUCBT) has been widely applied and its efficacy is well established. Recently, its use is substantially increasing in the Haplo setting. We retrospectively compared results of SUCBT ($n = 133$, 57 females and 76 males) and Haplo ($n = 184$, 83 females and 101 males) after TBF-based MAC in adults with de novo AML in first (CR1) or second (CR2) complete remission. Pts were transplanted between 2007 and 2015 in 77 EBMT centres (15 performed both SUCTB and Haplo). None had prior HSCT. TBF MAC was defined as a regimen containing a total dose of intravenous Busulfan $\geqslant$ 9.6mg/Kg. Median follow-up was 21 and 22 months in SCBT and Haplo, respectively. Haplo were performed more recently, 2014 vs 2011 for SUCBT ($P < 10^{-4}$). Most of the pts were transplanted in CR1 (76% and 70% in SUCBT and Haplo, respectively, $P = 0.2$). Median time from diagnosis to transplant was longer for Haplo (6.6 vs 5.7 months, $P = 0.01$). Median age was 41 (range 18–68) and 45 (range 18-66) years at SUCBT and Haplo ($P = 0.028$), respectively. ATG was most frequently used in SUCBT (87% vs 29%; $P < 10^{-4}$). In Haplo, bone marrow was the main source (80%) and post-transplant cyclophosphamide (PT-Cy) was administrated in 70% of the pts. Neutrophil engraftment was achieved in 88% of SUCBT and 96% of Haplo ($P = 0.018$). In univariate analysis, 2-years (2-y) relapse incidence (RI) was 11% for SUCBT and 16% for Haplo ($P = 0.44$). Cumulative incidence (CI) of grade II-IV acute GVHD (aGVHD) at 100-days and chronic GVHD (cGVHD) at 2-y were 28% and 37% for SUCBT, and 26% and 34% for Haplo ($P = 0.88$ and $P = 0.57$), respectively. CI of 2-y NRM was higher in SUCBT (44% vs 22%, $P < 10^{-4}$). The 2-y probabilities of LFS and GRFS in SUCBT and Haplo were 44% vs 61% ($P < 10^{-4}$) and 31% vs 54% ($P < 10^{-4}$), respectively. Overall, 65 pts died after SUCBT and 52 after Haplo. Causes of death were relapse (SUCBT: 13%, Haplo: 27%), GVHD (SUCBT: 24%, Haplo: 20%), infections (SUCBT: 46%, Haplo: 35%), others (SUCBT: 17%, Haplo: 18%). OS at 2-y was higher for pts receiving Haplo (67% vs 48%, $P = 0.0005$). No significant differences were found between pts given or not PT-Cy in the Haplo group. In multivariate analysis, NRM was significantly higher in SUCBT compared to Haplo (HR: 2.54, $P = 0.008$, 95%CI: 1.27–5.06). SUCBT did worse in terms of LFS, GRFS and OS (LFS, HR: 1.75, $P = 0.044$, 95%CI: 1.01–3.02; GRFS, HR: 1.72, $P = 0.027$, 95%CI: 1.0692.78; OS, HR: 1.75, $P = 0.05$, 95%CI: 1–3.07). Type of donor was neither associated with RI, nor to grade II-IV aGVHD or cGVHD. Other factors associated with poorer outcomes were age at transplant, use of female donors in male pts and Karnofsky PS < 90. No centre effect was found. These results were all confirmed using propensity score analysis. These findings indicate that TBF-based regimen is effective and safe in the Haplo setting. In the current cohort, NRM, LFS, GRFS and OS were improved for Haplo compared to SUCBT. High NRM in SUCBT was mostly due to infections. Impact of older age and poorer Karnofsky PS suggest that TBF at reduced intensity could be considered in older or unfit pts to improve outcomes.

Disclosure of conflict of interest: None.

O101

Previously Published

O102

The outcome of BEAC conditioning regimen prior to autologous stem cell transplant in non-Hodgkin lymphoma (NHL) and comparison with BEAM conditioning: a Lymphoma Working Party-EBMT study

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High dose therapy and autologous stem cell transplant (ASCT) is considered the standard consolidation therapy in several lymphoma subtypes. The optimal conditioning therapy for ASCT has not been established and most centres currently use the BEAM regimen (BCNU, VP-16, ara-C, melphalan). A recent shortage of melphalan has prompted transplant centres to use alternative conditioning regimens. The BEAC regimen (BEAM with melphalan substituted by cyclophosphamide) has previously been described and is, therefore, a reasonable alternative. However, there have been concerns raised about the toxicity of BEAC conditioning, particularly in relation to cardiac complications and multiple organ failure (MOF). We conducted a retrospective analysis of the EBMT database. Inclusion criteria were the following: BEAC or BEAM conditioning prior to ASCT; age > 18; histological diagnosis of follicular lymphoma, diffuse large B cell lymphoma, mantle cell lymphoma or peripheral T cell lymphoma; no prior transplant; peripheral blood stem cells; date of transplant 2007–2016. Planned tandem SCTs were excluded. 21722 patients (424 BEAC, 21298 BEAM) were identified fulfilling these criteria. Basic patient and transplant related details were obtained from the Med A submissions to the EBMT database. 383 BEAC conditioned patients with adequate essential data were matched with BEAM conditioned patients (ratio of 1:2) using the following matching criteria: age at SCT, gender, disease status at SCT, performance status at SCT, NHL subtype, year of SCT. The matched cohorts were compared in terms of non-relapse mortality (NRM), relapse (RR), progression free survival (PFS) and overall survival (OS). A total of 383 patients received BEAC conditioning regimen prior to ASCT at 29 different centres. Only 11 centres had used the BEAC conditioning 5 or more times and 1 centre performed 149 of the transplants. The number of BEAC conditioned ASCT ranged from 23 to 70 per year over the study period. There was a marked variation in the use of BEAC by country, with the majority of cases performed in 5 countries (Sweden 171, Finland 77, Israel 63, Portugal 43, Italy 34). The characteristics of the BEAC and the matched BEAM cohorts are given in Table I. With a median follow up of 28 months for the BEAC group, 25 patients have died from NRM events (6 infection, 5 MOF, 2 infection + cardiac toxicity, 1 infection + pulmonary toxicity, 1 cardiac

toxicity, 6 secondary malignancies, 4 unknown). In the matched BEAM cohort there were 34 NRM events (9 infection, 4 MOF, 1 infection + VOD, 2 infection + pulmonary toxicity, 4 cardiac toxicity, 5 secondary malignancies, 5 other causes, 4 unknown). At 1 year the cumulative incidence of NRM was 4% in the BEAC conditioned patients and 3% in the BEAM group (P = NS). The 2-year RR was 32% with BEAC and 33% with BEAM (P = NS). At 2 years the PFS was and OS were 63% and 78% for BEAC and 63% and 77% for BEAM conditioned patients (P = NS for PFS and OS). In this retrospective study the toxicity observed with BEAC conditioning as measured by NRM was similar to that seen with BEAM. The concerns regarding cardiac toxicity and MOF were not confirmed with 32% and 23% of NRM deaths in the BEAC and BEAM cohorts, respectively, being related to these toxicities. In addition, there were no significant differences between the two groups in terms of other outcomes, suggesting that BEAC is a safe conditioning regimen.

[O102]

Table I Characteristics of Patients

	BEAC (n=383)	BEAM (n=766)
Age at SCT, median (range)	57.6 (19-73)	57.9 (18-76)
Gender, n (%) Male	253 (66.1)	506 (66.1)
Female	130 (33.9)	260 (33.9)
Months from diagnosis-SCT, median (range)	11.5 (2.3-226)	11.7 (0.9-237)
Lymphoma subtype n, (%)		
Diffuse large B-cell lymphoma	159 (41.5)	318 (41.5)
Follicular Lymphoma	74 (19.3)	148 (19.3)
Mantle Cell Lymphoma	121 (31.6)	242 (31.6)
Peripheral T Cell	29 (7.6)	58 (7.6)
Performance Status		
Good	351 (91.6)	702 (91.6)
Poor	6 (1.6)	12 (1.6)
Not known	26 (6.8)	52 (6.8)
Disease status at SCT, n (%)		
CR1/VGPR1/PR1	196 (51.2%)	392 (51.2%)
CR/VGPR/PR>1	92 (24.0)	184 (24.0)
CR unknown	27 (7.1)	54 (7.1)
PR unknown	15 (3.9)	30 (3.9)
Primary Refractory	7 (1.8)	14 (1.8)
Relapse/Progression	46 (12.0)	92 (12.0)

Disclosure of conflict of interest: None.

O103
Previously Published

O104
Melphalan 140mg/m^2 demonstrates identical clinical outcomes to melphalan 200mg/m^2 amongst patients undergoing autologous transplant for multiple myeloma: a multicentre UK study

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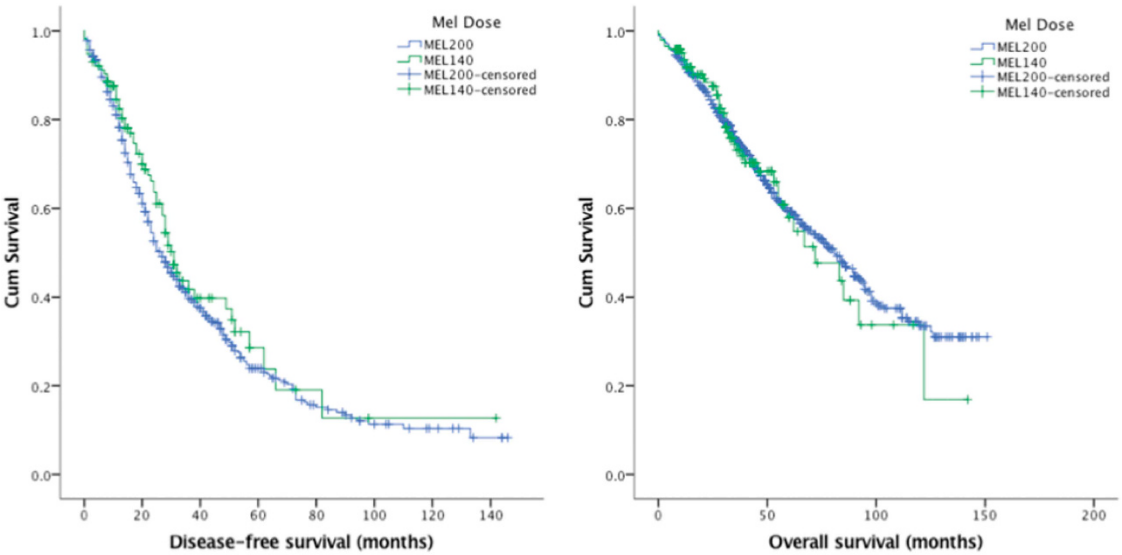
Dose-attenuated melphalan (MEL140) is used as a conditioning regimen for autologous stem cell transplant (ASCT) in older patients with multiple myeloma (MM), and in those with renal impairment or other substantial comorbidities, in order to minimise the risk of TRM and toxicities. Previous studies have compared MEL100 to MEL200, demonstrating that low-dose melphalan compromises progression-free survival[1]. However, multicentre studies have not investigated the efficacy of MEL140, despite its widespread use. Patients transplanted at University Hospitals Birmingham (2000–2012; n = 421)), Leeds Teaching Hospitals (2003–2014; n = 266) and Barts Health NHS Trust (2010–2013; n = 129), UK were included. MEL140 was used in all 3 centres for patients aged over 65 years, PS 2 or eGFR < 50mL/min/1.73m^2. The study was confined to first, single ASCT only and patients were identified from data submitted to the EBMT registry. For continuous variables, data represent medians, with Mann–Whitney U test for statistical significance. Categorical variables were assessed using the Chi-square test. The logrank test was used to define significance in the Kaplan–Meier survival analyses. A total of 816 patients underwent ASCT during the study period, of which 144 (17.6%) received MEL140. Patients receiving MEL140 were older (66 vs 58 years; $P < 0.001$), had a lower eGFR (59.0 vs 84.8 mL/min/1.73m^2; $P < 0.001$), were more likely to have an intermediate or high risk haematopoietic cell transplantation-specific comorbidity index (HCT-CI) score (43.1% vs 20.8%; $P < 0.001$) and had a higher ISS stage (52.5% stage III vs 22.9%; $P < 0.001$) compared to patients who received MEL200. Nonetheless, Kaplan–Meier survival analysis showed no significant difference in DFS or overall survival between MEL140 and MEL200 (Figure 1). Cox regression analysis, incorporating age, gender, eGFR, year of transplant and melphalan dose, confirmed that both DFS and overall survival were equivalent in MEL140, compared to MEL200 patients (HR = 0.99 (95% CI: 0.72–1.36); P = 0.95 and HR = 1.16 (95% CI: 0.80–1.67); P = 0.44 respectively). TRM was similar in both patient groups (3 (2.7%) in MEL140 and 12 (2.2%) in MEL200; P = 0.761). There was significant variation in MEL140 usage amongst transplant centres (10.8% in Leeds vs 21.1% in Birmingham vs 26.4% in Barts; $P < 0.001$) and this was not explained by regional differences in age, renal impairment or HCT-CI score. Kaplan–Meier survival graphs showing DFS (left) and overall survival (right) for all patients that underwent ASCT. This study demonstrates equivalent clinical outcomes between MEL140 and MEL200 conditioning regimens for ASCT in MM, despite higher patient age, greater renal impairment, higher comorbidity score and higher ISS stage in the MEL140 group. This indicates that patients receiving MEL140 are being treated appropriately and raises the possibility that more patients currently regarded transplant-ineligible, could benefit from reduced-dose melphalan. The variation in MEL140 usage amongst transplant centres is indicative of the deficiency in the evidence base, and highlights the need for guideline development and implementation.

Disclosure of conflict of interest: None.

Reference

1. Palumbo A, Bringhen S, Bruno B *et al*. Melphalan 200 mg/m^2 versus melphalan 100 mg/m^2 in newly diagnosed myeloma patients: a prospective, multicenter phase 3 study. *Blood* 2010; **115**: 1873–9.

Figure 1 [O104]



MEL140 median DFS = 31 months (95% CI: 26.6-35.4)
MEL200 median DFS = 27 months (95% CI: 23.6-30.4)
P=0.261

MEL140 median OS = 72 months (95% CI: 47.1-96.8)
MEL200 median OS = 81 months (95% CI: 71.1-90.9)
P=0.801

O105

Sequential conditioning with Thiotepa in T-cell replete HLA-haploidentical hematopoietic stem cell transplantation for the treatment of refractory hematological malignancies: comparison with matched related and unrelated donors

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The results of conventional allogeneic stem cell transplantation (SCT) in refractory hematological malignancies are poor. Sequential strategies, such as FLAMSA, have shown promising results in refractory acute myeloid leukemia (AML), but have not been validated in the haploidentical (Haplo) setting. We developed a new sequential approach combining chemotherapy with broad anti-tumor activity, followed by reduced-intensity conditioning (RIC) regimen for the treatment of wide spectrum refractory hematologic malignancies. Seventy-two patients (median age, 54 years) with refractory hematological malignancies (44 AML, 7 ALL, 8 MDS, 5 CMML, 2 MPN and 6 lymphomas) were included in this retrospective multicenter study. The Karnofsky score was $< 90\%$ in 39 patients (54%). The comorbidity index was $\geqslant 2$ in 41 patients (59%). Graft source was PBSCs in 65 patients (90%). Twenty-seven patients received Haplo and were compared to 16 patients with matched related donor (MRD) and 29 patients with unrelated donor (UD) who received the same regimen. TEC-RIC regimen consisted in total dose Thiotepa of 10 mg/kg, Etoposide 400 mg/m^2, Cyclophosphamide (Cy) 1600 mg/m^2 (day-15 to -10), and after 3 days rest, Fludarabine 150 mg/m^2, iv Busulfan 6.4 mg/kg and Thymoglobuline 5 mg/Kg (day-6 to -2). For patients older than 60 years and/or with comorbidities, Thiotepa, Etoposide and Cy total doses were reduced to 5 mg/kg, 300 mg/m^2, and 1200 mg/m^2, respectively. GVHD prophylaxis consisted of Cyclosporine and Mycophenolate Mofetil. High dose post-transplant Cy (PT-CY) was added in case of Haplo. Median follow-up was 14 months (range, 3.5–37). Neutrophil recovery was delayed in Haplo (median 18.5 days; range, 13-32) compared to MRD (median 13 days; range, 10-17) and UD (median 14 days; range, 10-47) ($P = 0.001$). The cumulative incidence of grade II-IV and grade III-IV acute GVHD was 11.1% and 3.7% in Haplo, 12.5% and 0% in MRD, 41.4% and 31% in UD patients ($P = 0.031$ and $P = 0.003$, respectively). Chronic GVHD developed in 8/20 evaluable Haplo patients (including 1 severe form), 6/13 MRD patients (1 severe form) and 11/19 UD patients (3 severe forms) ($P = 0.528$). At day+30, 69 patients were evaluable for response and 66 patients (95.7%) were in CR. At last follow-up, 21 patients relapsed, 28 died and 44 are still alive. Cumulative incidence of 1-year NRM was 16.7% in Haplo, 20.5% in MRD, and 31.3% in UD, respectively ($P = 0.362$). The 1-year OS and EFS were 73.6% and 60.8% in Haplo, 61.1% and 48.2% in MRD, 49.9% and 41.4% in UD, respectively ($P = 0.20$ and $P = 0.08$). Thirteen patients (including 6 Haplo) received prophylactic DLI (pDLI). In order to enhance the GVL effect, azacytidine was administered to 3 patients and sorafenib to one patient in combination with pDLI. After a median follow-up of 16.5 months post-pDLI, 12/13 patients were alive. TEC-RIC sequential conditioning regimen seems to be a safe and valid platform in Haplo setting with PT-CY for patients with wide-spectrum refractory hematological diseases. In comparison with MRD and UD allo-SCT, toxicities were not increased and survival was not inferior in Haplo. Thus, there seem to be no benefit in searching for UD when a Haplo donor is easily and quickly available. Two prospective multicenter studies based on this new sequential approach including early post-transplant immuno-intervention are currently being scheduled.

Disclosure of conflict of interest: None.

O106

Previously Published

O107

A Rapid and Sensitive molecular tool for the early diagnosis of hla loss relapses after partially-incompatible allogeneic HSCT

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Genomic loss of the mismatched HLA haplotype represents a frequent mechanism of leukemia immune evasion and relapse after partially-incompatible allogeneic HSCT, accounting for up to one third of relapses after haploidentical HSCT and a yet unknown proportion of relapses after unrelated donor HSCT. Detection of HLA loss variants has relevant clinical implications, since infusion of lymphocyte from the donor is expectedly inefficacious against these forms of relapse. Thus, sensitive, reliable and easy to perform assays are needed to render this diagnosis possible to all centers performing partially HLA-mismatched HSCT. Here we designed an innovative methodology to detect HLA loss relapses, based on the combination of quantitative PCR (qPCR)-based chimerism to detect host markers ("outside HLA" markers) with ad hoc designed qPCR reactions targeting the most frequent HLA allele groups ("inside HLA" markers). Concordance between the inside and outside HLA markers identifies classical (non-HLA loss) relapses, whereas presence of host-specific outside HLA markers with concomitant negativity of the patient-specific HLA identifies HLA loss relapses. For "outside HLA" markers, a commercial qPCR chimerism assay targeting 29 in/del polymorphisms was used (KMRtype and KMRtrack assays, GenDx, Utrecht). For "inside HLA" markers we designed qPCR reactions specific for the most frequent HLA-A, -C and -DPB1 allele groups, targeting both locus-specific and allele group-specific polymorphisms. We tested the specificity, efficiency and sensitivity of each reaction using HLA-typed reference DNAs, serially diluted in water and in artificial chimeric mixtures, and validated the utility of the reactions with samples from patients who experienced classical ($n=4$) or HLA loss ($n=5$) relapses. We designed and validated a total of 10 "inside HLA" reactions, capable to provide at least one informative HLA marker to over two thirds of a representative series of 165 consecutive patients who received haploidentical HSCT at our Institute. Each reaction was tested against a panel of HLA-typed cell lines ($n>20$) to confirm specificity and absence of crossreactivity. All the reactions displayed over 80% efficiency, with superimposable performance in water and in target-negative DNA ($R=0.99$, $P<0.0004$). Accuracy and precision in chimerism determination resulted very high for all the reactions, with almost perfect concordance between the expected and experimentally-determined quantification ($R=0.99$, $P<0.0001$). Maximal reproducible sensitivity (defined as the lowest dilution in which all replicates are positive within a 1.5 cycle threshold range) was at least 0.2% for all the reactions. The clinical utility of the newly developed assays was confirmed analyzing 9 cases of relapse after partially HLA-mismatched HSCT. In all cases we detected host-specific chimerism using outside HLA markers and, as expected, HLA markers resulted positive in case of classical relapses (4/4) and negative for HLA loss relapses (5/5). We developed a highly sensitive, reliable, and easy-to-implement molecular tool to unequivocally discriminate between classical and HLA loss relapses, facilitating further retrospective and prospective studies and allowing the implementation of this differential diagnosis in the therapeutic algorithm for post-transplantation relapses.

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O108

Immune monitoring in allogeneic hematopoietic stem cell transplant recipients: a survey from the EBMT- Cellular Therapy & Immunobiology Working Party

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Post transplant immune reconstitution plays a major role in determining the outcome of allogeneic hematopoietic stem cell transplantation (allo-HSCT), and is currently monitored with different techniques in different Centers, with the aim of identifying clinically relevant immunological biomarkers. However, it is unclear which and how many of these tests are currently performed on a routine basis, and which ones have the potential to guide patient care after allo-HSCT. The EBMT Cellular Therapy & Immunobiology Working Party (CTIWP) conducted a survey to identify current policies to monitor immune reconstitution in patients undergoing allo-HSCT and possibly reach a general consensus. This study followed the EBMT study guidelines. All EBMT Centers were invited to participate. Each participating Center received a questionnaire on the availability of specific immunomonitoring assays, specifying the use in clinical practice and/or within investigational trials. Policies for post-transplant immunomonitoring have been reported by 56 participating EBMT Centers active in 19 Countries and performing allo-HSCT from HLA identical related (56 centers), matched unrelated (54), haploidentical (55), unrelated cord blood (50). Complete blood counts and immunoglobulins are routinely tested for patients' care by all centers. Relative proportions of T cell subsets are currently tested by flow-cytometry as "standard of care" or "investigational" by 82% and 36% of centers respectively. B cell and NK cell counts are quantified routinely by 43% and 23% of Centers, and investigationally by 54% and 55% of Centers. The availability of molecular tests (STR, qPCR, Fish) to measure post-transplant engraftment are reported by all Centers, except three, as a standard of care measure. T cell receptor–expressing circles (TRECs) and/or K-deleting recombination excision circles (KRECs) are quantified within selected clinical trials by 36% of Centers. Interestingly, 66% of Centers evaluate, mostly as an investigational measure, antigen specific T cell responses by: proliferation assays (50%), interferon-gamma enzyme-linked immunospot-Elispot (45%), intracellular cytokine staining (48%) and tetramer/dextramer staining (34%). Most of these Centers test responses to Cytomegalovirus and Epstein Barr Virus, and 14 Centers use at least one of these assays on a routine basis. Most of the participating Centers

(68%) commonly test antigen-specific antibodies, mainly as responses to vaccines, and not routinely. T-cell receptors (TCR) and B-cell receptors (BCR) repertoires are measured by spectratyping in 20 out of 56 Centers (7 as clinical practice and 13 in selected trials), or, in selected trials, by next generation sequencing (in 18 out of 56 the participating Centers). Results of this survey indicate that country- and center expertise are associated with heterogeneous and distinct protocols, and underline the clinical need to harmonize methods and to provide practical recommendations for monitoring post-transplant immune reconstitution, both for routine purposes and investigational studies. Adequate reporting and connection between individual Centers exploiting these data will foster collaborative and comparative research studies, with the ultimate goals of improving patient care and refining our understanding of the immunological correlates to clinical outcome.

Disclosure of conflict of interest: None.

O109

Multiple inhibitory receptors are expressed on central memory and memory stem T cells infiltrating the bone marrow of AML patients relapsing after allo-HSCT

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In patients with acute myeloid leukemia (AML), relapse is the major cause of death after allogeneic HSCT. To investigate whether T-cell dysfunction is associated with post-transplant relapse, we longitudinally analyzed bone marrow (BM) and peripheral blood (PB) samples of 32 AML patients receiving HSCT from HLA-matched (HLAid, 20 pts) or HLA-haploidentical (haplo, 12 pts) donors. BM and PB were collected 60 days after HSCT and at relapse (median 251 days; 16 pts) or at 1 year in case of complete remission (CR; 16 pts). Samples from 10 healthy donors (HD) were used as controls. The expression of inhibitory receptors (IRs) on T-cell subsets was evaluated by multi-parametric flow cytometry. Results were analyzed with both the Flow-Jo software and the BH-SNE algorithm, an unbiased computational method. To evaluate T-cell effector functions, the CD107a degranulation assay was performed and the production of cytokines was measured by intracellular staining. The ability of BM T cells to kill AML blasts after in-vitro rapid expansion protocol (REP) was tested in co-colture experiments. We investigated the expression of PD-1, CTLA-4, KLRG1, LAG-3, 2B4 and Tim-3 as T-cell exhaustion markers. After haplo-HSCT, multiple IRs were significantly upregulated in BM and PB T cells at all time-points, compared to HD and independently from the clinical outcome. Conversely, after HLAid-HSCT, patients who relapsed, displayed a higher frequency of BM infiltrating T cells expressing PD-1, CTLA-4 and Tim-3 than CR pts ($P < 0.05$) and HD ($P < 0.01$). Results were confirmed by using the BH-SNE algorithm. We then investigated the profile of each memory T-cell subset in our cohort. In the BM of HD and CR-patients the expression of IRs was confined to late differentiated T cells. Differently, at relapse, PD-1, 2B4 and Tim-3 were also upregulated in BM infiltrating central memory ($P < 0.01$) and memory stem T cells ($P < 0.05$). To verify whether the phenotypic profile of T-cell exhaustion at relapse associates with functional impairment, we evaluated T-cell effector functions upon polyclonal stimulation. We observed a lower degranulation ability of both CD62L+ early differentiated ($P < 0.01$) and CD62L- late differentiated ($P < 0.05$) CD8 cells at relapse when compared to CR and HD. In 4 patients, we isolated and expanded by REP T cells expressing one or more IRs (IR+) or no IR (IR-). Expansion rates were high in both IR+ and IR- cells (mean fold increase 490 and 992, respectively at day 21). The degranulation ability measured ex-vivo in those patients (mean 9.2%) was dramatically increased upon REP expansion (80.0% and 79.9% for IR+ and IR-, respectively; $P < 0.001$). Similarly, the frequency of IFNg/TNFa producing CD8 cells increased in IR+ and IR- cells upon REP ($P < 0.05$), indicating that the T-cell dysfunction observed at relapse can be efficiently reversed. We next co-coltured IR+ and IR- cells with autologous leukemias. Strikingly, IR+ cells showed a greater ability to kill AML blasts (elimination index, EI = 68%) compared to IR- cells (EI = 40%; $P < 0.05$) at low effector to target ratio, suggesting that IR+ cells are enriched in leukemia specificities. After HSCT, the signature of exhausted T-cell in relapsing pts includes PD-1, CTLA-4, 2B4 and Tim-3. The IRs expression on early differentiated T cells at relapse suggests a wide, though reversible, immunological dysfunction mediated by relapsing AML blasts.

Disclosure of conflict of interest: None.

O110

Dynamics of expression of Programmed cell death protein-1 (PD-1) on T cells after allogeneic hematopoietic stem cell transplantation

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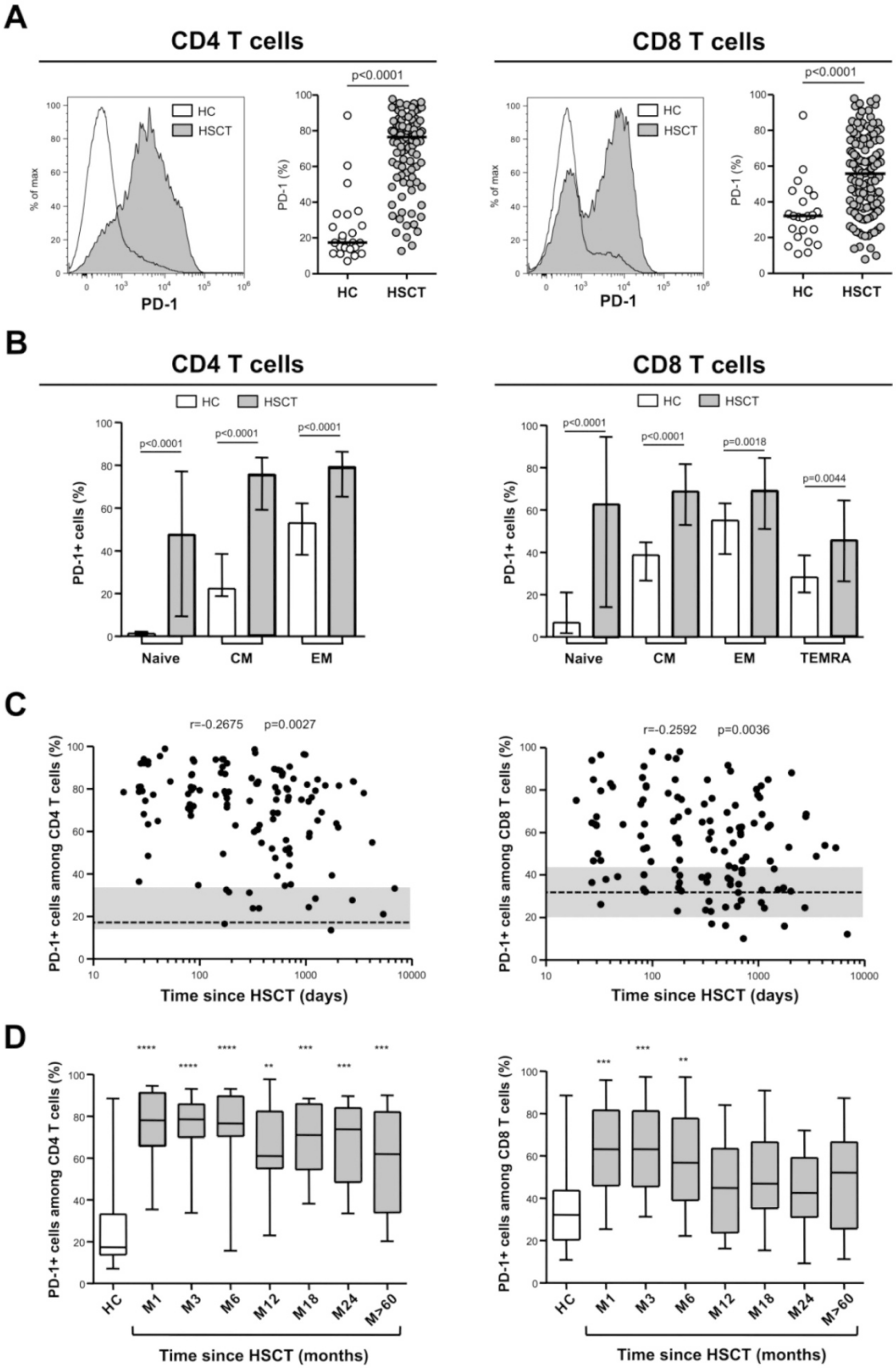
Blockade of the programmed-death 1 (PD-1) immune checkpoint represents a promising strategy to enhance anti-tumoral immune responses after allogeneic hematopoietic stem cell transplantation (allo-HSCT)1,2. However, observational studies suggest that PD-1 blockade can be complicated by the development of severe graft-versus-host disease (GvHD) 2,3. A better knowledge of the dynamics of PD-1 expression by T cells after allo-HSCT is necessary in order to optimize PD-1 targeting therapies and limit toxicities. We analyzed by flow cytometry 124 freshly drawn blood samples isolated from 98 allo-HSCT recipients. Twenty-three healthy blood donors served as controls (HC). We observed a strong increase in PD-1 expression at the surface of CD4 and CD8 T cells isolated from allo-HSCT recipients compared with HC (Fig 1A). Importantly, we observed the significant increase of PD-1 expressing cells in all CD4 and CD8 T cell subpopulations studied including naïve, central memory (CM), effector memory (EM) and terminal EM CD45RA+ (TEMRA) cells (Fig. 1B). We observed an inverse correlation between the time since allo-HSCT and PD-1 expression at T cell surface (Fig. 1C). PD-1 expressing cells were higher than normal already at one month after allo-HSCT (Fig. 1D). Thereafter, the proportions of CD4 PD-1+ T cells remained higher than in HC up to more than 5 years after HSCT, while the PD-1 expression on CD8 T cells started to normalize from 1 year after transplantation on (Fig. 1D). The stem cell source (BM vs PBSC), conditioning regimen (RIC vs MAC), use of total body irradiation and disease status at HSCT did not impact PD-1 expression. We observed higher proportions of PD-1+ CD4 but not of PD-1+ CD8 T cells in patients having received *in vivo* and/or ex vivo T-cell depletion (TCD) compared with patients receiving T cell replete grafts ($P = 0.0269$). CD8 T cells from patients receiving grafts from haploidentical donors expressed higher proportions of PD-1+ cells than CD8 T cells from patients receiving grafts from matched related ($P = 0.0492$) or unrelated donors ($P = 0.0049$). No association was found between PD-1 expression on T cells

Figure 1 [O110]



and post-transplant complications, including acute or chronic GvHD, disease relapse and CMV reactivation. We report here a rapid and long lasting increase of PD-1 expression by CD4 and CD8 T cells after allo-HSCT. Several factors, including TCD and transplantation from haploidentical donors, are associated with a further increase in PD-1 expression on T cells. These results will help harnessing the potential of PD-1 blockade after allo-HSCT.

References: 1 Villasboas *et al*., Oncotarget (2016) 2 Haverkos *et al*., Blood 128.22 (2016): 1163 3 Singh, A. K., *et al*. Bone marrow transplantation (2016) 6. Image: (A) Expression of PD-1 on T cells after allo-HSCT. (B) Expression of PD-1 on T cell subsets (naïve: CD45RA+ CCR7+; CM: CD45RA- CCR7+; EM: CD45RA- CCR7- and TEMRA: CD45RA- CCR7-). (C) Relationship between PD-1 expression and days after HSCT. Median percentage (dashed line) and interquartile range (gray area) of PD-1 expression from HC. (D) Proportions of PD-1 expressing cells at different time-points after HSCT.

Disclosure of conflict of interest: None.

O111

Relapse of myeloid malignancies after allogeneic stem cell transplantation–a single center analysis

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Allogeneic stem cell transplantation (allo-SCT) can cure a considerable number of patients with high-risk myeloid malignancies, but still relapse remains the major cause of treatment failure. We retrospectively studied relapse kinetics, treatment and outcome of AML and MDS after allo-SCT at our center during a 13 year period. A total of 447 pts (median age 52 years, range 17–72, 55% male) received their first allo-SCT from a related (31%), unrelated (67%) or combined donors (2%) for myeloid malignancies at the University Hospital Dusseldorf between 2002 and 2015. Diagnoses were: 217 de novo AML (AML, 49%), 103 MDS (23 %), 53 MPN (12%, 32 CML, 21 OMF) and 74 sAML (16%, 69 evolving from MDS and 4 from MPN). Median follow up was 23.2 months (range 0.02–167.2). Median survival after allo-SCT of the whole cohort was 51.3 months (range 0.02–167.2). A total of 160 patients (35.8%) relapsed after a median of 4.5 months (range 0.43–110.4). The majority (113, 70%) were hematologic relapses (HR), 33 pts (21%) had molecular or cytogenetic relapses (MR) and 14 patients had extramedullary relapses (9%, XR, 8 isolated and 6 combined with HR). The great majority of relapses (115, 73%) occurred within the first 3 years (1st year: 73%, first + second year: 88%, first + second + third year 96%). Only 7 pts relapsed beyond the 3rd year. Median time to relapse differed by diagnosis (AML 3.7 months, range 0.43–88.6, MDS 14.7 months, range 0.9- 110 ms; MPN 5.6 months, range 0.6-90 ms, sAML 3.5 months, range 0.9-61.5, AML vs MDS $P = 0.002$, MDS vs sAML $P = 0.005$, MPN vs AML $P = 0.045$, MPN vs sAML p = n.s). Median survival time after relapse was 8.4 months and 2-year survival was 31.3 %. A total of 119 (74.4%) patients died a median of 4.6 month after relapse (range 0.2–105) and 41 (25.6%) are alive after treatment for relapse (9 with disease and 32 in CR). Following relapse, the majority of pts ($n = 143$, 89%) received at least one salvage therapy, while 9 pts received BSC only (8 pts no information). Primary salvage therapies were hypomethylating agents (HMA, $n = 101$ azacytidine, $n = 1$ decitabine), intensive chemotherapy ($n = 10$), sorafenib ($n = 11$) and radiotherapy ($n = 7$). DLI were applied in 85 pts and 2nd allo-SCT was performed in 19 pts. Type of treatment changed over time with increasing use of HMA ($n = 39$ before 2009 vs $n = 63$ after 2009, $P < 0.001$) and treatment results improved (median OS 4.5 months before 2009 vs 10.5 months after 2009, Breslow $P = 0.005$, 2 year OS 27% before vs 36% after 2009). Patients who were treated for MR had a better prognosis than patients with HR (OS 26.3 months vs 4.8 months, $P < 0.001$) as had patients with MDS vs AML (OS 89.3 months vs 5.6 months, $P < 0.001$). Of 36 patients who survived in remission > 2 years 23 (63.9%) had received HMA and DLI, 6 (23.1%) had received a second transplant, 2 DLI only, 4 tyrosinekinase-inhibitors, 2 interferone alpha and DLI and 1 intensive chemotherapy. A substantial number of patients who relapse with myeloid malignancies after allo-SCT can re-achieve remission and long term survival, especially with HMA+DLI or 2nd allo-SCT. Relapse of MDS carries a better prognosis than AML. Techniques to further improve the detection of MRD are urgently needed because early treatment of molecular relapse results in significantly better survival.

Disclosure of conflict of interest: GK and TS received research funding, lecture fees and travel support from Celgene. The remaining authors declare no conflict of interest.

O112

Unmanipulated haploidentical donor transplantation is superior to matched sibling donor transplantation in eradicating pre-transplantation minimal residual disease as determined by multiparameter flow cytometry

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This study compared the effects of pre-transplantation minimal residual disease (pre-MRD) on outcomes in AML patients who underwent human leukocyte antigen-matched sibling donor transplantation (MSDT) or who received unmanipulated haploidentical allografts. We compared outcomes in 340 AML patients who received MSDT ($n = 82$) versus unmanipulated haploidentical allografts ($n = 258$). MRD was determined using multiparameter flow cytometry. Patients who received allografts from haploidentical donors and MSDT had similar 2-year probabilities of leukemia-free survival (LFS) ($P = 0.703$) and overall survival (OS) ($P = 0.142$). Patients with negative pre-MRD had a lower incidence of relapse than those with positive pre-MRD in MSDT settings (7% vs 38%, $P < 0.001$), but relapse was comparable in haploidentical allograft settings for patients with negative pre-MRD (8%) versus positive pre-MRD (13%, $P = 0.167$). Of the patients with positive pre-MRD ($n = 76$), those who underwent MSDT had a higher incidence of relapse (38%) than those receiving haploidentical allografts (13%; $P = 0.017$) plus lower probabilities of LFS (54% vs 80% $P = 0.007$) and OS (64% vs 83%, $P = 0.062$). Multivariate analysis showed that for pre-MRD-positive AML patients, haploidentical allograft was associated with a low incidence of relapse (HR, 0.131; 95% CI, 0.037–0.467; $P = 0.002$) and with better LFS (HR, 0.221; 95% CI, 0.085–0.574; $P = 0.002$) and OS (HR, 0.325; 95% CI, 0.111–0.952; $P = 0.040$). Pre-MRD had no negative effects on outcomes after haploidentical transplantation. For pre-MRD-positive AML patients, haploidentical allograft was associated with lower incidence of relapse and better survival compared with MSDT. This suggests it is better to eradicate pre-MRD and has the stronger graft-versus-leukemia effects.

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Disclosure of conflict of interest: None.

Figure 1 [O112]

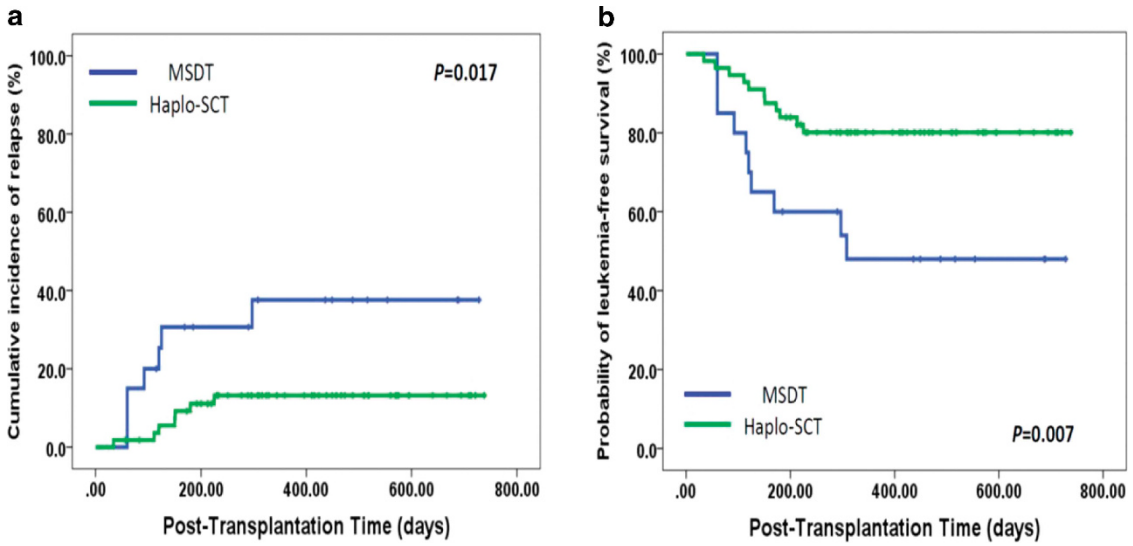

Figure 1. Relationship between pre-stem cell transplantation minimal residual disease (pre-SCT MRD), as determined by multiparameter flow cytometry, and transplant outcomes for pre-MRD positive patients with acute myeloid leukemia ($n = 76$). Kaplan-Meier estimates of (A) cumulative incidence of relapse and (B) leukemia-free survival.

O113

Molecular monitoring of acute myeloid leukemia using targeted ultra-deep sequencing

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Molecular monitoring based on assessment of minimal residual disease (MRD) is becoming increasingly more important after allogeneic stem cell transplantation (SCT) in acute myeloid leukemia (AML). A large proportion of adult AML cases however lack targets for quantitative polymerase chain reaction (qPCR), hampering molecular monitoring at high sensitivity. We have recently shown that mutations suitable for MRD analysis can be identified in the vast majority of AML patients using exome sequencing and can be quantified with high sensitivity using ultra-deep targeted sequencing (1). Here we tested the clinical value of this method for molecular monitoring before and after allogeneic SCT. Nineteen adults and six children with AML were monitored for MRD using ultra-deep sequencing. For adult patients with AML with mutated NPM1 a total of 37 bone marrow samples obtained just before and three months after SCT were analyzed for NPM1 mutation. One of the adult patients and the six children were monitored for other, non-recurrent, leukemia-specific mutations (identified in diagnostic sample using exome sequencing as in (1)) during treatment with chemotherapy with or without allogeneic SCT. Ultra-deep sequencing was performed in multiplex on the Illumina MiSeq platform, using Truseq-library preparation with strict demultiplexing. Based on the linearity and sensitivity of the assay, MRD positivity was defined as variant allele frequency (VAF) $\geqslant 0.03\%$. Results from ultra-deep sequencing were compared with results from chimerism analysis (short tandem repeat-PCR/fluorescence in situ hybridization) and/or conventional MRD analysis (flow cytometry/qPCR). MRD positivity was detected in 9/37 bone marrow samples from the adult patients. Of these, 4 were detected pre-SCT, and 5 post-SCT. In MRD positive samples, the NPM1 mutation load ranged from VAF 0.033-1.1%. All patients relapsing ($n = 5$) showed NPM1 MRD positivity in at least one of the samples. In patients with NPM1 MRD positivity either pre- or post-SCT, the relapse-free and overall survival were significantly shorter compared with patients with NPM1 MRD negativity at both time points ($P = 0.002$ for both). There was no correlation between results from chimerism analysis and NPM1 mutation load. In cases that were assessed with ultra-deep sequencing for other, non-recurrent, leukemia-specific mutations, there was a high concordance between the mutation loads of different mutations assessed in the same samples. The kinetics during chemotherapy mirrored that detected with flow cytometry, with the exception that ultra-deep sequencing could detect MRD positivity in several samples determined as MRD negative with flow cytometry. In one patient where there were available blood samples before relapse of AML, ultra-deep sequencing showed MRD positivity 2 months before morphological relapse. Molecular monitoring using targeted ultra-deep sequencing is a highly sensitive technique. The analysis can be patient-tailored and is therefore applicable to both cases with recurrent mutations and cases with non-recurrent mutations. This permits molecular monitoring and thus chances for early relapse-preventing intervention for virtually every AML patient.

Disclosure of conflict of interest: None.

Reference

1. Malmberg EB, Ståhlman S *et al*. Patient-tailored analysis of minimal residual disease in acute myeloid leukemia using next generation sequencing. *Eur J Haematol* 2016; e-pub ahead of print 20 May 2016.

O114

Cord blood transplantation recapitulates fetal ontogeny with a distinct molecular signature that supports CD4+ T-cell reconstitution

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[O114]

Figure 1

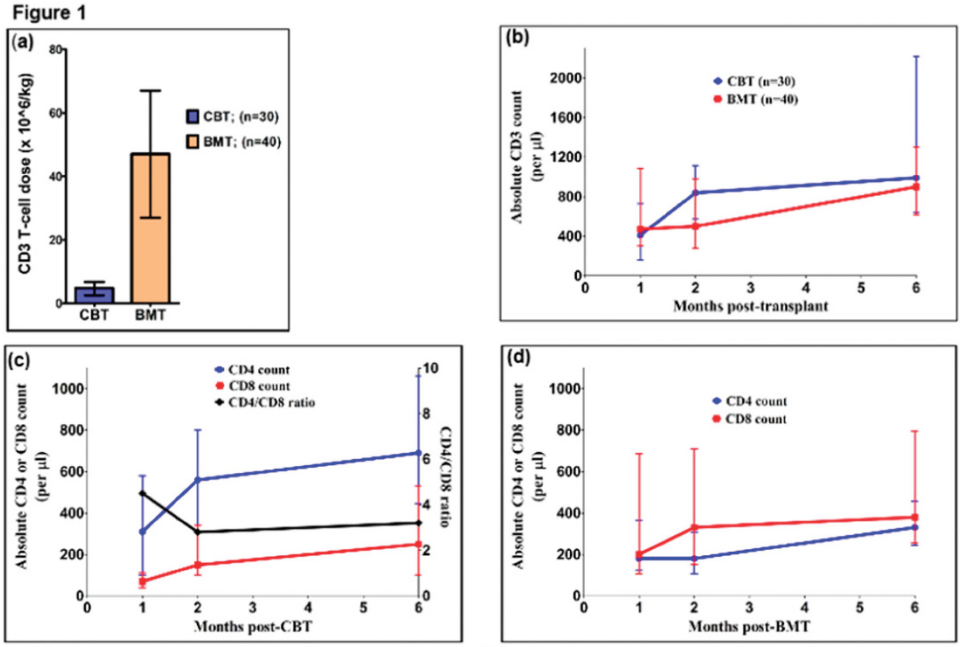

Figure 1 (a) is a bar graph showing T cells carried with a cord blood and a bone marrow graft. A median of 4 x 10^6/kg T cells are infused with a cord blood graft compared with 10 times more T cells (45 x 10^6/kg) infused with a bone marrow graft. The bar graph represent median and error bars represent 25th and 75th centile (b) is a line graph showing T-cell renconstitution after T-replete CBT and BMT. Despite 10 times lower number of T cells infused with the cord blood graft, a significantly higher CD3+ T-cell recovery is observed 2 months post-CBT compared with after BMT. (c) and (d) is a line graph showing CD4+ and CD8+ T-cell recovery after CBT and BMT respectively. The T-cell recovery observed after T-replete CBT was asymmetrically CD4+ T-cell biased in contrast to CD8+ T-cell biased immune-reconstitution after T-replete BMT. The dots represent the median and the error bar represent 25th and 75th centile. The black line represents CD4:CD8 ratio plotted on right Y axis.

Figure 2

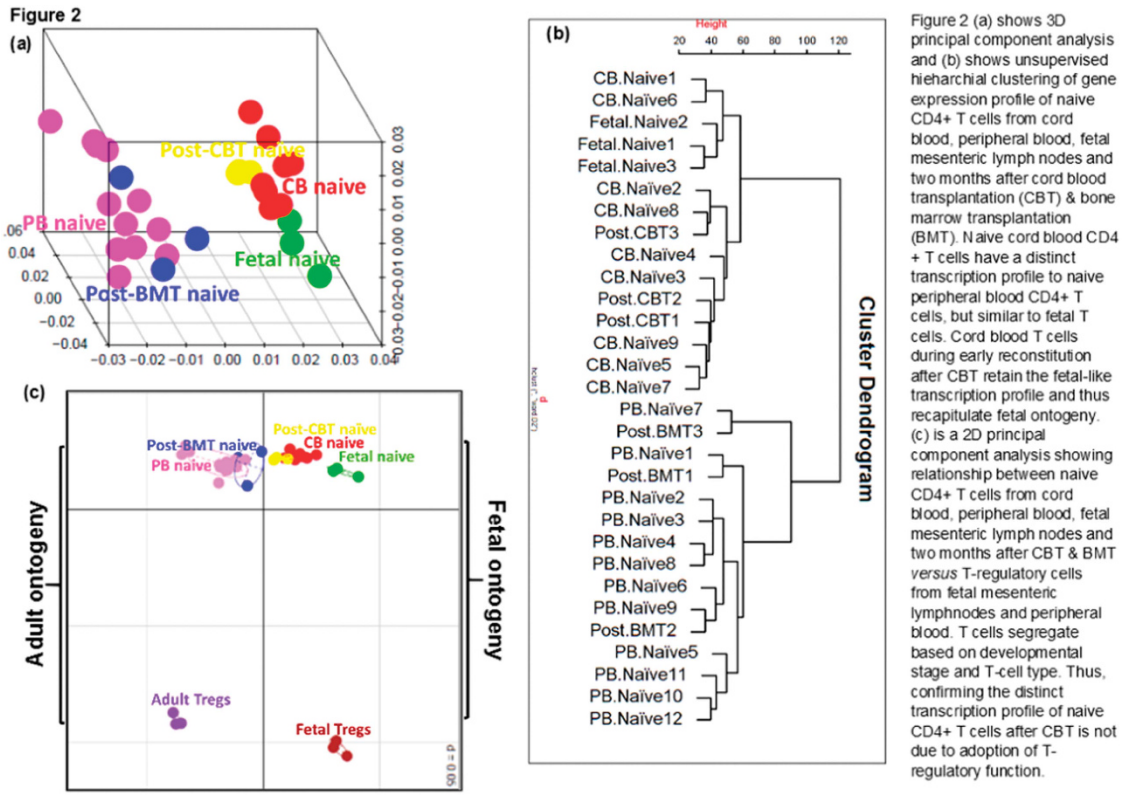

Figure 2 (a) shows 3D principal component analysis and (b) shows unsupervised hieharchial clustering of gene expression profile of naive CD4+ T cells from cord blood, peripheral blood, fetal mesenteric lymph nodes and two months after cord blood transplantation (CBT) & bone marrow transplantation (BMT). Naive cord blood CD4 + T cells have a distinct transcription profile to naive peripheral blood CD4+ T cells, but similar to fetal T cells. Cord blood T cells during early reconstitution after CBT retain the fetal-like transcription profile and thus recapitulate fetal ontogeny. (c) is a 2D principal component analysis showing relationship between naive CD4+ T cells from cord blood, peripheral blood, fetal mesenteric lymph nodes and two months after CBT & BMT *versus* T-regulatory cells from fetal mesenteric lymphnodes and peripheral blood. T cells segregate based on developmental stage and T-cell type. Thus, confirming the distinct transcription profile of naive CD4+ T cells after CBT is not due to adoption of T-regulatory function.

for Children, London; [7]Department of Haematology, University College London Cancer Institute; Anthony Nolan Research Institute, London and [8]University College London, Cancer Institute, Royal Free Campus, London

Lymphopoiesis is thought to occur in distinct layers during different stages of ontogeny, but the role of fetal ontogeny in the unique and enhanced CD4+ biased lymphopoiesis derived from the T cells carried with the cord blood graft is not known (Fig. 1). Gene expression profile (GEP) of CD4+CD45RA+CCR7+ (naïve) T cells from normal donor cord blood ($n = 3$) and normal donor peripheral blood ($n = 3$) were compared in 3 separate experiments. These GEPs were compared with those of reconstituting naïve CD4+ T cells at two months after T-replete CBT ($n = 3$) and BMT ($n = 3$). GEPs of naïve CD4+ T cells and T-regulatory cells (Tregs) from the fetal lymph nodes (18-22 weeks gestational age) and adult peripheral blood were retrieved (GSE25119) and their relationship with our experimental samples was elucidated. GEP of naïve CD4+ T cells from the cord blood and that of lymphocytes reconstituting following T-replete CBT were similar to the GEP of fetal CD4+ T cells but distinct to that of naïve CD4+ T cells from the peripheral blood and that of lymphocytes reconstituting after T-replete BMT (Fig. 2 a and b). Fetal ontogeny is biased towards T-regulatory function. We therefore compared GEPs of naive CD4+ T cells and Tregs. Naïve CD4+ T cells and Tregs segregated depending on the developmental stage and T-cell type (Fig. 2 c). Thus, confirming the distinct GEP of naïve CD4+ T cells after CBT is due to recapitulation of fetal ontogeny and not due to adoption of T-reg function. In the 3 experiments comparing naïve CD4+ T cells from cord blood and peripheral blood - 288, 273 and 213 genes were differentially expressed. Sixty genes overlapped in the 3 experiments. These sixty genes are therefore likely to represent the molecular "signature" of cord blood CD4+ T cells. Cord blood T cells are in a highly proliferative state driven by the relatively lymphopenic environment of the fetus. Therefore, we speculated that some of the genes representing the naïve cord blood CD4+ T-cell "signature" may be induced by the lymphopenic environment. We attempted to identify such genes by examining those induced in steady state peripheral naïve CD4+ T cells present in the bone marrow graft after infusion into a lymphopenic transplant recipient. Nineteen of 60 overlapping genes representing the "signature" of naïve cord blood CD4+ T cells were also differentially expressed in reconstituting naïve peripheral blood CD4+ T cells following BMT. These 19 genes also remained differentially expressed in the reconstituting naïve CD4+ T cells following CBT. The up or down regulation of these 19 genes was higher in the reconstituting naïve CD4+ T cells after CBT than after BMT. In particular, genes of the T-cell receptor (TCR) signalling pathway and its transcription factor complex – activator protein-1 (AP-1) were highly upregulated in cord blood CD4+ T cells. The ligation of TCR with self-antigen presenting cells *in vitro* mediated enhanced proliferation of cord blood CD4+ T cells compared with peripheral blood CD4+ T cells ($P < 0.05$). Furthermore, a small molecule inhibitor of AP-1 proportionally inhibited cord blood CD4+ T-cell proliferation ($P < 0.05$). Reconstituting cord blood CD4+ T cells retain the properties of fetal ontogenesis, and enhanced TCR signalling rapidly restore the unique CD4+ T-cell biased adaptive immunity after T-replete CBT.

Disclosure of conflict of interest: None.

GVHD (clinical-2)

O115
Previously Published

O116
Umbilical cord blood transplantation versus unrelated donor transplantation in adults with relapsed or primary refractory acute myeloid leukemia: a report from Eurocord, the Acute Leukemia Working Party and the Cord Blood Committee of the Cellular Therapy & Immunobiology Working Party of the EBMT

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A recent retrospective study demonstrated a better outcome of umbilical cord blood (UCB) transplantation vs HLA-matched (MUD) or HLA-mismatched (MMUD) unrelated donor hematopoietic stem cell transplantation (allo-HCT) in AML patients (pts) with positive pre-transplantation minimal residual disease (MRD) (Milano *et al*., NEJM 2016). This prompted us to compare the outcomes of UCBT vs MUD or MMUD allo-HCT in AML pts with active disease at transplantation. The study population consisted of patients with either primary refractory or relapsed AML given UCBT, MUD or MMUD allo-HCT from 2004 to 2015 at EBMT-affiliated centers. Data from 2963 pts with primary or secondary AML were included in this study. Two hundred eighty five pts underwent an UCBT, 2001 a MUD and 677 a 9/10 MMUD allo-HCT. In comparison to MUD or MMUD recipients, UCBT pts were younger (48 vs 55 and 55 yrs, respectively, $P < 0.001$), were less frequently transplanted with primary refractory disease (37% vs 50% and 42%, respectively, $P < 0.001$), and were more frequently conditioned with a myeloablative regimen (52% vs 46% and 42%, respectively, $P < 0.001$). In multivariate Cox analyses, in comparison to UCBT, MUD recipients had a lower incidence of relapse (HR = 0.7, $P = 0.001$), a lower incidence of nonrelapse mortality (HR = 0.6, $P < 0.001$), better GVHD-free leukemia-free survival (GRFS, HR = 0.8, $P < 0.001$) and better survival (HR = 0.6, $P < 0.001$). Further, in comparison to UCBT, MMUD recipients had a lower incidence of relapse (HR = 0.8, $P = 0.02$), a lower incidence of nonrelapse mortality (HR = 0.7, $P = 0.008$), better GRFS (HR = 0.8, $P = 0.01$) and better survival (HR = 0.7, $P < 0.001$). Similar qualitative observations were made in a propensity weighted Cox survey. These data suggest that in AML pts with active disease at transplantation, allo-HCT with MUD or 9/10-antigen MMUD results in better transplantation outcomes than UCBT.

Disclosure of conflict of interest: None.

O117

The value of allogeneic stem cell transplantation in patients with intermediate risk (ELN) acute myeloid leukemia with no FLT3-ITD, no NPM1 mutations and no CEBPA double mutations

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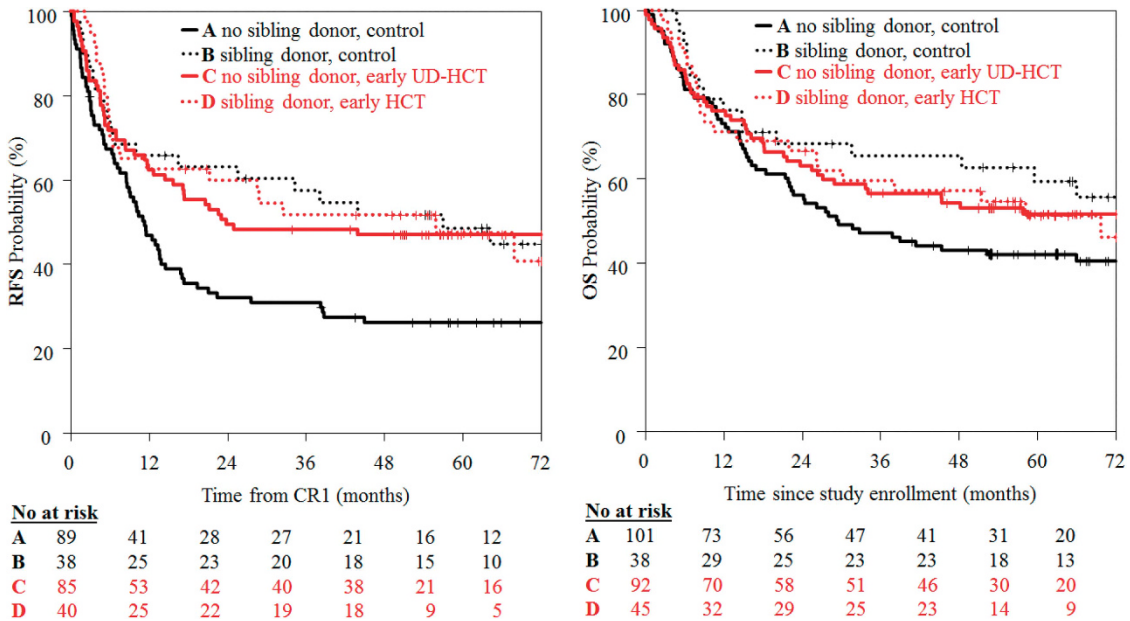
The value of allogeneic hematopoietic cell transplantation (alloHCT) in patients with intermediate risk AML in the absence of FLT3-ITD and NPM1 mutations, called triple-negative AML by some authors, referring to the absence of CEBPA double mutations, is poorly defined. The purpose of this analysis was to evaluate the impact of alloHCT on the overall (OS) and relapse free survival (RFS) in this group of patients in first remission (CR1) in comparison to post remission chemotherapy (CT). We analyzed data of 3041 AML patients who were enrolled into two large prospective, randomized trials (AML96, NCT00180115 and AML2003, NCT00180102) of the Study Alliance Leukemia (SAL). The trials included patients aged 16-60 years with newly diagnosed AML. In the AML2003 study, donor status was evaluated at study entry, making this data eligible for a donor versus no-donor analysis. Within the subgroup of interest, alloHCT was offered to all patients with an HLA-identical sibling donor in CR1 (donor group). Only patients with relapsed/refractory AML were scheduled for matched unrelated alloHCT (UD-HCT). Within the intensified treatment arm, patients who had >10% bone marrow blasts on day 15 after first induction were scheduled for early UD-HCT. Selection criteria were documented CR1, the absence of FLT3-ITD, CEPBA double mutations and NPM1 mutations, and a karyotype not defined as favorable or adverse according to ELN. For donor versus no-donor analysis, 276 patients with a median age of 49 years were evaluable for the analysis of OS from diagnosis while 252 patients had reached CR1 and were evaluable for RFS. The availability of an HLA-identical sibling had a significant impact on RFS ($P = 0.002$) and a trend to better OS ($P = 0.08$) in the control arm where only patients with relapsed/refractory patients received UD-HCT. In the intensified arm with early UD-HCT, the availability of an HLA-identical sibling had no impact on survival. Accordingly, in the subgroup of patients with >10% day 15 marrow blasts or induction failure, patients who were randomized to the intensified arm with early UD-HCT had a trend towards superior RFS and OS compared to patients in the control arm, reflected by a hazard ratio (HR) of 0.5 (95%CI 0.3–1.0, $P = 0.06$). Notably, the transplantation rate in the donor group was only 53% while 15% of patients in the no-donor group received alloHCT. Therefore, and as donor versus no-donor analysis was only possible within the AML 2003 patient cohort, we additionally performed as-treated analyses with alloHCT as time-dependent intervention in both cohorts, AML96 and AML2003. As-treated analysis showed a substantial advantage in terms of OS (HR 0.58, 95%CI 0.37–0.9, $P = .02$) and RFS (HR 0.51 (95%CI 0.34–0.76, $P = 0.001$) for patients who had received alloHCT in CR1. Our analyses suggest that medically fit intermediate-risk AML patients with no FLT3-ITD, no NPM1-mutation, and no double CEBPA-mutations should proceed to alloHCT after induction chemotherapy. Legend to the figure Kaplan-Meier-Plots on Relapse-free Survival and Overall Survival, by availability of a matched sibling donor at baseline and treatment arm (early UD-HCT versus control). RFS, Relapse free survival; OS, Overall survival; UD, unrelated donor; HCT, hematopoietic cell transplantation.

Disclosure of conflict of interest: None.

Figure 1 [O117]



O118
Previously Published

O119
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O120
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O121
Post transplant cyclophosphamide (PT-Cy) in association to standard GVHD prophylaxis in sibling and unrelated allogeneic stem cell transplantation (HSCT) for patients with acute leukemia, a survey from the ALWP of EBMT

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Post-transplant Cyclophosphamide (PT-Cy) as graft versus host disease (GVHD) prophylaxis, pioneered in the setting of unmanipulated haploidentical transplantation, is effective reducing the incidence of GVHD. Use of PT-Cy for GVHD prophylaxis from HLA matched sibling (MSD) or unrelated (UD) donors is less established. With the aim to evaluate the applicability of PT-Cy as GVHD prophylaxis in MSD and UD transplants we conducted a surveyon 625 patients (pts) transplanted from 2008-2015 for AML ($n=471$) and ALL ($n=154$). The majority of the pts were transplanted in CR1 ($n=384$, 61%), CR2/3 ($n=106$, 17%) or advanced disease ($n=135$, 22%). Median age at transplant was 44 years, 14% of the pts had secondary leukemia and 26% ($n=151$) had a Karnofsky performance status $<90\%$. Donor type was MSD ($n=255$, 41%), 10/10 UD ($n=245$, 39%) and 9/10 UD ($n=125$, 20%) with peripheral blood (PB) being used in 79% of cases ($n=494$). Median follow up was 12 months. 52% of pts ($n=316$) received a myeloablative conditioning regimen (MAC) and 48% ($n=297$) a reduced intensity conditioning (RIC). All pts received PT-Cy as GVHD prophylaxis, mainly in combination with tacrolimus and MMF ($n=110$), CSA±MMF ($n=95$) or CSA±MTX ($n=70$), according to transplant center policy. ATG was also used in 33% of pts ($n=206$). Ninety-six percent of patients achieved neutrophil engraftment. The cumulative incidence (CI) of acute GVHD grade II-IV and grade III-IV were 27% and 10%, respectively. At 2 years the CI of chronic GVHD was 32% with 14% being extensive. Overall CI of relapse and NRM were 33% and 17%, respectively. Disease recurrence was the most common causes of death (52%), followed by infection (19%) and GVHD (11%) as causes of NRM. Overall 2 year OS, LFS, GRFS were 59%, 50% and 35%, respectively. In the univariate analysis outcomes were not different according to the different combination of GVHD prophylaxis. LFS was not different for patients transplanted for AML (56%) or ALL (50%) $P=0.87$ or for those transplanted with a MSD (51%), 10/10 UD 57% or 9/10 UD 56%, $P=0.63$. According to disease status, LFS was 64%, 51% and 32% for patients transplanted in CR1, CR2 or in advanced disease status, respectively, $P<10\text{-}4$. Patients with secondary leukemia had lower 2 year LFS (39% vs 57%, $P<10\text{-}4$). In the multivariate analysis adjusted for type of diagnosis, disease status, secondary leukemia, age, type of donor, stem cell source, CMV serostatus, conditioning regimen, center effect. Donor CMV serostatus was the sole factor associated with an increased risk of grade II-IV acute GVHD (HR 4.5, 95%CI 1.6–12.4, $P=0.03$). Advanced disease (HR 2.25, 95%CI 1.49–3.42, $P<10\text{-}4$), and donor CMV status (HR 1.51, 95%CI 1.02–1.32, $P=0.03$) were associated with increased risk of relapse. Disease status remained the only factor associated with LFS (for CR2 or CR3: HR 1.49, 95%CI 1.00–2.23, $P=0.04$, and for advanced disease: HR 2.37, 95%CI 1.7–3.29, $P<10\text{-}4$). Disease status was also significant for OS with type of diagnosis (AML vs ALL: HR 0.67, 95%CI 0.45–0.98, $P=0.04$) and secondary leukemia (HR 1.64, 95%CI 1.08–2.48, $P=0.01$) as other independent factors. The use of PT-Cy in the setting MSD or UD transplants for adults with acute leukemia is effective to avoid prohibitive acute GVHD and GVHD related mortality. Although somewhat preliminary these results may serve as the basis for prospective randomized trial aiming in better defining the package of GVHD prophylaxis in unrelated HSCT.
Disclosure of conflict of interest: None.

O122
Second allograft for relapsed or refractory acute myeloid leukemia after first allogeneic stem cell transplantation: a study on behalf of the SFGM-TC

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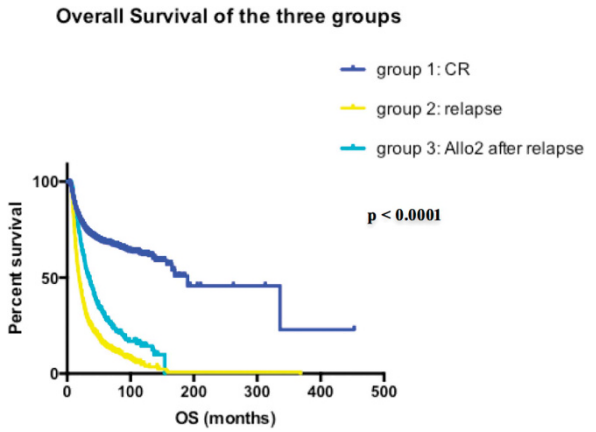
Patients with relapsed or refractory acute myeloid leukemia (AML) after allogeneic hematopoietic stem-cell transplantation (HSCT) have a poor prognosis. Retrospective studies showed that such patients experiment a low rate and short duration of complete remission (CR).[1] The therapeutic strategies in this situation are still controversial: donor lymphocyte infusion, second HSCT (HSCT2), chemotherapy, tapering immune-suppression or supportive care.[2] We aimed to evaluate the tolerance and efficiency of a HSCT2 in patients with relapsed or refractory AML after first HSCT (HSCT1). We performed a retrospective multicenter study on patients from the SFGM-TC registry. From January 2004 to January 2014, patients with AML who received at least one allogeneic HSCT were included. We discriminated three groups: group 1 contains patients who did not relapsed, group 2 contains patients treated with conventional drugs for relapse after HSCT1 and group 3 contains patients who received a HSCT2 for relapsed/refractory AML after HSCT1. The decision of a HSCT2 was made by physicians depending on patients' general condition, comorbidities, disease status and graft availability. The tolerance was evaluated on the outcome of graft versus host disease (GvHD). The efficiency was evaluated on the CR rate and the overall survival (OS). During this period, 4033 AML patients were included: 2096 males and 1937 females (sex-ratio = 1.08). The median age at diagnosis was 48 years (range 4–72). Among the relapsed/refractory AML, 1216 patients (30.2%) received rescue conventional therapy, and 186 patients (4.6%) received a HSCT2. Characteristics such as secondary AML, cytogenetic prognosis, conditioning regimen, HLA-type of donor, aGvHD outcome or failure to achieve a CR after HSCT1 were similar between patients of the second and third groups. CR before HSCT1 was obtained in 73.6% of patients rescued by conventional treatment and in 52.1% of patients treated by HSCT2 ($P<0.0001$). Chronic GvHD after HSCT1 was more frequent in patients of the third group (39.5%) than in patients of the second group (21.6%) ($P=0.003$). Among patients with HSCT2, 52.4% patients received a myeloablative conditioning (MAC). Peripheral stem cells were transplanted in 75.8% patients, 9.3% patients received bone marrow cells and 14.8% patients received cord blood cells. Most patients received HSCT2 with unrelated donor (59.2%). At d100, 94 of 186 patients (50.5%) achieved CR and 98 of 186 patients (52.7%) showed a full donor chimerism. Early death after HSCT2 outcame for 32 of 186 patients

(17.2%). After HSCT2, cumulative incidence of grade 2-4 aGvHD was 34.3% of patients and cGvHD occurred in 17.9% of patients (69.2% limited cGvHD and 30.8% extensive cGvHD). After a median follow up of 53.4 months (range 14.3–92.5), we observed a gain of OS in favor of the group of patients treated with a HSCT2 compared to patients of the second group: OS rate at 4 years and a half was 33.8% vs 17.5% and the median OS was 34.6 vs 19.2 months respectively ($P < 0.0001$). Patients with relapsed/refractory AML after HSCT1 could be rescued by HSCT2 with significant gain of survival and reasonable toxicity. HSCT2 feasibility should be evaluated according to the comorbidities, the disease status and donor characteristics. However, the rate of relapse remains strong. Strategies using new therapies such as CAR T-cells, targeted therapies or new immune-suppressive agents with or without HSCT2 should be evaluated.

Figure 1 [O122]



Disclosure of conflict of interest: None.

Infectious complications (2)

O123

Addition of rituximab in reduced intensity conditioning regimens for B-cell malignancies does not influence transplant outcomes: an EBMT registry analyses

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Rituximab (R), a CD20 monoclonal antibody, has been integrated in reduced intensity conditioning (RIC) regimens for allogeneic hematopoietic cell transplants (HCT) in patients with B-cell malignancies to decrease risk of recurrence. Single center data suggests that R-RIC regimens may be associated with decreased chronic GVHD and better overall survival. We wanted to validate this finding in a larger cohort. We conducted a retrospective analysis using the EBMT registry of adult patients (pts) with B-cell malignancies (FCC NHL, CLL/SLL, MCL NHL, DLBCL) undergoing RIC HCT (2001-2013) with either R-RIC or non-rituximab (RIC). Patients undergoing myeloablative HCT (TBI > 6 Gy, or busulfan > 9 mg/kg) or alemtuzumab containing regimens were excluded. Umbilical cord and haploidentical HCT were excluded. A total of 3803 (RIC: 3453 (91%); R-RIC: 350 (9%)) pts were included. Median age and median follow up were, 55 years (19.1 -77.3) and 43.2 months (0.3 -179.8), respectively. There was no difference in diagnoses (FCC, DLBCL, MCL, CLL/SLL and unspecified CLL, constituted 29.2%, 17.3%, 17.2%, 13.6% and 22.7%) or disease status (PR 33.3%, relapse/progression 23.3%, CR/nCR 39.4% and primary refractory 3.1%, and other 0.8%), between the 2 groups. The following characteristics were significantly different in RIC vs R-RIC: median age higher in RIC (55 y vs 54.2 y, $P = 0.008$); median year of transplant higher in R-RIC (2009 vs 2010, $P < 0.0001$); more matched related donor in R-RIC (57.7% vs 51.9%, $P = 0.044$); CMV D/R -/- 25.7% (RIC) compared to 16.1% (R-RIC) and +/+ 39.2% (RIC) compared to 46.3% (R-RIC), $P = 0.002$; GVHD prophylaxis CSA/MMF 41.7% in RIC vs 24.4% in R-RIC; CSA/MTX 31.1% in RIC vs 45.9% in R-RIC ($P < 0.0001$). There was no difference in sex mismatch, stem cell source, infused cell dose in the 2 groups.

[O123]

Outcomes	*Strata*	*% (95% CI)*	P-*value*
1y relapse incidence (RI)	HCT no R	15 (14–16)	0.37
	HCT with R	13 (10–17)	
1 y non-relapse mortality (NRM)	HCT no R	22 (20–23)	0.62
	HCT with R	21 (17–26)	
1 y disease free survival (DFS)	HCT no R	62.2 (60.6–63.9)	0.78
	HCT with R	64.4 (59.5–69.7)	
1 y Overall survival (OS)	HCT no R	70.7 (69.2–72.3)	0.81
	HCT with R	69.9 (65.2–75)	
100d acute GVHD grade II–IV	HCT no R	12 (11–14)	0.64
	HCT with R	12 (9–16)	

There was no difference in incidence (RIC: 56.3% vs R-RIC: 54.3%) or extent (limited: 50% vs 55.3%; extensive 50% vs 44.7%) of chronic GVHD among the evaluable patients (RIC 1462; R-RIC 153). In MV analyses, the HR for R-RIC vs RIC for RI, NRM, DFS, OS, and acute GVHD gr 3-4 were 0.93 (0.72-1.21), 1.02 (0.81-1.27), 0.97 (0.83-1.15), 1.01 (0.84-1.2), 0.98 (0.71-1.35), respectively. We did not have outcome data to compute GVHD-free, relapse-free survival. In a large registry cohort, we were not able to show that, the addition of rituximab in conditioning regimens was associated with improved transplant outcome of pts undergoing RIC HCT for B-cell malignancies. The interaction of rituximab with choice of preparative regimen, use of ATG in unrelated donor HCT and GVHD prophylaxis needs to be further analyzed. This data may guide the further development of drugs targeting B-cell pathway for GVHD prophylaxis.

Disclosure of conflict of interest: None.

O124

Regional intra-arterial steroids for steroid resistant/ dependent GVHD is associated with lower tendency of viral reactivation and disease

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Graft-versus-host disease (GVHD) is a major complication of allogeneic stem cell transplantation, resulting in death in the majority of steroid-resistant patients. ATG, as well as monoclonal antibodies cause severe and long-lasting depression of immunity resulting in the emergence of opportunistic infections. On the contrary, the efficacy of IAS is mainly based on the local control of inflammation and therefore is associated with decreased of the severe and global immune-suppression effect provoked by other immunosuppressive regimens. This report is aimed to assess the safety and efficacy of 2 regional intra-arterial steroid (IAS) protocols in the largest published cohort of patients with resistant/dependent hepatic and/or gastrointestinal GVHD. 120 patients with 122 episodes of steroid resistant or dependent grade 3–4 hepatic ($n = 19$), gastrointestinal GVHD ($n = 71$) or both ($n = 32$) were given intra-arterial treatment. In total, 164 procedures were carried out (1–5 per patient) with 2 protocols (Table 1). Gastrointestinal initial response (IR) and complete response (CR) were documented in 67.9% and 47.6% episodes respectively, while hepatic IR and CR was documented in 54.9% and 33.3% episodes respectively. In comparison of treatment to isolated artery vs combined treatments, there was a trend for better gastrointestinal CR in the isolated treatments (CR 59.2% vs 34.4%), and there was no statistical significance in the hepatic CR. The type of IAS protocol had no effect on response or survival. Viral reactivation was lower than other reports in the literature. Thirty-eight patients (31.7%) had CMV reactivation, 14 had CMV disease (11.7%; 11 gut, 3 pulmonary; no correlation to the protocol). Seventeen (14.1%) had EBV reactivation, and 3 (2.5%) had EBV associated disease (significantly more common with the modified protocol (4 vs 13; $P = 0.03$). Regional treatment of severe GVHD with IAS treatment is effective and safe. GI treatment is more effective than intrahepatic treatment. Administration of IAS in seems to reduce untoward effects of prolonged systemic immunosuppressive treatment, as compared to reportstype of other immunosuppressive medications.

Disclosure of conflict of interest: None.

[O124]

Table 1

	Initial protocol	Modified protocol
GI	MP to SMA 25mg/m^2 (max 60mg) MP to IMA 25mg/m^2 (max 60mg) +/- MP to GDA 25mg/m^2 (max 40mg)	MP to SMA 300mg/m^2 (max 500mg) MP to IMA 175mg/m^2 (max 300mg) MP to IIA 60mg/m^2 X2 (max 100mg per vessel) +/- MP to GDA 60mg/m^2 (max 100mg)
Hepatic	MP to hepatic artery 75mg/m^2 (max 125mg) + MTX 10 mg/m^2	MP to hepatic artery 600mg/m^2 (max 1000mg). NO MTX.

Abbreviations: GDA – gastro-duodenal artery, GI – gastrointestinal, IIA - Internal iliac arteries, IMA – inferior mesenteric artery, MP – methylprednisolone, MTX – methotrexate, SMA – superior mesenteric artery.

GDA treatment was given only with upper GI symptoms.

O125

Donor Interleukin-7 receptor α-chain genotype predicts chronic GVHD after allogeneic HSCT

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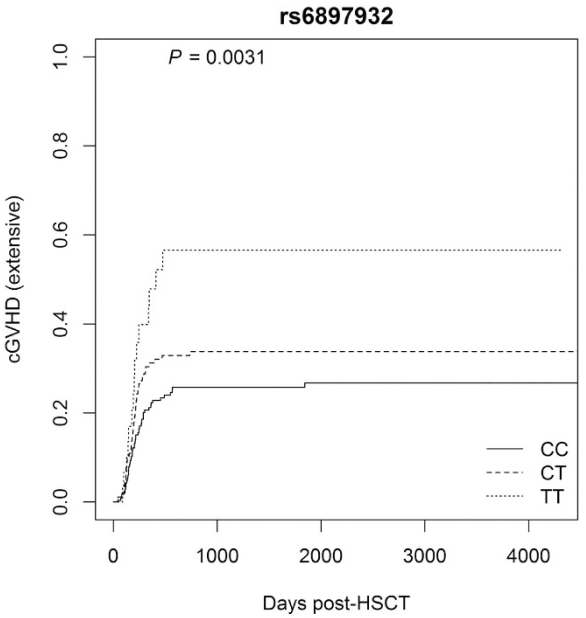
Myeloablative allogeneic stem cell transplantation (HSCT) is challenged by acute and chronic GVHD and by long-lasting immunodeficiency. Interleukin-7 (IL-7) is a cytokine essential for de novo T-cell generation in the thymus and peripheral T cell homeostasis. Previous studies indicate that SNP rs6897932 in the IL-7 receptor α-chain (IL-7Rα) of the donor and increased plasma levels of IL-7 in the recipient are associated with adverse outcome after HSCT. In this study, we investigated the impact of donor IL-7Rα rs6897932 genotype on GVHD and immunological reconstitution. We included 460 Danish patients undergoing HSCT from 2004-2014. Median age was 26.3 years (range 0.3–63.0 years). Diagnoses included AML ($n = 136$), ALL ($n = 118$), other malignancies ($n = 118$) and benign diseases ($n = 88$). Donors were either MRD ($n = 147$), MUD ($n = 244$) or MMUD ($n = 69$). BM ($n = 329$) and PB ($n = 131$) were used as stem cell source. Conditioning regimens were based on TBI ($n = 293$) or high-dose chemotherapy alone ($n = 167$), and included ATG in 179 patients. DNA from donors was genotyped for the IL-7Rα SNP rs6897932 using a multiplex bead-based assay. T, B and NK cells were counted using flow cytometry at 1 year post-HSCT, and levels of soluble IL-7 receptors (sIL-7R) were measured by Luminex. OAS was 33.9%, with a TRM of 21.0% and a relapse rate of 21.8% within 6.9 years (1.9-12.8) of follow-up. Donor carriage of rs6897932 T was associated with inferior overall survival (HZ = 1.51 for CT/TT vs CC genotype, $P = 0.011$) in a multivariable model adjusting for recipient age, diagnosis, donor type, stem cell source and ATG. In a competing risk model, rs6897932 T was

associated with increased TRM (cumulative incidence estimates: CC = 14.3% and CT/ TT = 32.5%, $P = 0.00014$), but not associated with risk of relapse ($P = 0.17$). Extensive chronic GVHD occurred in 118 patients (25.7%), and was significantly associated with donor rs6897932 genotype with a step-wise increase in OR = 1.6 ($P = 0.011$, Figure 1) for each T-allele in a multivariable model. Grade 3-4 acute GVHD was seen in 42 patients (9.1%). The risk of grade 3-4 aGVHD was step-wise increased with OR = 1.6 ($P = 0.060$) for each donor T-allele in a multivariable model. Numbers of CD3+, CD4+ and CD8+ T cells as well as B cells and NK cells were comparable for all genotypes at 1 year post-HSCT, but immunoglobulins were decreased with the number of T-alleles in rs6897932 carried by the donor (IgG: CC = 7.5 g/L,CT = 7.1 g/L,TT = 5.4 g/L, $P = 0.067$; IgM: CC = 0.79 g/L,CT = 0.72 g/L,TT = 0.46 g/L, $P = 0.043$). To explore the mechanism behind these associations, we investigated effects of rs6897932 genotypes on plasma levels of IL-7 and soluble IL-7Rα (sIL-7Rα) in a cohort of 122 adults transplanted for haematological malignancies. Interestingly, donor carriage of the rs6897932 T allele was associated with reduced levels of sIL-7R (median CC: 152 ng/mL; CT: 106 ng/mL; TT= 9 ng/mL, $P = 0.0031$), but was not associated with IL-7 levels. The IL-7Rα rs6897932 genotype of the donor is highly predictive of acute and chronic GVHD as well as TRM. This may be due to an imbalanced immune reconstitution caused by reduced binding of IL-7 to the soluble receptor in donors carrying the T allele, potentially leading to enhanced proliferation of alloreactive T cell clones and GVHD. IL-7Rα SNP typing of donors may optimize donor selection and facilitate individualization of treatment and prophylaxis of cGVHD.

Figure 1 [O125]



Disclosure of conflict of interest: None.

O126
Third party fecal microbiota transplantation (FMT) in hematopoietic cell transplantation (HCT) recipients

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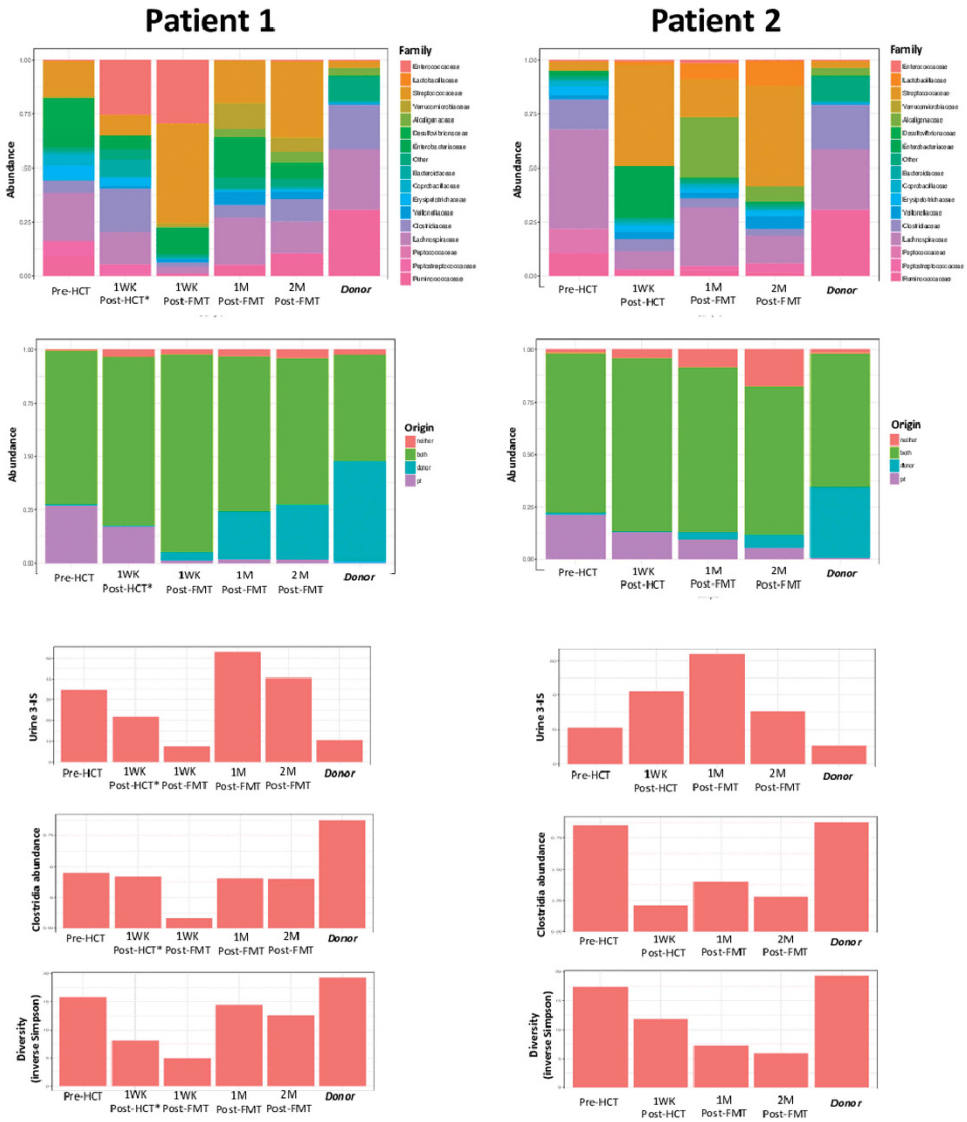
Recent studies have described the changes that occur in the intestinal microbiome during allogeneic hematopoietic cell transplantation (HCT), which are associated with several outcomes including acute GVHD, bacteremia, non-relapse mortality and relapse. We hypothesized that the use of third party fecal microbiota transplantation (FMT) may be able to restore the diversity of the intestinal microbiome following allogeneic HCT. In this open-label single-arm pilot study, adult patients (⩾18 years old) underwent allogeneic HCT myeloablative or fludarabine/melphalan conditioning. Any donor source and GVHD prophylaxis regimen was allowed. Previously collected third party FMT was administered no later than 4 weeks after neutrophil engraftment and at least 48 hours after stopping antibiotics. Participants received a single standard dose of oral FMT, which was 15 FMT capsules per day for two consecutive days, for a total of 30 FMT capsules. The presence of active acute GVHD of the gastrointestinal tract prior to FMT excluded patients from undergoing FMT. The primary endpoint of this study was feasibility of FMT in HCT recipients, defined as ⩾80% of participants being able to swallow ⩾15 capsules. Correlative analysis was performed on serial stool (16s rRNA sequencing) and urine (liquid chromatography/tandem mass spectrometry for 3-indoxyl sulfate) samples collected prior to HCT (once), post-HCT/pre-FMT (once), and post-FMT (5 collections). Eighteen patients were enrolled on the study (now closed to accrual). Five patients did not receive FMT, either due to the development of severe early acute GI GVHD ($n = 3$) prior to FMT or patient decision ($n = 2$). At the time of abstract submission, 13 patients have received FMT at a median of 27 days (range 19–45) following HCT. Clinical characteristics of recipients and HCT are shown in Table 1. Participants were able to swallow all 30 FMT capsules. Median follow up of these patients is 60 days (range 8–201) following FMT. Patients have tolerated FMT well, with only one treatment-related significant adverse event (abdominal pain) observed. There have been no cases of bacteremia or emergent severe acute GVHD thus far. Analysis of correlative samples collected from the first two patients indicate expansion of donor operational taxonomic units following FMT, with additional studies (urine 3-IS, clostridia abundance, Simpson's Diversity Index) suggesting maintenance/recovery of intestinal microbiome diversity (Figure 1). Preliminary results indicate that empiric third party FMT following allogeneic HCT appears to be feasible, safe, and associated with expansion of recipient microbiome diversity. Larger studies are planned to confirm the optimal schedule of FMT after HCT and investigate its influence on clinical outcomes.

Table 1 [O126]

Characteristic	*Value*
Median age (range)	63 (26–71)
Gender, *n*	F: 7; M: 6
Diagnosis, *n*	AML: 4; MDS:3; NHL:3; MDS/MPN:1; CLL:1; MF:1
Graft source, *n*	PBSC: 12; BM: 1
Donor, *n*	Matched unrelated: 9; matched related: 2; haplo-identical:2
Conditioning, *n*	RIC: 10; MA:3
GVHD prophylaxis, *n*	Tac/siro: 9; Tac/MTX:2; ptCy/tac/MMF: 2

Disclosure of conflict of interest: None.

Figure 1 [O126]



*Patient 1 received oral vancomycin for c. diff colitis post-HCT/pre-FMT

O127

What is the outcome in patients with acute leukemia who survive svere acute graft-versus-host disease?

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What is the outcome of patients with acute leukemia who survive severe acute graft-versus-host disease? Acute graft-versus-host disease (GVHD) is a major complication of allogeneic hematopoetic stem cell transplantation (HSCT).With new promising therapies,survival may improve in patients with severe acute GVHD.We wanted to analyze the long-term outcome among patients who survive severe acute GVHD. Patients and methods This is a landmark analysis of 23,567 patients with acute leukemia who survived $>$ 6 months after HSCT during 2002-2014.Patients with severe acute GVHD, grades III-IV ($n = 1,738$) were compared to controls with no or mild,grades0-I ($n = 17,292$) and moderate,grade II ($n = 4,533$) acute GVHD. Results Patients with severe acute GVHD had a higher non-relapse mortality (NRM), which at five years was 32% (30-34,7,95% confidence interval) compared to 11,7% (10.2–13.4) in those with no or mild GVHD and 18,5 (16,5-20,5) among those with moderate acute GVHD ($P < 10\text{-}5$). The cumulative incidence of chronic GVHD at five years was 47,8% (44,6-51) in the study group as opposed to 30,4 (29,6-31,2) and 41,7 (39,8-43,6) in the two control groups,respectively ($P = 10\text{-}5$).The patients surviving severe acute GVHD also had more extensive chronic GVHD than the control groups ($P < 10\text{-}5$). The probability of relapse at five years in the study group was 18,4%(16,5-20,5),as compared to 27,4% (26,6-28,1) in the controls with no or mild acute GVHD and 22,6% (21,2-23,9) in those with moderate GVHD ($P = 10\text{-}5$). Leukemia-free survival (LFS) at five years was 49,2% (46,5-51,9) in the study group as opposed to 60,9% (60-61,7) and 58,9% (57,3-60,5) in the two control groups respectively ($P < 10\text{-}5$). The differences between the patients surviving severe acute

GVHD and the controls regarding NRM,chronic GVHD,relapse, survival and LFS were also significant in multivariate analysis ($P < 10\text{-}2\text{-}10\text{-}5$). To conclude, patients who survive severe acute GVHD have a higher NRM, more extensive chronic GVHD, a lower relapse probability and a lower LFS than other HSCT patients. This study forms a basis for a comparison in outcome using novel therapies to treat severe acute GVHD.
Disclosure of conflict of interest: None.

O128
Previously Published

O129
Previously Published

O130
Post-transplant cyclophosphamide-based HLA 7/8 mismatched allogeneic transplantation is associated with lower incidence of chronic GVHD and similar survival outcomes in comparison with conventional HLA 8/8 unrelated transplantation

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Allogeneic stem cell transplantation (alloSCT) using HLA-mismatched unrelated donor (MMUD) has been associated with higher incidences of graft rejection, severe GVHD and non-relapse mortality (NRM) when compared with conventional matched unrelated donor (MUD). Several studies reported that the use of high-dose post-transplant cyclophosphamide (PTCy) in the setting of haploidentical transplantation is feasible and effective in preventing GVHD, thus overcoming the negative impact of HLA-disparity on survival. Our aim was to determine the efficacy and feasibility of PTCy-based MMUD transplantation and to compare outcomes with MUD transplantation. We retrospectively analyzed 86 adult recipients of alloSCT (April/2013 to April/2016) in a single institution, comparing two simultaneous groups: PTCyMMUD ($n = 26$) vs MUD ($n = 60$). Median age was 50y (range 16–69). Most patients had a disease risk index (DRI) intermediate or high (87%). All PTCyMMUD were HLA 7/8, with 92% being differences in HLA-class I antigens. Peripheral blood stem cells graft was used in 92% of the cases. No differences were found between groups regarding age, sex, donor/recipient sex, disease type or status, DRI, stem cell source, and number of infused CD34+ and CD3+ cells. More patients within the MUD group received RIC regimens (78.3% vs 46.2%, $P = 0.005$). Median time to neutrophil engraftment was 16 days in both groups (range 10–37). Patients in MUD group showed shorter time to platelet engraftment (12d vs 17d, $P = 0.007$). There were no significant differences in graft failure (PTCyMMUD: 4% vs MUD: 10%, $P = 0.57$), incidence of severe mucositis (20% vs 18.4%, $P = 0.54$), or SOS (0% vs 1.7%, $P = 1.0$). The PTCyMMUD group presented significantly higher incidence of hemorrhagic cystitis (28% vs 8.3%, $P = 0.035$), all of them of low/moderate severity. There were no differences between groups regarding incidence of severe fungal (PTCyMMUD: 12% vs MUD: 20%) or bacterial (12% vs 20%) infections, or CMV reactivation/CMV disease (73.3% vs 82% / 10.5% vs 6%) ($P = $ NS). Death due to progression was more frequent in MUD group (15% vs 3.8%, $P = 0.44$). Cumulative incidences (CI) of acute GVHD grades II-IV and III-IV were similar between both groups (PTCyMMUD: 39% and 13% vs MUD: 20% and 13%, respectively, p = NS). CI of chronic GVHD and moderate/severe chronic GVHD were significantly higher in the MUD group (55% and 47% vs 25% and 15%, respectively, $P = 0.02$). Patients in the MUD group showed a trend to higher relapse (CI: 24% vs 9%, $P = 0.1$). No differences were found regarding NRM (CI: 25% PTCyM-MUD vs 32% MUD; $P = 0.54$). With a median follow up of 16 months (range 3–43), PFS and OS at 1 year were similar in both cohorts, although a trend to better survival was seen for PTCyMMUD group (PFS 65.8% vs 64.4%, $P = 0.645$; OS 69.3% vs 62.9%, $P = 0.55$). Our study shows that HLA 7/8 MMUD transplant using PTCy is a suitable alternative for those patients lacking a MUD, and is associated with significant lower incidence of cGVHD, with no increase on relapse, and with comparable survival. This results need to be confirmed in a larger cohort of patients with longer follow-up.
Disclosure of conflict of interest: None.

MRD, chimerism and immune reconstitution

O131
Infectious complications in multiple myeloma patients after high dose chemotherapy and autologous stem cell transplantation–multicenter analysis of the Polish Adult Leukemia Group PALG

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Multiple myeloma (MM) has become chronic disease since introduction of modern drugs and autoSCT. Immunodeficiency related to the disease and therapy type influence the risk of infections, remaining the most important cause of morbidity and mortality in MM. The objective of the study was to analyze the incidence, etiology and outcome of infections in pts undergoing autoSCT in the era of novel anti-myeloma drugs given for induction. 10 Polish transplant centers participated in the study. Data on the incidence, etiology and outcome of infections up to 100 day after transplant were collected retrospectively for years 2012-2014. During analyzed period, a total number of 1487 autoSCT for MM were performed, according to Poltransplant. Infections were reported for 376 pts in median age 58 (range 21–72) yrs. Before transplant pts were treated with induction based on thalidomide and/or bortezomib. According to HCT-CI pts were classified into 3 groups: 48% low, 35% intermediate and 17% high risk. All pts but 6 were conditioned with melphalan, in 5 TMI and in 1 treosulphan-melphalan were used. Pts were grafted with PBSC in dose 4.2(2.8-10.5)x10e6 of CD34+cells/kg. Neutrophil recovery occurred in 358 pts at day +11(8-28). 8 pts died before +21 day or had no hematological recovery (2 pts). The overall incidence of bacterial, viral and fungal infections was 20.5%, 2% and 1.83%, respectively. The number of bacterial episodes was 431 in 313 pts with median time to infection development 9 (range 1–61) days. 98% of infections occurred

during neutropenia. 252 episodes were microbiologically confirmed, 30 clinically confirmed, in 145 cases FUO was diagnosed. Among bacterial complications BSI were seen in 117 pts (including 24 with catheter-related), UTI in 53 and pneumonia in 26 pts. Neutropenic fever in carriers of resistant bacteria was seen in 46 pts. Gram-negative bacteria predominated (60%), with the most common Escherichia coli in 28 (12%), Klebsiella pneumoniae in 21 (9%) and Pseudomonas aeruginosa in 16 (7%) pts. The most common Gram-positive bacteria was MRSE in 33 (14%), followed by Enterococcus sp in 13 (6%) pts. Clostridium difficile diarrhoea was seen in 22 pts. MRD species included ESBL+(50% of E. coli and 64% of Klebsiella pneumoniae), MBL+(15% of Klebsiella pneumoniae) and VRE representing 20% of Enterococcus sp. There were 25 episodes of viral infections: VZV (12), HSV (5), CMV (4) and influenza (4). Median time to viral infection was 52 (range 12–99) days. Invasive fungal infections (IFI) were diagnosed in 22 pts, as proven (4), probable (11) and possible (6). In 20 pts Aspergillus sp. was considered causative pathogen. Median time to IFI was 16 (range 12–39) days. There were 15 (1.0%) deaths due to infections after autoSCT with median time to death from transplant 12 (range 3–67) days. 9 pts died due to septic shock caused by MRD species. In 4 pts IFI contributed to death. No deaths were caused by viral infections. The risk factors of death due to infections were analysed. The most important factor was infection with MDR bacteria, causing the risk of death 5.28 higher (OR; CI 1.29-21.6) vs other infections ($P = 0.0183$). Age, gender, HCT-CI, conditioning, time of infection onset were not found to be risk factors for death from infection. Infections with resistant bacteria during neutropenia in MM pts undergoing autoHCT remain an issue.
Disclosure of conflict of interest: None

O132
Epstein-Barr virus-related disease after allogeneic HSCT and use of pre-emptive rituximab: clinical features and outcome

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Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disease (PTLD) is a life-threatening complication after allogeneic stem cell transplantation (allo-HSCT). EBV monitoring in high-risk patients during the first 100 days after allo-HSCT and pre-emptive therapy with rituximab at Uppsala University Hospital between 2004 and 2012 were studied retrospectively. Patients who received anti-thymocyte globulin (ATG), anti-lymphocyte globulin, or alemtuzumab in the conditioning regimen were defined as high-risk patients according to institutional guidelines. 214 of 319 consecutive allo-HSCTs performed in 313 patients were regarded as high-risk for PTLD. EBV DNAemia $\geqslant 1000$ copies/mL plasma was observed in 53 (25%) of the high-risk patients. Pre-emptive rituximab was given to 34 patients, in combination with reduction of immunosuppression ($n = 24$) or chemotherapy ($n = 4$). Common clinical features of EBV disease in rituximab treated patients were lymphadenopathy ($n = 16$) and/or fever ($n = 26$); rarely central nervous system disease ($n = 4$) or hemophagocytic lymphohistiocytosis ($n = 1$) was diagnosed. Rituximab was started median 50 days post-HSCT (range 14–112). Response-rate to rituximab was 88%. Death was attributable to EBV in one case of PTLD. 1- and 5-year overall survival was 71% and 52% for patients with rituximab treatment for EBV DNAemia. Rituximab treatment was not associated with inferior survival neither in univariate nor in multivariate analysis. ATG was associated with EBV disease ($P < 0.001$). No cases of EBV DNAemia or disease were diagnosed in the 28 patients who had received alemtuzumab. The incidence of biopsy-confirmed PTLD among high-risk patients was reduced from 15% to 3% ($P = 0.03$) compared to historical controls from 2001-2002 when higher doses of ATG were used (median 18.75 mg/kg vs 6 mg/kg now). In conclusion, the strategy to monitor for EBV and give pre-emptive rituximab is considered safe and effective.
Disclosure of conflict of interest: None.

O133
Immunomodulatory role of polymyxin B hemoperfusion in gram negative sepsis following stem cell transplant

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Gram negative sepsis is a major clinical concern in patients following bone marrow transplant or myelosuppressive phase following chemotherapy. Endotoxin is responsible for the pro-inflammatory cytokine storm leading to poor clinical outcome due to multiple organ dysfunction syndrome including myelosuppression. Polymyxin B extracorporeal hemoperfusion device selectively binds endotoxin and neutralize its toxicity including the effects of the pro inflammatory cytokines.

[O133]
Table 1 Summary of patient details

Patient	*Age (yrs)*	*Sex*	*Diagnosis*	*Stem cell transplant*	*Blood culture*	*PMxHP therapy*	*Primary outcome*	*Secondary outcomes*	
								Bone marrow engraftment	*30 days mortality*
1	53	M	Relapsed AML	Haploidentical	*Klebsiella pneumoniae*	2	Sepsis controlled	Yes	Survived
2	16	M	Relapsed B ALL	Haploidentical	*Escherichia coli*	1	Sepsis controlled	Yes	Survived
4	20	M	Refractory Pre B ALL	Haploidentical	*Klebsiella pneumoniae*	1	Sepsis controlled	Yes	Survived
5	57	F	AML in CR1	Haploidentical	*Klebsiella pneumoniae*	2	Sepsis controlled	Yes	Survived

Prospective study of patients who developed multi drug resistant (carbapenem resistant) gram negative sepsis in the neutropenic phase following stem cell transplant at our center in the last six months. All patients were given polymyxin B hemoperfusion (PMxHP) therapy in addition to parenteral antibiotics. Primary outcome measured was sepsis control within 48 hours of therapy. Secondary outcomes measured were bone marrow engraftment and 30 days' mortality post therapy. Four patients were included during the study period. Mean age of study population was 37 years. All patients had undergone replete haploidentical stem cell transplantation. One patient (patient 2) had donor specific antibodies; hence he was desensitized and received non-myeloablative induction protocol. All patients had blood culture proven carbapenem resistant gram negative sepsis with high inflammatory markers during their neutropenic phase. Following PMxHP therapy all patients became afebrile alongside decreasing intensity of inflammatory markers. All had improvements in their APACHE II score (21 to 7). Mean WBC at time of procedure was 0.15 K/uL which improved (mean 1.5 K/uL) 48 hours post procedure. All patients' bone marrow engrafted and 30 days survival was 100%. There were no procedure-related complications such as bleeding, platelet drop, citrate reaction or access related issues (3 patients received therapy via the existing hickman's catheter). Average platelet during therapy was 15 k/uL. Anticoagulation used for the extracorporeal therapy was either citrate based or heparin-free.

Uncontrolled sepsis can progress to life threatening complications. Preemptive use of polymyxin B hemoperfusion device in patients with gram negative sepsis especially during the neutropenic phase following stem cell transplant is lifesaving. PmxHP in addition to endotoxin removal also modulates the levels of pro and anti-inflammatory mediators and removal of activated inflammatory cells; aiding in bone marrow recovery and subsequent patient clinical improvement. It appears to be safe to be used even in patients with severe thrombocytopenia.

Disclosure of conflict of interest: None.

Reference

1. Cruz DN *et al*. Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review. *Crit Care* 2007; **11**: 1–12.

O134

Interferon-gamma production-based virus specific T cell detection by functional flow cytometry after allogeneic haematopoietic stem cell transplantation

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Morbidity and mortality caused by Epstein-Barr virus (EBV), cytomegalovirus (CMV) or adenovirus (ADV) reactivation remains significant in the allogeneic haematopoietic stem cell transplantation (HSCT) setting. Besides antiviral therapy adoptive transfer of virus specific T cells is an increasingly available and rapid treatment option for these patients. Since May 2015, 15 patients (9 children, 6 adults) have received virus specific T cell therapy from third party donors at our institution. Altogether 6 CMV, 3 ADV, 2 EBV, 1 BK virus, 1 CMV+ EBV and 2 CMV + ADV infected patients were treated with T-lymphocyte products selected by CliniMACS Prodigy® Cytokine Capture System (CCS) technology. For donor selection a screening procedure of functional flow cytometry based on interferon-gamma (IFNγ) production of T cells in the presence of viral antigens (Peptivator) was used. Following Prodigy CCS magnetic selection, graft purity was also determined by a similar flow cytometry based technique. To evaluate the clinical efficacy, viral copy numbers measured by PCR methodology were monitored after T cell therapy. Findings of 168 healthy donors and 251 screening tests were evaluated regarding the frequency of virus specific CD4+ and CD8+ T cells (109 CMV, 40 EBV and 60 ADV and 42 BK virus tests). In healthy donors average percentage of virus specific T cells within the CD4+ and CD8+ T cell populations were the following: 0,1365% and 0,3103% for CMV; 0,0045% and 0,0390% for EBV; 0,0199% and 0,0050% for ADV, respectively. At a 0,01% cut off value, 80% of the screened persons were suitable as donors for CMV-, 50% for EBV- and 55% for ADV-specific antiviral treatment. The average purity of the grafts was 84% for CMV, 72% for EBV and 61% for ADV T cell products. Although the average recovery was low (for example, 30% in case of CMV), the mean number of IFNγ producing T cells was highly sufficient, resulting in 1,02·106 of CD4+ T cells and 1,13·106 of CD8+ T cells for immunotherapy. Viral copy numbers decreased in most cases few weeks after T cell therapy with the resolution of clinical symptoms. No flare of GvHD has been observed. Our preliminary data suggests that there is correlation between the percentage of the IFNγ producing T cells in the blood and the number of T cells in the graft used for immunotherapy. Administration of virus specific T cells from third party donors selected by CCS technology is an effective antiviral treatment option after allogeneic HSCT. Functional flow cytometry test is a quick and sensitive method for donor screening and for purity check of the T cell grafts, as well as for monitoring immunoreconstitution of virus specific T cells after adoptive T cell therapy.

Disclosure of conflict of interest: None

O135

Risk factors for HPV positivity in Patients who received allogeneic stem cell transplants

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As the life expectancy for Hematopoietic Stem Cell Transplant (HCT) recipients continues to improve, the incidence of HPV associated diseases and HPV related malignancies has become an increased concern.(1) Herein, we aimed to determine the prevalence of Human Papilloma Virus (HPV) associated diseases among recipients of hematopoietic allogeneic cell transplantation (HCT) at MD Anderson Cancer Center, and to assess the risk factors for HPV related diseases using a matched case-control study design. This is a retrospective study of female patients who underwent allogeneic HCT from 2005-2015. HPV-positive subjects were identified using electronic medical database and cases were matched by type of transplant with HCT recipients HPV- negative. A total of 170 females were included in the study. Forty HPV-positive and 130 HPV-negative controls were identified. Most patients were White (70%), followed by Hispanic (12%), and Black (8%). Underlying medical conditions included Acute Myeloid Leukemia/Myelodysplastic syndrome (AML/MDS) ($n = 96$; 56%), Lymphoma ($n = 25$; 15%), Chronic Myeloid Leukemia ($n = 15$; 9%), Chronic Lymphocytic Leukemia ($n = 4$; 2%), Acute Lymphocytic Leukemia ($n = 23$; 14%), and others ($n = 6$; 4%). Patients received the following types of HCT: Matched-Unrelated donor (MUD) ($n = 85$; 50%), Matched-Related donor (MRD) ($n = 85$; 50%). In the univariate analysis, HPV positivity was less likely on patients with underlying AML/MDS ($P = 0.04$), MUD ($P = 0.17$), myeloablative conditioning $P = 0.06$, and use of cytoxan as graft-versus host disease (GVHD) prophylaxis ($P = 0.12$), and the time between transplant and HPV testing was longer for HPV positive patients (median: 669 days; IQR: 390 – 938 days) vs HPV-negative (median: 364 days; IQR: 173 – 721 days) ($P = 0.004$). In the multivariate logistic regression analysis the stronger predictors of HPV-positive status after transplant were younger age, smoking and chronic GVHD of the skin and hair.

[O135]
Table 1 Predictors of HPV in HCT patients by logistic regression analysis

Predictors	*Odds Ratio*	*95% Confidence Interval*	P-*value*
Age (per 10 years)	0.54	(0.38, 0.76)	< 0.001
Smoking	2.53	(1.08, 5.94)	0.032
Graf-versus-host-disease Skin-Hair	2.79	(1.28, 6.10)	0.01

In this matched-control study, predictors of HPV positivity in HCT recipients included younger age, smoking and chronic skin GVHD. The determinations of risk factors for HPV positivity after transplant is key, as such patients will benefit from more close cervical cytology follow-up, and consideration for stricter HPV screening strategies especially for patients with chronic GHVD, as well as counseling including tobacco cessation. Importantly, median time between transplant and HPV testing was longer on HPV-positive recipients (~2 years), which needs to be evaluated in more depth to determine if these findings are related to delaying on preventive testing on HCT recipients with more post transplant complications i.e. chronic GHVD, prolonged hospitalizations. Further prospective evaluation of HCT patients with and without HPV-positive disease is needed to determine clear strategies for optimal prevention and treatment.

Disclosure of conflict of interest: None.

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O136

Safety and outcome of brincidofovir/(CMX001) in patients with adenoviraemia: a single-centre experience

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Prior to the use of cidofovir, the mortality in patients with invasive adenoviral disease following allogeneic haematopoietic cell transplantation (HCT) was high. Immune reconstitution plays a major role in treating the infection and could be delayed in patients who develop graft versus host disease (GVHD) needing prolonged immunosuppression. Renal toxicity and poor graft function are some of the complications of cidofovir treatment. Gut intolerance and inability to tolerate probenecid (used concurrently with cidofovir to reduce nephrotoxicity) as well fluid overload from hyper hydration can be a challenge when administering cidofovir. Brincidofovir (BCV) is a lipid-conjugated analog of cidofovir, which is converted into the active compound cidofovir diphosphate upon intracellular release of the drug, has in-vitro activity against adenovirus and has not been associated with renal toxicity. Eleven patients, who underwent haematopoietic stem cell transplantation at the Bristol Royal Hospital for Children, were treated for adenoviraemia between January 2015 and December 2016 (Table 1). All patients had adenovirus detected in more than one site: blood and stools or respiratory secretion. Cidofovir was used as first line treatment, unless contraindicated (renal dysfunction, fluid overload, failure of cidofovir -increase in viral load or 2 weeks therapy, disseminated adenoviraemia), in which case Brincidofovir (at a dose of 2mg/kg/dose twice weekly) was made available through the Named Patient Program from Chimerix. Treatment was continued until plasma adenoviral PCRs were negative on atleast 2 consecutive assays. 10/11 patients cleared adenoviraemia; 1-died of disseminated adenoviraemia pre-engraftment. All 5 patients who received Brincidofovir after failing Cidofovir, responded to treatment and cleared adenoviraemia. A reduction by atleast 2 log in maximum AdV viral load by PCR was seen in a median of 2 weeks (range 2–6 weeks). Median lymphocyte count was 0.21×109/L (range 0–0.365). Treatment was interrupted in one patient due to abdominal cramps and diarrhoea with increase in alanine aminotransferase (ALT -4 times upper limits of normal ULN). Gut symptoms resolved; ALT normalised following brief interruption of Brincidofovir; increased when BCV was resumed for second reactivation with escalation of immunosuppression to treat GVHD, but was limited to 2 times ULN. Gut symptoms did not recur. The patient subsequently tolerated the drug well and completely resolved the infection.

[O136]
Table 1 Patient demographics

Age:	*Median: 5.8 years (range: 0.7–11.2 yrs)*	
Diagnosis	ALL	6
	AML	3
	Severe aplastic anaemia	1
	JMML	1
Type of transplant	Matched unrelated donor (10/10)	6
	Mismatch donor (9/10)	1
	5/6 UCB	4
Serotherapy	Alemtuzumab	6
	ATG	1
Treatment	Cidofovir	2
	Brincidofovir	4
	Cidofovir +Brincidofovir	5
GVHD	Yes	8
	No	3

Brincidofovir has shown to be a safe and effective option for patients with adenoviraemia in a clinical setting. It is well tolerated with low toxicity profile. Low incidence of gut intolerance and abnormal serum aminotransferase levels (9%) was noticed without hyperbilirubinemia, which normalised on brief interruption.

Disclosure of conflict of interest: None.

O137

Interdisciplinary german survey about BK polyomavirus associated haemorrhagic cystitis in adult allogeneic stem cell transplantation

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There are no epidemiological data on BK virus associated haemorrhagic cystitis (BKHC) in adult allogeneic stem cell transplantation in Germany available and associations with clinical conditions like Graft versus host disease (GvHD) are controversially discussed. Therefore, we conducted a nationwide survey among haematologists and urologists about this disease. We developed two questionnaires, one for haematologists (26 items) and one for urologists (20 items) concerning BKHC in adult allogeneic stem cell transplantation with epidemiological data and clinical implications. The survey was sent out at least three times to EBMT registered centres performing at least five transplantations per year, leading to 39 centres. The recruiting time was between January and June 2016. Total response rates were 76.9% among haematologists

and 74.4% among urologists. BKHC seems to appear less frequent in this survey than it is described in the literature. Six deaths in the last five years due to this disease have been reported. Interestingly, haematologists as well as urologists mostly think that local therapy is most effective while 50.0% stated that there is no real effective oral or intravenous medication. Additionally, there is a huge diversity of reported therapies ranging from intravenous immunoglobulins to bladder irrigation with palifermin. Associations with other clinical conditions mentioned were heterogenic, e.g. transplantation type, CMV reactivation, acute GvHD, nephropathy and worse clinical outcome. There was a significant discrepancy between haematologists and urologists concerning the association with acute GvHD ($P = 0.004$). We need prospective, multicentre clinical studies to evaluate local therapy and for developing a risk stratification model since this disease can be severe with morbidity and rarely mortality. In our opinion this should be an interdisciplinary approach. Furthermore, a European survey among EBMT registered centres with a validated questionnaire could supply more important information to improve planned prospective studies.

Disclosure of conflict of interest: None.

O138

Evaluation of infectious complications after haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide following reduced-intensity and myeloablative conditioning: a study on behalf of the francophone society of stem cell transplantation and cellular therapy (SFGM-TC) study

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Hematopoietic stem cell transplantation (HSCT) is a major treatment for many hematological disorders. However, this treatment comes with significant risks linked to toxicity and infectious complications which may lead to death. Recently haploidentical transplants without ex vivo T-depletion have been developed through the use of post-transplant cyclophosphamide, thus reducing the risk of lethal GVHD. Toxicity data are still limited and few studies have evaluated infectious complications following haploidentical transplants without ex vivo Tcell depletion. In this study, we evaluated the incidence of infectious complications in patients who received haploidentical HSCT with post-transplant cyclophosphamide. Data from 21 French centers and one Belgian center were retrospectively collected. Between January 2013 and December 2014, 159 patients all older than 18 years, affected with hematological malignancy and having undergone a haploidentical HSCT were included. Informed consent was obtained in accordance with the Declaration of Helsinki. Clinical data were obtained through ProMISe (Project Manager Internet Server), the internetbased system shared by all Francophone transplantation centers. In total, 159 patients were included (Table 1). The median age at transplantation was 51.2 years (20-72 years). All patients were treated with post-transplant cyclophosphamide combined with an anticalcineurin and mycophenolate mofetil as GVHD prophylaxis. The median follow-up of the cohort was 14 months. Meanwhile, 49 patients (13%) developed acute GVHD (grade 2-4). Forty-three patients (27%) developed chronic GVHD. Median overall survival wasn't reached and the median progression-free survival was 571 days. At the end of the study, 69 patients had died, 29 were in relapse and 36 presented treatment related toxicity. TRM was of 14% and 22% at day 100 and 365 respectively. At least one infectious complication occurred in 135 patients. These were mostly clinically or microbiologically documented. Median time from transplant to the first occurrence of infectious complication was 12 days. Twenty five percent of patients presented between 3 and 5 infectious complications. The average number of infectious complications per patient was 2.9 (0-12). Fifty-two percent of those infections were bacterial, 33% viral (39% of which related to CMV and 28% to BK virus), and 4.5% were parasitic or fungal (50% of which related to aspergillosis). Overall 436 infectious episodes were reported: bloodstream infections (62%) (bacteremia, viremia, fungemia or parasitaemia), respiratory (10%), urinary tract (8%), digestive tract (6%), skin (3%), septic shock and multi organ failure (6%), others (5%). Among those complications, 46% were bacteria related, 36% were virus related (17% of which due to BK virus and 39% to CMV), 7% were parasitic or fungal related (in these cases, 61% aspergillosis related). In total, 26 cases (6%) of BK virus infections were observed. In conclusion, in these preliminary results, except for maybe in the case of BK infections, incidence of infectious disease after haploidentical HSCT seem not to differ to related or unrelated HSCT. Further prospective studies are necessary to confirm these results, especially by evaluating infectious viremia with BK virus after HSCT haploidentical with post-transplant cyclophosphamide following reduced-intensity and myeloablative conditioning for this patient population.

[O138]

Table 1: Patient disease and treatment characteristics

	N (%)
Disease classification	N = 159
acute myeloid or lymphoid leukemia	71 (44.7)
myelodysplastic or myeloproliferative disease	34 (21.4)
hodgkin's or non-Hodgkin's lymphoma	45 (28.3)
chronic myeloid leukemia	1 (0.6)
multiple myeloma or solitary plasmacytoma	8 (5)
Disease status at the time of HSCT	N = 151
complete or very good partial response	87 (57.7)
partial response	15 (9.9)
relapse	26 (17.2)
progression or refractory	15 (9.9)
stable disease	8 (5.3)
Conditioning	N = 159
reduced intensity conditioning	125 (79)
myeloablative conditioning	34 (21)
Stem cell source	N = 159
bone marrow	121 (76)
peripheral blood	38 (24)
Relationship to recipient	N = 159
sibling	68 (42.8)
child	58 (36.5)
parent	33 (20.7)

Disclosure of conflict of interest: None.

O139

Better outcome with haploidentical donors compared to HLA-matched sibling donors after allogeneic hematopoietic cell transplantation for Hodgkin's lymphoma: a retrospective study from the SFGM-TC

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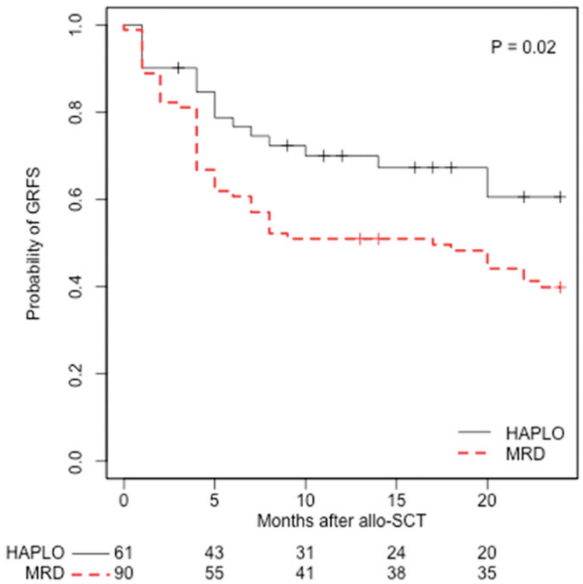
Prognosis is poor for patients with refractory Hodgkin's lymphoma (HL). Despite promising advances in the field of immunotherapy, allogeneic hematopoietic cell transplantation (allo-HCT) with an HLA-matched donor after non-myeloablative (NMA) or reduced-intensity conditioning (RIC) remains the only option to achieve long-term remissions with low treatment-related mortality (TRM). Encouraging results using NMA/RIC allo-HCT from familial haploidentical (HAPLO) donors with post-transplant cyclophosphamide have been recently reported. Nonetheless, studies comparing HAPLO donor to HLA-matched sibling donors (MRD) are missing in the specific setting of refractory HL. In this retrospective, multi-centre study we evaluated the outcome of 151 patients with refractory HL undergoing a RIC/NMA allo-HCT from either a HAPLO or MRD. After review of our PROMiSE database, we included 151 patients with refractory HL who received a RIC or NMA allo-HCT from a HAPLO or MRD between January 2011 and December 2015 at 31 SFGM-TC centres in France, Switzerland, and Lebanon. We defined GRFS as the probability of being alive without evidence of relapse, grade 3-4 acute GVHD or chronic GVHD (all grades included). HAPLO patients received the following conditioning regimens: Flu-Cy-TBI ($N=58$, 95%), Thiotepa-Flu-Bu ($N=2$, 3%), Flu-Bu-TBI ($N=1$, 1%). Most patients in the MRD group received a RIC consisting of Flu-Bu ($N=62$, 69%). GVHD prophylaxis in the HAPLO group consisted of post-transplant cyclophosphamide (PT-Cy) associated with a calcineurin inhibitor and mycophenolate mofetil (MMF) started at day +5 in all patients, according to the SFGM-TC guidelines. In the MRD group, 33 patients (37%) received cyclosporine with MMF while 52 (59%) received cyclosporine with methotrexate at day +1, day +3 and day +6. One patient received sirolimus and MMF. Stem cell source was bone marrow in 44 patients (29%) and peripheral blood in 107 patients (71%). Median age at transplant was 31 (range 12–68). Prior autologous stem cell transplant was reported in 133 patients (88%). Disease status at transplant per Cheson 1999 criteria was complete response in 87 patients (58%), partial response in 23 patients (15%), stable or progressive disease in 29 (19%). No data regarding disease status at transplant could be obtained in 12 patients (8%). Median follow-up in patients alive and free of relapse was 23 months (range 2–157). Significantly higher GRFS was observed with HAPLO donors compared to MRD (61% versus 40% at 2 years, $P=0.02$) in univariate analysis. This was also confirmed in multivariate analysis (HR = 1.76, CI = 1.04 – 3.00, $P=0.03$). We did not find significant differences in standard endpoints between HAPLO and MRD such as overall survival (80% versus 82% at 2 years, $P=0.89$), event-free survival (73% versus 72% at 2 years, $P=0.73$), cumulative incidence of relapse (18% versus 16% at 2 years, $P=0.89$) and non-relapse mortality (8% versus 12% at 2 years, $P=0.38$). In conclusion, we observed better outcome in terms of GRFS after RIC/NMA allo-HCT from HAPLO donors compared to MRD. Our findings suggest familial HAPLO donors should be favoured over HLA-matched siblings in patients undergoing RIC/NMA allo-HCT for refractory HL.

Figure 1 [O139]



Disclosure of conflict of interest: None.

O140

Long-term follow-up of patients undergoing reduced intensity allogeneic stem cell transplantation for mantle cell lymphoma. a study of the Lymphoma Working Party-EBMT

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Intensive chemotherapy followed by autologous stem cell transplantation (autoSCT) is the standard strategy in young and fit patients with mantle cell lymphoma (MCL). However, with longer term follow up most patients relapse following an autoSCT and the curative potential of this approach has not been established. An alternative strategy is to employ reduced

intensity allogeneic stem cell transplantation (RICalloSCT) although the long term efficacy of this therapy has not been demonstrated. We have therefore studied the long term outcome of patients receiving a RICalloSCT for MCL as reported to the EBMT. Eligible for this retrospective study were patients aged 18 years or older who had a first RICalloSCT (10/10 matched donor, sibling or unrelated) for MCL between January 2000 and December 2008 and were registered with the EBMT. Baseline patient, disease and transplant data were collected from MED-A forms. Statistical analysis used the log rank test to assess the impact of baseline characteristics on survival endpoints. In multivariate analysis, prognostic factors for survival were estimated using Cox regression models and for relapse incidence (IR) and non-relapse mortality (NRM) by Fine and Gray models (SM1). 324 patients (252 male) with a median age at SCT of 57 years (range 31–70) were included. The median time from diagnosis to transplant was 33 months (range 2–331) and 43% of patients had received more than 3 lines of therapy before the RICalloSCT, including a prior autoSCT in 46(SM2) %. Non-relapse mortality (NRM) was 10% at 100 days and 24% at 1 year and was significantly lower for patients receiving ATG (RR 0.59, $P = 0.046$). There was no impact of donor type, prior autoSCT and disease status at transplant on NRM. Acute graft versus host disease grades II-IV occurred in 113 patients and chronic GVHD (cGvHD) in 42% at 1 year post transplant. After a median follow up of 72 months (range 3–159), 118 patients relapsed at a median of 8 months post RICalloSCT (range 1–117). The cumulative incidence of relapse was 25%, 39% and 40% at 1, 4 and 5 years, respectively, and was significantly worse in patients with chemorefractory disease (HR 0.49, $P = 0.01$) or those receiving CAMPATH (HR 2.59, $P = 0.0002$). In a landmark analysis the development of cGVHD was associated with a significantly lower relapse risk. The 1 and 4 year progression-free survival (PFS) rates were 51% and 31%, respectively, and was significantly worse for patients with chemorefractory disease (HR 0.6, $P = 0.02$). The overall survival (OS) was 62% and 40% at 1 and 5 years, respectively, and was associated with chemorefractory disease (HR 0.45, $P = 0.0002$) at transplant. The outcomes of RICalloSCT for patients who had relapsed after a prior autoSCT were no different to those observed in patients undergoing a RICalloSCT as a first transplant procedure. RICalloSCT results in long term disease free survival in about 30% of patients, including those patients relapsing after a prior autoSCT. Late relapses are rare suggesting that allogeneic transplantation may be a curative procedure for this disease.

Disclosure of conflict of interest: None.

O141
Previously Published

O142
Salvage Brentuximab Vedotin prior to allogeneic hematopoietic cell transplantation in classical Hodgkin lymphoma does not impact survival but reduces the incidence of chronic GVHD: a retrospective study of the EBMT Lymphoma Working Party

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Brentuximab vedotin (BV) is an anti-CD30 antibody-drug conjugate approved for treatment of relapsed classical Hodgkin lymphoma (cHL) after autologous hematopoietic cell transplantation (HCT) or after failing two lines of combination chemotherapy in transplant ineligible patients. Preliminary data from small series suggest that BV might improve outcomes after allogeneic HCT when used as pre-transplant salvage therapy. Between 2010 and 2014, 435 adult patients underwent an allogeneic HCT for cHL at EBMT participating centers. We compared the outcome of 218 patients who did not receive BV prior to allogeneic HCT (no BV group) with that of 217 who received BV before allogeneic HCT (BV group). Furthermore, 30 patients in the no BV group and 60 patients in the BV group received BV post allogeneic HCT, almost exclusively for relapse/progression post transplant. Only 3 patients received post transplant BV as maintenance therapy. The median follow-up for survivors was 41 months (IQR: 28-55) and 341 had a prior autologous HCT. Patients in the BV group were younger at the time of HCT (median age: 33 vs 35 years), more heavily pretreated (median pre-allograft treatment lines: 4 vs 3), transplanted more recently (median year: 2013 vs 2011), and had a shorter follow-up (median follow up for alive patients 32 vs 50 months). The two groups were comparable in terms of recipient gender, performance status and comorbidity at allogeneic HCT, disease status at HCT, use of prior autologous HCT, type of donor, type of conditioning received or *in vivo* T cell depletion. In univariate analysis, salvage BV was associated with higher 2-year cumulative incidence of relapse (IR: 47% vs 35%; $P = 0.01$) but had no effect on the 2-year cumulative incidence of non relapse mortality (NRM), PFS or overall survival (OS: 70% vs 63%; $P = 0.15$). Similarly, BV had no effect on cumulative incidence of day +100 acute GVHD grade II-IV or incidence of chronic GVHD at 2 years (37% vs 44%; $P = 0.06$). In multivariate analysis, pre-allograft BV had no effect on NRM, IR, PFS, OS or acute GVHD, but significantly reduced chronic GVHD incidence (Hazard ratio = 0.67; 95%CI = 0.47–0.96; $P = 0.03$). Older age, poor performance status, use of pretransplant radiotherapy and advanced disease status at time of allogeneic HCT adversely affected OS. The use of salvage BV prior to allogeneic HCT facilitates the procedure in a high number of patients but does not affect relapse or survival outcomes. The significant decrease in the incidence of chronic GVHD in patients who received BV prior to the allogeneic HCT is an interesting finding that needs to be further studied.

Disclosure of conflict of interest: None.

O143
Prospective phase 2 trial of high-dose gemcitabine/busulfan/melphalan (Gem/Bu/Mel) with autologous stem-cell transplant in poor risk relapsed or refractory hodgkin's lymphoma: a comparison with a concurrent matched cohort treated with beam

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Better high-dose regimens than BEAM are needed for autologous stem-cell transplantation (ASCT) for refractory or poor-risk relapsed Hodgkin's lymphomas (HL). Our group has developed a regimen of infusional gemcitabine/busulfan/melphalan (Gem/Bu/Mel) exploiting gemcitabine inhibition of DNA damage repair. The encouraging preliminary results of Gem/Bu/Mel in HL patients led us to further study it in a phase 2 trial in primary refractory or poor-risk relapsed HL (NCI-2012-01885). Trial eligibility required age $\leqslant 65$, normal end-organ function and $\geqslant 1$ of the following: 1) primary refractory HL (persistent active disease after frontline therapy), 2) relapse after CR1 5 cm at the time of HDC or persistently PET+ at 1 month post-HDC. The trial had 80% power to detect a 2-year PFS improvement from 50% to 65%. We compared the study population with a concurrent cohort including all patients eligible for the trial who received BEAM due to no financial coverage for transplant in a clinical trial or patient preference. Due to the trial's timing no patients received maintenance brentuximab. The Gem/Bu/Mel trial enrolled 80 patients between 06/2011-04/2015. The concurrent BEAM cohort included 41 patients. Both cohorts were balanced except for a higher prevalence of PET+ tumors at HDC ($P = 0.003$) and bulky relapses ($P = 0.02$) in the Gem/Bu/Mel group. Gem/Bu/Mel toxicities included mucositis (49% G2, 40% G3), skin (22% G2, 11% G3), transaminitis (30% G2, 19% G3) and 1 case of G2 pneumonitis, with no cases of VOD or $G \geqslant 2$ cardiac, renal or CNS toxicity. There were no transplant-related deaths in either cohort. Post-HDC.

[O143]

	GemBuMel (N = *80*)	*BEAM* (N = *41*)	*P*
Median age (range)	31 (13–65)	39 (23–65)	0.02
Primary refractory/poor-risk relapse	41% / 59%	36% / 64%	0.6
No. prior relapses			
1	80%	70%	0.28
>1	20%	30%	
Median # prior chemotherapy lines	2 (2-6)	2 (2-7)	0.3
Prior disease-free interval (mo)			
< 12	81%	78%	0.6
⩾12	19%	22%	
Prior xRT	21%	22%	0.9
Relapse within prior xRT field	10%	2%	0.04
Extranodal relapse/PD	36%	43%	0.4
B symptoms at relapse/PD	11%	17%	0.2
Bulky relapse (>5 cm)	39%	20%	0.03
PET+ tumors at HDC	30%	12%	0.02
Status at HDC: CR/PR/No response	70%/22%/8%	88%/12%/0%	0.05

Gem/Bu/Mel is safe and effective in patients with refractory or poor-risk relapsed HL, with superior outcomes to a concurrent matched cohort of patients treated with BEAM. Gem/Bu/Mel is an effective platform for further post-ASCT maintenance therapies, eg, with brentuximab.

Disclosure of conflict of interest: None.

O144

Long-term impact of up-front ASCT combined with Rituximab in Non Hodgkin Lymphoma (NHL): an analysis of toxicity and fatigue in Lymphoma Study Association (LYSA) trials, the SIMONAL study

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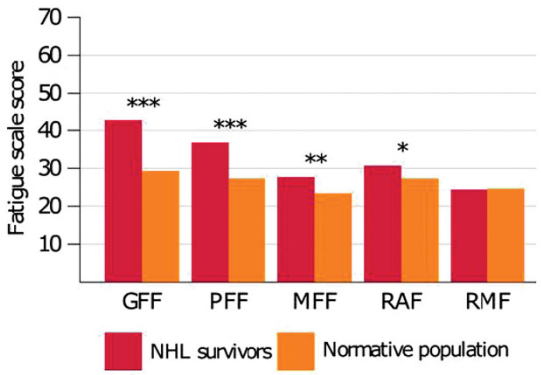
NHL survivors are at high risk for second cancers (SC), late toxicities and persistent fatigue. Little is known about new agents such as rituximab (RITUX) in particular when combined with upfront ASCT. The impact of treatment regimens on late morbidity was analyzed in a large cohort of survivors with 10-yr follow-up (FU). In 2015, a fatigue (MFI-20) and a self-assessment Life Situation Questionnaire (LSQ) were mailed to survivors treated in 12 successive LYSA randomized trials (1993-2007) for Diffuse Large B cell (DLBCL) and follicular (FL) lymphomas. Of 8113 pts enrolled into trials, 5247 were alive at last FU. Addresses were obtained for 3317 survivors of whom 1671 (50%) returned the questionnaires. We focused herein in 346 patients who received upfront ASCT as consolidation. Matching was done according to propensity scores. Linear regression models were used to assess factors linked to increased fatigue level. There were 190 males and 156 females (median 57 yrs, 48% > 60 yrs). 45 pts had FL and 301 DLBCL. 75 pts received CHOP-like chemotherapy and 271 pts high-dose CHOP (mainly ACVBP). RITUX was combined to chemotherapy in 137 pts (40%). 73% of patients experienced weight gain during follow up and 17% were obese. Only 34% reported no comorbidity. Upfront ASCT was associated with more infections (17 vs 11%, $P = 0.002$) and more pulmonary diseases (14 vs 9%, $P = 0.005$) but not with second cancers (8 vs 6%). 217 pts (63%) expressed persistent fatigue (MFI score $\geqslant$ 40). 13% reported anxiety, 20% lack of attentiveness, 25% memory difficulties and 42% sexual dysfunctions. 24% could not reintegrate active professionnal life. Fatigue scores were significantly higher than normative general population (Figure 1). However, comparison with an age-, sex- and follow-up time- matched subset of patients without ASCT showed no significant difference (Table 1). In multivariate analysis, increased fatigue level for ASCT patients was associated ($P < 0.01$) with obesity, pulmonary diseases, and immediate fatigue after treatment completion. There was no impact on fatigue of any induction regimen nor rituximab. This first study reporting on long-term NHL survivors after up front ASCT confirms a moderate altered health status. However, initial combination of Rituximab chemotherapy and upfront ASCT have no impact on the level of persistent fatigue, nor on the prevalence of primary second cancer.

Figure 1 [O144]



	Fatigue scale score				
	Matched		ASCT		P-value
	Means	(SD)	Means	(SD)	
General fatigue	39.8	(26.7)	42.1	(26.0)	0.25
Physical fatigue	34.5	(27.7)	35.8	(26.6)	0.54
Reduced activity	31.1	(23.5)	31.5	(22.8)	0.84
Reduced motivation	25.6	(22.9)	24.6	(22.2)	0.59
Mental fatigue	27.1	(24.8)	27.2	(25.9)	0.96

Disclosure of conflict of interest: None.

O145

Haploidentical transplantation for Hodgkin lymphoma relapsed after autologous transplant: reduced incidence of relapse and of chronic GVHD compared to HLA-identical related donors

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Haploidentical stem cell transplant (Haplo-SCT) represents a potential curative strategy for relapsed or refractory Hodgkin lymphomas (HL)[1-3]. Recent publications suggested that Haplo-SCT may represent an alternative option when a HLA matched-identical sibling (HLAid) or a matched unrelated donor (MUD) is not available, with comparable rates in terms of overall survival (OS), non-relapse mortality (NRM) and progression-free survival (PFS) in patients with lymphoma[4-6]. Less is known about the outcome of Haplo-SCT relative to HLAid-SCT in patients with HL relapsed after autologous transplant (HDC)[6]. We compare these two strategies in a retrospective study conducted at our institution. Between February 1999 and August 2016, we treated 64 patients either with HLAid- ($n=34$) or Haplo-SCT ($n=30$) for a HL relapsed after HDC. The two groups were balanced in terms of age ($P=0.8$), gender ($P=0.7$), time elapsed between HDC and allogeneic transplant ($P=0.1$), numbers of previous chemotherapy lines ($P=1$), disease status at transplant ($P=0.4$), conditioning regimen ($P=0.1$) and haematopoietic cell transplant-comorbidity index (HCT-CI) ($P=0.1$). Graft source was mainly represented by bone marrow (BM) stem cells in the Haplo-SCT cohort while peripheral blood stem cells (PBSC) were mainly used for HLAid-SCT ($P<0.0001$). All patients engrafted. Median day for neutrophil and platelet engraftment was significantly shorter in HLAid-SCT cohort (14 vs 19, $P=0.007$; 11 vs 23, $P<0.0001$, respectively). With a median follow-up of 47 months for all alive patients, 3-years OS, PFS and 1-year NRM was 53%, 42% and 14%, respectively. The main variable affecting outcome was represented by disease status at transplant: patients in complete remission (CR) had better 3-y OS and PFS compared with patients in partial remission (PR) or progressive/stable disease (PD/SD): 86% vs 45% vs 14% ($P<0.0001$) and 70% vs 40% vs 0% ($P<0.0001$), respectively. Multivariate Cox regression analysis confirmed that disease status was the main variable associated with OS (HR for pts not in CR: 14.2, $P=0.002$) and PFS (HR for pts not in CR: 6.6, $P=0.004$). When we compared disease outcome by donor type, we observed that 3-yr PFS was significantly improved for patients receiving Haplo- compared to HLAid-SCT (60% vs 29%, $P=0.04$ (Figure 1a), due to a significant reduction of relapse rate after Haplo-SCT (16% vs 61%, $P=0.001$) (Figure 1b). The 1-yr NRM and OS were similar. The 1-year cumulative incidence (CI) of grade 2-4 acute graft-versus-host-disease (GVHD) was not different (24% vs 33% $P=0.4$) while the 3-year CI of moderate-severe chronic GVHD was significantly lower after Haplo-SCT (4% vs 40%, $P=0.02$). Finally, the composite end-point 1-y GVHD-free/relapse-free survival (GRFS) was significantly better after Haplo-HSCT than HLAid (49% vs 17%, $P=0.03$). Overall, our data suggest that allo-SCT and in particular haploidentical SCT may play a key role in the management of relapsed HL failing auto-SCT.

Disclosure of conflict of interest: None.

[O145]

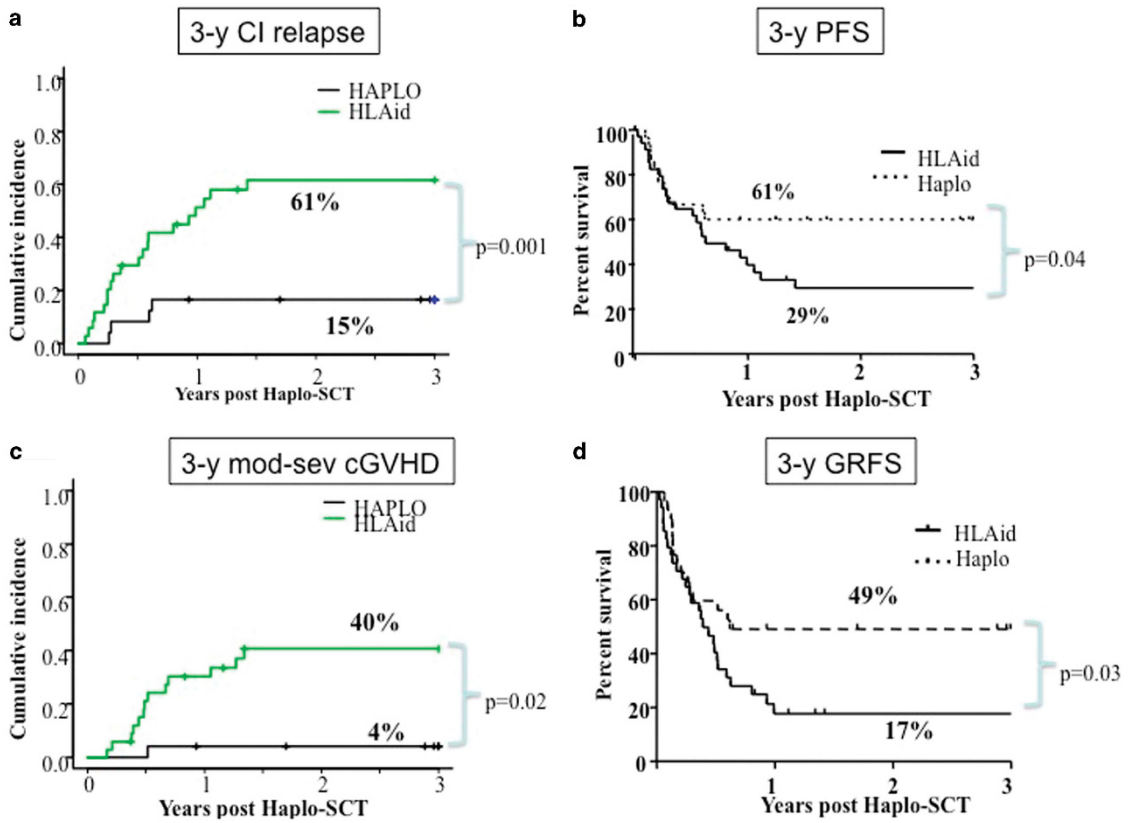

Figure 1: Comparison of patients outcome between patients receiving HLAid-SCT vs Haplo-SCT in terms of a) 3y-CI of relapse, b) 3y-PFS, c) 3y-CI of moderate-severe cGVHD, d) 3y-GRFS.

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O146

Autologous stem cell transplantation (ASCT) or whole-brain radiotherapy (WBRT) as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with newly diagnosed primary cns lymphoma (PCNSL): results of the IELSG32 randomized Phase II Trial

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IELSG32 is a randomized phase II trial focused on two key questions on patients (pts) with PCNSL. Results of the 1st randomization have demonstrated that MATRix (methotrexate, cytarabine, thiotepa, rituximab) is the induction combination associated with significantly better outcome (Ferreri *et al*. Lancet Haematol 2016). Herein, we report the results of the 2nd randomization that addresses the efficacy of ASCT, as an alternative to WBRT as consolidation after high-dose-methotrexate-based induction. HIV-neg pts (18-70 yo) with PCNSL were randomly assigned to receive 4 courses of methotrexate-cytarabine (arm A); or the same combination plus rituximab (B); or MATRix combination (C). ASC were collected after 2nd course. Pts with stable disease or better were further randomized between WBRT 36 ± 9 Gy (arm D) and BCNU-thiotepa conditioned/ASCT (arm E). Primary endpoint of the 2nd randomization was 2-year PFS (intention-to-treat bases): to demonstrate an improvement from 65% (P0) to 85% (P1), 52 pts/arm (one-sided; α 5%; β 95%) were required. Consolidation treatment would be considered effective if ⩾40 pts were progression-free survivors at 2 ys (pre-determined efficacy threshold). Effects of treatments on cognitive functions and QoL were assessed with the IPCG tests and EORTC-QLQ. 219 of the 227 enrolled pts (53 centers; 5 countries) were assessable and referred to 1st randomization (arm A 75; B 69; C 75). 167 pts had responsive or stable disease after induction: 49 pts were excluded from 2nd randomization (poor mobilization, poor condition, refusal); 118 pts were thus randomized (59 pts/arm) and constitute the study population (median age 58 ys; range 18–70). There were no differences in clinical parameters between the two arms. There were 6 protocol violations: 4 pts randomly allocated to arm D were treated with ASCT and 2 pts allocated to arm E were irradiated; 5 pts (D 2; E 3) refused consolidation. Both consolidation therapies were well tolerated. Grade-4 non-hematological toxicity was uncommon (⩽5% of pts); as expected, hematological toxicity was more common in arm E. There were 2 toxic deaths (infections), both in arm E. IPCG tests showed a fast improvement in most cognitive functions after treatment, which was followed by a significant impairment of attention/executive functions and late verbal memory among pts treated with WBRT, whereas pts treated with ASCT exhibited improvement in most functions and QoL. Both WBRT and ASCT were active with an improvement in CR rate from 54% after induction to 95% (95%CI:90–100) after consolidation in arm D, and from 53% to 93% (95%CI:87–99) in arm E. At a median f-up of 40 months (range 24–76), there were 20 events in arm D and 25 in arm E. WBRT and ASCT were both effective, and achieved the pre-determined efficacy threshold: 40 progression-free survivors at 2 ys among both the first 52 arm-D and 52 arm-E pts. The 2-yr PFS was 80% (95%CI:70–90) in arm D and 70% (95%CI:59–81) in arm E ($P = 0.17$). In multivariate analysis, IELSG risk group and induction arm were associated with PFS. 42 arm-D and 37 arm-E pts are alive, with a 2-yr OS of 85% (95%CI:75–95) and 71% (95%CI:60–82) ($P = 0{\cdot}17$), respectively. WBRT and ASCT are both feasible, active and effective as consolidation strategies in pts ⩽70 ys with PCNSL. Potential impairment of specific cognitive functions after WBRT should be considered at the time of therapeutic decision.

Disclosure of conflict of interest: None.

Chronic leukemia and MDS

O147

Haplo-identical transplantation (haplo-HSCT) in patients with myelodysplastic syndrome (MDS): a report from the European Society of Blood and Marrow Transplantation

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The only curative treatment in patients with intermediate or high-risk MDS is allogeneic hematopoietic stem cell transplantation (HSCT) usually resulting in disease-free survival between 30 and 50% at long-term depending from the disease risk and the type of donor. The use of HLA mismatched unrelated donor (marrow, peripheral blood or umbilical cord blood) usually gives worse results than HLA-matched sibling or unrelated donor (Blood 2013 Saber, BBMT 2015 Robin). Family haplo-identical in patients with MDS is also an alternative option. The present study reports the European activity for haplo-identical transplantation in MDS patients. All consecutive patients with a primary diagnosis of MDS transplanted from an HLA-mismatched related donor from 2007 to 2014 were included in this study if they had HLA and diagnosis information. Data were analyzed using multivariable Cox proportional hazards and cause-specific hazards models. Missing data were handled through multiple imputations by chained equations methods. 230 patients were identified in the European registry Promise. Median age at transplant was 56 years (IQR: 46-64). WHO at time of transplant were RCMD in 31 (13.5%), RA/RARS/del5q in 12 (5.2%), RAEB-1 in 36 (15.7%), RAEB-2 in 67 (29.1%) and MDS transformed in AML in 84 (36.6%). Marrow blast were $<$ 5% in 72.2% at time of transplant. 181 (78.7%) patients had 2 or more HLA mismatches with the donor while other patients had only one HLA-mismatch (21.3%). 117 (51.5) patients received a reduced intensity (RIC) regimen and 62 (27.3%) received a total body irradiation. *In vivo* T-cell depletion was performed in 105 (46.1%) patients while ex-vivo T-cell depletion was performed in 34 (14.9%) patients. GvHD prophylaxis was based on post-transplant cyclophosphamide (PTC) in 102 (44.7%) patients; 3-year overall survival (OS), disease-free survival (DFS) were 32% (95%CI: 26–41%) and 29% (95%CI: 23–37), respectively. Cumulative incidence of 3-year non-relapse mortality (NRM), grade II-IV acute GVHD and chronic GVHD were: 49% (95%CI: 41–56), 31% (95%CI: 25–38) and 30% (95%CI: 23–36), respectively. Regarding only patients treated by PTC, 3-year OS, DFS and NRM were 38%, 34% and 41%. NRM was particularly high in patients having received a myeloablative conditioning (MAC) regimen as (59% vs 40%). The best outcome were observed in patients with a WHO diagnosis with less than 5% marrow blasts (OS: 60%, DFS: 51%, NRM: 34%). Multivariable analyses showed that the following risk factors impacted OS, PFS, and NRM: transformation into AML, not in CR at time of transplant, a female donor for a male recipient, myelo-ablative conditioning regimen and the absence of PTC (see Table1).

[O147]

	DFS		*OS*		*NRM*	
	Hazard ratio	*P-value*	*Hazard ratio*	*P-value*	*Hazard ratio*	*P-value*
Tranformation in AML	1.84	0.033	2.19	0.010	1.83	0.069
Non CR at time of transplant	1.93	0.001	1.90	0.002	1.76	0.017
Female donor for male recipient	1.53	0.062	1.67	0.030	1.94	0.016
MAC	1.47	0.048	1.56	0.026	1.70	0.023
PTC	0.49	0.038	0.44	0.025	0.40	0.027

DFS in patients transplanted from an haplo-identical donor is close to outcome reported in HLA-mismatched donor other than haplo. Results have been improved by PCT which was associated with a significant better DFS and OS. Nevertheless, NRM remains relatively high at 41% after PCT.

Disclosure of conflict of interest: None.

O148

Long-term survival of patients with MDS after allogeneic transplantation: a report from the Chronic Malignancies Working Party of EBMT

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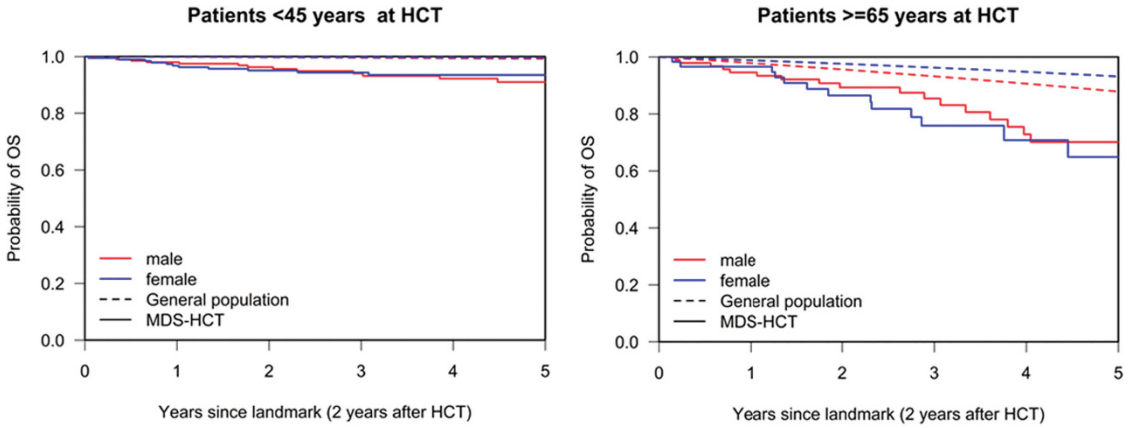
The median age at diagnosis of Myelodysplastic Syndromes (MDS) is 76 years. The incidence of MDS increases with increasing age and men have a higher incidence than women. Currently, allogeneic hematopoietic stem cell transplantation (HCT) is the only curative treatment option for patients with MDS. When interpreting outcomes after HCT the age- and sex-specific life expectancy has to be considered. Therefore, we studied excess mortality after HCT in comparison to an age-, sex-, country- and calendar year-matched general population in various time periods after HCT for different age cohorts. Data from adult patients with MDS who had received a first allogeneic HCT between January 2000 and December 2012, and who were registered with the EBMT database, were analyzed. Patients who received mismatched related HCT, cord-blood transplantation and patients with more than 20% marrow blasts at any time during their history were excluded from the analysis. Survival probabilities were calculated by means of the Kaplan-Meier estimator. Excess mortality compared to an age-, sex-, country- and calendar year-matched general population was estimated by relative survival methods. In total 3813 patients were included into the analysis. The median follow-up of patients alive at the end of follow-up was 49 months. The number of transplants increased from 56 in year 2000 to 660 in 2012. Median age at HCT increased from 47 (range 18–66) to 57 years (18-74). 60% of patients were male. 39% of the patients had an HLA-matched sibling donor and 58% received reduced-intensity conditioning. For the whole cohort of patients, the overall survival (OS) was 46% (95% CI: 45–48%) at 5 years and 40% (95%-CI: 37–42%) at 10 years. For patients $<$ 55 years or $\geqslant$ 55 years at the time of HCT 10-year OS probabilities were 48% (95%-CI: 45–51%) and 31% (95%-CI: 28–34%) and for patients with or without excess blasts (EB) at HCT the 10-year OS probabilities were 33% (95% CI: 30–37%) and 46% (95% OS CI: 43–49), respectively. The probability to be alive event-free at

Figure 1 [O148]



2 years after HCT was 52% (95% CI: 50–54%). In the population who reached this landmark, the probabilities to be alive at 10 years after HCT were 82% (95% CI: 78–86%) and 65% (95% CI: 59–72%) for patients < 55 years or $\geqslant 55$ years at HCT and 68% (95% CI: 62–74%) and 81% (95% CI: 77–85%) for patients with or without EB at HCT. For patients below the age of 45 at HCT who survived the first two years after HCT event-free, the probability to be alive 5 years later was 91% (95% CI: 86–96%) for men compared to 99% survival chance in the matched general population and 94% (95% CI: 90–97%) for women compared to 99.5%. For patients 65 years or older at HCT, these numbers were 70% (95%-CI: 58–85%) and 88% for men and 65% (95%-CI: 49–86%) and 93% for women. Long-term follow-up data derived from the EBMT registry show that patients experience excess mortality compared to the general population, also beyond the 2-years landmark. However, especially for older male patients, the risk of dying from causes also relevant for an age-matched population was substantial. For elderly patients this background mortality should be considered when interpreting results after HCT. The results also indicate that a significant fraction of patients can be cured by HCT.

Disclosure of conflict of interest: None.

O149

Fludarabine/treosulfan is a promising condition for MDS/CMML-patients: a retrospective single center study

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Allogeneic haematopoietic cell transplantation (HCT) of MDS/CMML is still a challenge with a disease free survival (DFS) between 35 - 40%, transplant related mortality (TRM) between 15-20% and relapse rates (RR) between 20-30 %. However, improved results with Fludarabine and Treosulfan conditioning has been published 1,2. Therefore, we have implemented this regimen at our center and now the first results are presented and compared with former transplantation data. A retrospective single center study of 164 patients with MDS ($n = 148$) and CMML ($n = 16$), who underwent allogeneic HCT between 1. Jan 2000 – 31. Oct 2016 at Copenhagen University Hospital. From 2000-2014, a non-myeloablative conditioning (NMA) with Fludarabine 90 mg/m2 + TBI 2 Gy was used for patients > 50 years. A myeloablative conditioning (MAC) with cyclophosphamide 120mg/kg + TBI 12 Gy was used for patients $\leqslant$ 50 years. From September 2014 the reduced toxicity conditioning (RTC) Fludarabine 150 mg/m2 + Treosulfan 42 g/m2 has been implemented for patients $\leqslant 65$ years. Patients > 65 years are still treated with NMA. Immunosuppression: NMA: Tacrolimus and MMF, MAC: Cyclosporin and MTX and Flu/Treo: Tacrolimus and MTX. ATG has not been added for matched unrelated donors (MUD).

[O149]

Regimen	*NMA (Flu-TBI 2 Gy)*	*MAC (Cy-TBI 12 Gy)*	*Flu/Treo*
Patients ($n = 164$)	95 pt	38 pt	31 pt
Median age, years	61 (range 37–75)	38 (range 13–59)	60 (range 28–66)
CMML	9 pt (9%)	3 pt (8%)	4 pt (13%)
Stem cell source	PB: 98% BM: 0% UCB: 2 %	PB: 50% BM: 50%	PB: 100%
Donor MUD/SIB	70%/30 %	61%/39%	74%/26%
More than 5% blast at time of HCT	6 pt (6%)	11 pt (28%)	9 pt (29%)

The two years overall survival (OS) for Flu/Treo (2): 86 % (CI: 65–94). For NMA (0): 60% (CI: 49–69) and MAC (1): 55% (CI: 38–69). The median follow up time were: Flu/Treo: 1,2 years; NMA: 4,7 years and MAC: 7,2 years. A significant difference in OS in favor of Flu/Treo was found when compared to MAC ($P = 0{,}023$), NMA ($P = 0{,}047$) and both groups ($P = 0{,}032$). No difference in OS between MAC and NMA (Fig 1) was found. Two patients treated with Flu/Treo have relapsed corresponding to a cumulative incidence of relapse (CIR) after 2 years of 0,088 (CI: 0,014–0,251). CIR for NMA: 0,237 (CI: 0,156–0,328) and MAC: 0,184 (CI: 0,080–0,323). TRM after 2 years: Flu/Treo: 0,150 (CI: 0,044–0,315); NMA: 0,196 (CI: 0,122–0,284) and MAC: 0,316 (CI: 0,175–0,467). Acute GvHD (grade 1–4) rate was comparable for Flu/Treo and NMA (0,24(CI: 0,10–0,40) vs 0,26 (CI: 0,18–0,36))) and reduced compared to MAC (0,55(CI: 0,38–0,70)). Fludarabine/Treosulfan is a promising conditioning regimen for MDS/CMML pts. Two years OS was significantly improved compared to standard MAC and NMA, which may be explained by a lower relapse rate without a corresponding increase in TRM.

Disclosure of conflict of interest: None.

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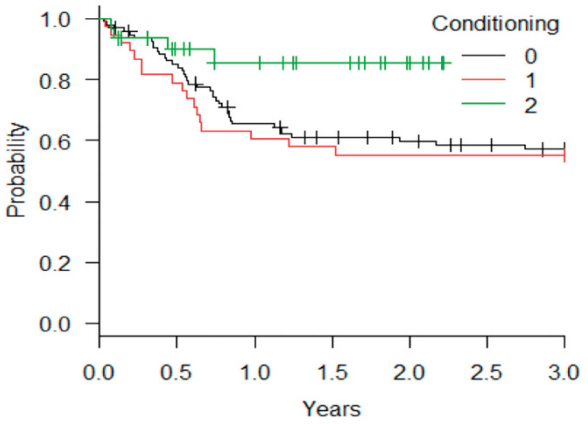
Figure 1 [O149]



O150

Ibrutinib for bridging to allogeneic hematopoietic stem cell transplantation (alloHCT) in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) is safe and effective: Updated results of a study by the EBMT Chronic Malignancy and Lymphoma Working Parties, the French Cooperative Group for CLL, and the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC)

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The advent of the B cell receptor inhibitor (BCRi) ibrutinib has improved the outlook of patients with CLL and MCL failing chemoimmunotherapy (CIT). However, the impact of ibrutinib on the feasibility and safety of a subsequent alloHCT is unknown. Here we present updated results of an EBMT survey on the outcome of alloHCT following prior exposure to ibrutinib in patients with CLL or lymphoma (EBMT study code LWP 2013-N-03/CMWP 44204425). Eligible were patients aged >18 years registered with the EBMT data office for a planned alloHCT for CLL or lymphoma after pre-exposure to ibrutinib at any time before transplant. Baseline patient, disease, and transplant data was collected from MED-A forms. Centers were requested to provide additional treatment and follow-up information. As of Dec 2, 2016, 63 patients (76% male) were included. Diagnosis was CLL in 43 patients, MCL in 17 patients, and other lymphoma in 3 patients. The median age at HCT was 56 (38-72) years and the median number of treatment lines prior to ibrutinib 2 (1-9). 80% of the patients with lymphoma but none of the CLL patients had a prior autoHCT. Patients had been on ibrutinib for a median of 187 (11-671) days. In 3 patients, ibrutinib had been stopped because of disease progression >120d before transplant, whereas the interval between ibrutinib withdrawal and alloHCT was 15-120d in 39%, 4-14d in 42%, and 0-1d in 14% of the patients. Of the CLL patients, 37% had a TP53 lesion, and 87% and 65% met at least one of the 2007 and 2014 EBMT criteria for high-risk CLL, respectively. Disease status at alloHCT was sensitive in 81% of the CLL patients, and in 89% of the patients with lymphoma. The median time to reach neutrophils of >0.5/nl and platelets of >20/nl was 17 (6-68) and 14 (5-46) d post transplant, respectively. Acute GVHD grade 2-4 (3-4) was observed in 37% (7%) of 58 evaluable patients, and overall and extensive chronic GVHD occurred in 41% and 24% of 46 patients at risk. With a median observation time of survivors of 7 (1-29) months, there were only 3 non-relapse deaths, translating into a 1-year non-relapse mortality (NRM) of 9%. 1-year relapse incidence (REL), progression-free survival (PFS), and overall survival (OS) was 36%, 58%, and 73% for CLL, and 36%, 59%, and 70% for MCL. 2-year OS from start of ibrutinib was 78% for CLL and 74% for MCL. In the 40 evaluable patients with CLL, sensitive compared to refractory disease status at alloHCT was associated with significantly better REL and EFS. In 31 CLL patients transplanted while still responding to BCRi, 1-year REL, EFS and OS were 28%, 63% and 80%, respectively. In these 31 patients, not counting relapse events that could be successfully retreated with ibrutinib, 1-year ibrutinib-sensitive survival was 73%. TP53 status, duration of ibrutinib exposure, interval between ibrutinib withdrawal and alloHCT, and type of conditioning had no impact on REL. Ibrutinib for bridging to alloHCT for CLL and MCL does not appear to adversely affect engraftment, GVHD risk, and NRM. Given the relatively good outlook of patients who undergo alloHCT while still responding to ibrutinib, this drug appears to be capable of making patients with otherwise refractory CLL transplant-eligible. Moreover, this preliminary data does not suggest short-term inferiority of switching from ibrutinib to HCT (compared to continuing ibrutinib without HCT) for patients with BCRi-sensitive CLL.

Disclosure of conflict of interest: PD: Janssen — Advisory Board, The remaining authors declare no conflict of interest.

O151

Bridging with Idelalisib appears safe in patients with chronic lymphocytic leukemia (CLL) prior to allogeneic hematopoietic stem cell transplantation (alloHCT): A Report from the EBMT Chronic Malignancies Working Party

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In future, many patients with high-risk CLL will be intolerant or refractory to the BTK-inhibitor ibrutinib when they are referred for allogeneic hematopoietic cell transplantation (alloHCT). The phosphatidylinositol 3-kinase (PI3Kδ)-inhibitor, idelalisib, is active also in ibrutinib-refractory CLL. The PI3-kinase exerts pleiotropic effects on cell metabolism, migration, proliferation, survival, and differentiation in lymphoid tissues. Autoimmune-mediated side effects such as colitis, hepatitis, and pneumonitis have been reported on treatment with idelalisib. Exposure to idelalisib could thus interfere with subsequent alloHCT. Therefore, we analyzed the outcome of patients with CLL who had received idelalisib prior to alloHCT. Patients were eligible if registered with the EBMT data office for a planned alloHCT for CLL after exposure to idelalisib at any time before transplantation. Minimal essential transplant data were collected on standard forms. Centres were requested to provide information on idelalisib treatment and follow-up. As of Dec 2, 2016, 32 patients with CLL (63% male) had received alloHCT after exposure to idelalisib in 2015 or 2016. Median age at alloHCT was 57 (36-67) years. 44% of patients had CLL with deletion 17p and/or deletion 11q. Almost all patients (96%) had a Karnofsky Performance Status of 80% or higher. The median number of treatment lines prior to alloHCT was 3 (1-7), including treatment with ibrutinib in six patients (19%). Idelalisib plus Rituximab was the last regimen prior to alloHCT in 29 patients (91%). Complete remissions and partial remissions were reported for 10% and 75% of patients. Reduced intensity and myeloablative conditioning was administered in 78% and 22% of patients. Anti-thymocyte globulin was given to 63% of patients and alemtuzumab to 28% of patients. Donors were HLA-identical siblings for 44% of patients, mismatched related donors for 16% of patients and unrelated volunteers for the remaining patients. One patient each received cord blood or a bone marrow while the remaining graft sources were peripheral blood stem cells. No primary graft failure and one secondary graft failure were reported. The median time to neutrophils of >0.5/nl and platelets of >20/nl was 19 days (11-40) and 15 days (8-50) after alloHCT, respectively. Acute GVHD grade 2-4 was observed in 44% of evaluable patients, and overall chronic GVHD in 25% of patients at risk. Twenty-six patients were alive after a median observation time of 4 (0-19) months after alloHCT. Four patients experienced relapse or progression and five patients succumbed from complications after alloHCT. This translated into 6-month cumulative incidences of 7% and 10% for non-relapse mortality (NRM) and relapse/progression. The probability of 6-month progression-free and overall survival was 83% (95%-CI, 68–100%) for both endpoints. Notably, of those 6 patients who had been exposed to ibrutinib and idelalisib two patients have relapsed and two patients have died from complications. This report shows that idelalisib-based salvage therapy can successfully bridge patients with CLL to alloHCT. Adverse safety signals with respect to engraftment, acute GVHD and early mortality could not be identified. Longer follow-up is needed in order to assess disease-control after alloHCT in this ultra high-risk patient population. Updated outcomes will be presented at the annual meeting.

Disclosure of conflict of interest: None.

O152
Previously Published

O153
Previously Published

O154
Previously Published

Hidden gems the EBMT selection

O155
Previously Published

O156
Maribavir versus valganciclovir for pre-emptive treatment of cytomegalovirus viraemia: a randomized, dose-ranging, phase 2 study among haematopoietic stem cell transplant and solid organ transplant recipients

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[1]UZ Leuven, [2]Shire

Transplant recipients experience toxicity issues, including myelosuppression and renal dysfunction, with available anti-cytomegalovirus (CMV) therapies, and this is an area of unmet medical need. Maribavir (MBV) is a potent and selective orally bioavailable anti-CMV agent that could potentially address the shortcomings of current therapy. This Phase 2 study (EudraCT 2010-024247-32) assessed safety, tolerability and anti-CMV activity of MBV versus valganciclovir (VGC) among haematopoietic stem cell transplant (SCT) and solid organ transplant (SOT) recipients. Patients ($\geqslant$18 years; 1000–100,000 blood/plasma CMV DNA copies/mL; no CMV organ disease) were stratified by transplant type (SCT vs SOT) and randomized 1:1:1:1 to receive oral MBV 400, 800 or 1200 mg twice daily (BID), or VGC (Weeks 1–3: 900 mg BID, after Week 3: 900 mg once daily; adjusted for renal function), for up to 12 weeks. Primary safety analysis focused on incidence of treatment-emergent adverse events (TEAEs). Primary efficacy endpoint was proportion of patients with confirmed undetectable plasma CMV DNA within 3 and 6 weeks of treatment ('responders'). Pre-specified subgroup analysis was conducted to assess undetectable plasma CMV DNA within 6 weeks for SCT and SOT patients separately. Treatment effect estimates were calculated for the pooled MBV group versus VGC and compared statistically; no statistical tests were performed on safety endpoints. Between May 2012 and July 2014, 159/161 randomized patients received study drug (119 MBV (61 SCT); 40 VGC (21 SCT)); median (range) age 58 (18–76) years. Efficacy results are shown in Table 1. The proportions of Week 3 and Week 6 responders were similar for MBV versus VGC for the overall group; in the SCT subgroup, there was a numerically higher proportion of Week 6 responders for MBV versus VGC. CMV clearance was similar across doses. TEAEs reported in $\geqslant$20% of patients in any treatment group are shown in Table 2. Most TEAEs were mild-to-moderate in severity. Dysgeusia occurred more frequently with MBV than VGC, but with no apparent dose effect. Gastrointestinal AEs (nausea/vomiting/diarrhoea) occurred more frequently in those receiving MBV than VGC. Of interest, neutropenia (ANC $<1000/mm^3$) occurred less frequently with MBV (5%) than VGC (18%). MBV 400–1200 mg BID had similar efficacy to VGC at clearing CMV viremia when administered for up to 12 weeks among all transplant recipients, with a similar treatment effect across all MBV doses. Among SCT recipients, viraemia clearance was achieved by a numerically greater proportion of patients in the MBV group than the VGC group. MBV was generally well tolerated, with a safety profile similar to previous studies and less treatment-emergent neutropenia based on laboratory assessments, compared with VGC, which may be of benefit to transplant recipients, especially SCT patients. Study funding: Shire Development, LLC.

Disclosure of conflict of interest: JM, CC, PJ, XP, FS: nothing to disclose. JW, AW: employees of and hold stock options in Shire. OW: advisory board or consulting for Amgen, Alexion, Astellas, Basilea, Biotest, Bristol-Myers-Squibb, Chiesi, Hexal, Janssen, MSD, Novartis, Roche, Pfizer, Sanofi and TEVA. SV:

[O156]

Table 1.

Primary endpoint	MBV dose			All MBV doses, n=119	VGC n=40
	400 mg BID, n=40	800 mg BID, n=40	1200 mg BID, n=39		
Treatment effect estimate (SCT and SOT), n/N (%)*; 95% CI					
Week 3 responders	26/39 (67); 50, 81	23/40 (58); 41, 73	23/38 (61); 43, 76	72/117 (62); 52, 70	22/39 (56); 40, 72
				OR 1.42; 95% CI 0.62, 3.24; p=0.41	
Week 6 responders	31/39 (79); 64, 91	33/40 (83); 67, 93	28/38 (74); 57, 87	92/117 (79); 70, 86	26/39 (67); 50, 81
				OR 2.12; 95% CI 0.91, 4.96; p=0.08	
Subgroup analysis, n/m (%)†					
Week 6 responders – SCT	16/20 (80)	16/21 (76)	14/20 (70)	46/61 (75)	10/21 (48)
Week 6 responders – SOT	15/20 (75)	17/19 (89)	14/19 (74)	46/58 (79)	16/19 (84)

*Denominator N is the number of randomized patients with non-missing data.

†Denominator m is the number of randomized patients in the subgroup.

Table 2.

TEAEs reported in ≥20% of patients in any treatment group	MBV dose			All MBV doses, n=119	VGC n=40
	400 mg BID, n=40	800 mg BID, n=40	1200 mg BID, n=39		
Dysgeusia	18 (45.0)	16 (40.0)	14 (35.9)	48 (40.3)	1 (2.5)
Nausea	9 (22.5)	7 (17.5)	11 (28.2)	27 (22.7)	6 (15.0)
Diarrhoea	7 (17.5)	7 (17.5)	10 (25.6)	24 (20.2)	4 (10.0)
Vomiting	4 (10.0)	8 (20.0)	12 (30.8)	24 (20.2)	4 (10.0)
Oedema peripheral	3 (7.5)	9 (22.5)	5 (12.8)	17 (14.3)	7 (17.5)

employee of and held stock options in Shire/Viropharma at the time of the study.

O157

Establishing a standardized system to capture chronic graft-versus-host disease (GVHD) data in accordance to the national institutes (NIH) consensus criteria

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Onset of chronic GVHD (cGVHD) occurs after Day 100 and within the first year following allo-HCT in approximately 90% of patients. It is therefore relevant for centers to maintain a systematic approach to collect and accurately document GVHD data after Day 100 to properly monitor incidence, complications, and patient outcomes. In 09/2014, our center formed a dedicated GVHD team consisting of a physician, NP, and RN to assess allo-HCT recipients for GVHD within days 101 to 180 (D180), and 181 to 365 (D365). The committee met monthly to reach consensus regarding GVHD diagnosis and maximum grading. aGVHD was graded according to IBMTR classification. cGVHD was defined according to 2005 NIH consensus criteria. To assist with diagnosis and grading, 3 internal electronic GVHD data capture forms were created based on NIH and IBMTR criteria. Each patient had a GVHD assessment form completed at D180 and D365 to document organ involvement and GVHD syndrome. Depending on the patient's GVHD sydnrome, up to 2 additional forms were completed to capture acute and/or chronic grading. Updated NIH cGVHD criteria were released in 12/2014. In an effort to maintain the national standard, a new electronic GVHD assessment form was created this year to capture the updated criteria. We collaborated with the CIBMTR to ensure our reporting would align with their revised cGVHD forms anticipated for release in 2017. BMT CTN reporting requirements were also taken into consideration. In addition, the 3 previous GVHD forms were streamlined into 1 dynamic 'Chronic and Late Acute GVHD Assessment' form. This enhanced form guides users from diagnosis to the appropriate acute or chronic scoring section based on user responses. In an effort to improve data quality, the monthly consensus review was also modified. Starting in 12/2015, the attending leading the GVHD committee was appointed to author each patient's D180 and D365 GVHD forms; capturing the diagnoses and grading according to the team's consensus. To properly monitor GVHD incidence and outcomes, chart review was completed for patients who received an allo-HCT from 09/2013-09/2016 ($n = 419$). GVHD data was confirmed for accuracy by the GVHD team and compiled into a database. Chronic GVHD documentation compliance improved from 82% (06/2015) to 100% since launching the 'Chronic and Late Acute GVHD Assessment' form. Combining 3 GVHD forms into 1 dynamic form reduced duplicate entry by 18 fields. In addition, critical data is no longer missed as the form notifies users when a field is not answered. Accurate GVHD data for 419 patients who received an Allo-HCT from 09/2013-09/2016 can now be accessed. Ongoing assessment of an average of 16 patients/time period is conducted monthly. Using a dedicated clinician team to assess GVHD allows standardized data capture. Technology is also a valuable tool in assisting with GVHD evaluation, improving data quality, and enhancing efficiency. MSK's cGVHD data now adheres to 2014 NIH consensus criteria and BMT CTN reporting requirements. Our data will also coincide to the CIBMTR's new GVHD collection forms when released in 2017. Other centers can implement a similar methodology to ensure uniform GVHD assessment across all patients.

Disclosure of conflict of interest: None.

O158

Optimizing anti-thymocyte globulin exposure to improve survival chances after hematopoietic cell transplantation for acute leukemia and myelodysplastic syndrome

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Anti-thymocyte globulin (ATG) is used to prevent graft-versus-host-disease (GvHD) following allogeneic hematopoietic cell transplantation (HCT). However, ATG can also cause delayed immune reconstitution, negatively influencing survival. We studied the relation between exposure to ATG and clinical outcomes in adult patients with acute leukemia and myelodysplastic syndrome. In a retrospective analysis, consecutive patients receiving a (9 or 10/10 allele) matched T-cell repleted allogeneic peripheral blood HCT with ATG (Thymoglobulin: 8mg/kg in 4 from day -8) as part of reduced intensity conditioning (Fludarabine 90mg/m2 and TBI 200cGy) were included (March-2004 to May-2015). Active-ATG levels were measured using a validated bioassay and pharmacokinetic (PK) exposure measures were calculated with a validated population PK-model. Main outcome of interest was overall survival (OS); other outcomes were relapse- and non-relapse mortality, acute- and chronic-GvHD and evaluation of current and optimal dosing. Cox proportional-hazard models and Fine-Gray competing risk models were used. 146 patients (74 acute-myeloid leukemia, 36 acute-lymphoblastic leukemia and 36 myelodysplastic syndrome) with a median age of 50 (18.1-69.9) years were included. Median follow up was 37 (0.6-139) months. Active-ATG exposure after HCT was found the only multivariate predictor for 5-year OS. Optimal exposure after HCT (60-95 AU*day/mL; $69 \pm 8\%$) yielded superior OS compared to below ($32 \pm 8\%$, hazard ratio (HR) 3.36, 95% confidence interval (CI) 1.69–6.68, $P = 0.00057$) and above-optimal exposure ($48 \pm 6\%$, HR 2.5, 95%-CI 1.29–4.84, $P = 0.0064$. Above-optimal exposure led to higher relapse-related mortality (HR 2.66, $P = 0.027$), while below-optimal exposure increased non-relapse mortality (HR 4.17, $P = 0.0060$, grade 3-4 acute-GvHD (HR 3.09, $P = 0.035$) and chronic-GvHD (HR 2.56, $P = 0.048$). Dosing based on absolute lymphocyte counts led to higher optimal target attainment compared to weight-based dosing regimens. ATG-exposure after HCT influences survival chances. These results stresses the importance of improving the efficacy and safety of ATG-dosing in HCT by amending dosing. Individualizing ATG-dosing, based on lymphocyte counts rather than body-weight, could result in improved survival chances after HCT.

Disclosure of conflict of interest: J. Kuball is scientific co-founder and CSO of Gadeta BV. The remaining authors declares no conflict of interest.

O159

Upfront alternate donor HSCT for children with severe aplastic anemia: a single center prospective clinical trail outcome

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Alternate donor (AD) hematopoietic stem cell transplantation (HSCT) for children with severe aplastic anemia (SAA) remains challenges mainly associated with graft failure and Graft versus Host Disease (GVHD). So it has been considered in the second choice of treatment status. But the survival outcomes from AD HSCT in childhood SAA have been improved steadily over the past decades. To answer the question whether the AD HSCT can be the first line therapy for SAA children, we start this single center prospective upfront AD HSCT study. Based on the success of the AD HSCT for children with SAA previously in our center, the upfront AD HSCT protocols were

approved by the local Ethics Committees. This trail was registered in ChiCTR (www.chictr.org) in 2010. Fludarabine (180mg/m2-200mg/m2) +Cyclophosphamide (120mg/kg) +Anti-thymocyte globulin (ATG, thymoglobulin 10mg/kg) +TBI 3GY were the basic conditioning regimen and peripheral blood stem cell was as the main stem cell source. 84 children with acquired AA (include 47 SAA, 31 VSAA and 6 NSAA but infusion dependent) were recruited in this upfront AD HSCT study in our center from Jan 2010 to Dec 2015 with the median age 7 (1 ~ 18) years old. 28 patients were with 10/10 matched unrelated donor (MUD), 42 with 8-9/10 mismatched unrelated donor (MMUD) and 14 with 5-8/10 mismatched related donor (MMRD). All patients didn't receive ATG before HSCT. The median interval from diagnosis to HSCT was 5 (1-84) months. The average nucleated cell doses were $(12.11 \pm 3.87) \times 108$/kg and the CD34+ cell doses were $(5.46 \pm 2.7) \times 106$/kg. Except 1 graft failure (rescued by second HSCT) 83 (98.8%) were engrafted with neutrophil and platelet recovery occurring at a median of 13 days (range, 9–19) and 18 (10-190) post-transplant. 59.2% and 9.9% patients suffered from grade I-II and grade III-IV acute GVHD respectively, 26.6% and 6.3% from mild and moderate chronic GVHD respectively, and nobody developed an extend chronic GVHD. After median follow up 27 (0.1-84) months, 10 of 84 patients died (3 died of PTLD, 2 died of severe aGVHD, 4 died of severe infection and the rest 1 died of VOD). 2 patients suffered poor graft function with long interval from diagnosis to HSCT (84 months and 102 months respectively). Among them 18 patients were under uncontrolled infection when they received AD HSCT, and 15 were rescued by AD HSCT, only 3 patients were dead of severe infection (all died before engraftment, 1 at 12 days and another 2 at 2 days post-transplant). The estimated 5-year overall survival (OS) and event-free survival (EFS) of the entire cohort was $87.9 \pm 3.6\%$ and $84.6 \pm 2.7\%$ with no difference among the MUD, MMUD and MMRD cohort ($93.1 \pm 4.7\%$, $89.2 \pm 5.1\%$ and $74.7 \pm 11.3\%$ respectively, $P = 0.24$). Meanwhile the outcomes were compared with the OS of the patients received MSD HSCT or received ATG treatment before HSCT during the same period in our center, there still were no any difference between these two groups (87.9% vs 85.6%, $P = 0.925$ and 87.9%vs 89%, $P = 0.715$ respectively). These excellent outcomes suggest that unmanipulated AD PBSC is a good HSCT source for children with SAA. It's reasonable to consider AD HSCT as first line therapy for SAA children if suitable donor can be found quickly. HSCT rescued therapy was important for some under uncontrolled infection VSAA children.

Disclosure of conflict of interest: None.

Pediatric (PDWP)

O160

EWOG-MDS study SCT RC RIC 06: Reduced intensity conditioning for children and adolescents with refractory cytopenia of childhood

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Refractory cytopenia of childhood (RCC) is the most common subtype of myelodysplastic syndrome (MDS) in this age group. According to the EWOG-MDS policy, patients with RCC without chromosomal aberrations were eligible for hematopoietic stem cell transplantation (HSCT) with a reduced intensity conditioning regimen (RIC) consisting of fludarabine and thiotepa. Here, we report the outcome of children with RCC included in the prospective EWOG-MDS study SCT RC RIC 06. One-hundred-and-sixty-nine patients (89 males/80 females) were diagnosed with RCC at a median age of 9.8 (0.8-21.4) years. Prior to HSCT, patients were transfusion-dependent for platelets (107) and/or red blood cells (125) and/or had neutropenia (156). None of them had an abnormal karyotype. Forty-one patients received immunosuppressive therapy consisting of anti-thymocyte globuline (ATG) and cyclosporine-A (CSA) prior to HSCT. The median time from diagnosis to HSCT was 166 days (18 days-6 years). Patients were grafted from a matched sibling donor (MSD) (51), an alternative family donor (3) or an unrelated donor (UD) (115). UD were matched in 9/10 (33) or 10/10 (81) HLA antigens. Stem cell source was bone marrow (147) or peripheral blood (22). All patients were prepared with thiotepa (15 mg/kg) and fludarabine (160 mg/m2). Prophylaxis for graft-versus-host-disease (GVHD) was CSA +/− MTX/MMF +/− ATG for MSD, and CSA, MTX/MMF and ATG for patients transplanted from an UD. After a median follow-up of 2.1 (0.3-9.4) years, 161 patients are alive, resulting in a probability of overall survival of 0.94 (0.90-0.98). Graft failure or delayed hematopoietic recovery was the main cause of treatment failure, including primary and secondary graft failure (GF) in 9 patients (5%) each and delayed platelet engraftment in 5 patients (3%). Twenty-one patients (12%) received a second allograft (17) or a stem cell boost (4). Sixteen patients were successfully rescued, whereas five died following the second procedure. An additional three patients died due to GVHD (2) or EBV associated lymphoproliferative disease. The cumulative incidence of grade II-IV and grade III-IV acute GVHD was 19% and 10%, respectively. Twenty-six of 152 patients (17%) at risk developed chronic GVHD, which was mild (14), moderate (6) or severe (6). Event-free survival was significantly worse for patients transplanted from a 9/10 UD compared to patients receiving an allograft from a MSD or a completely matched UD (0.69 (0.53-0.85) versus 0.88 (0.78-0.98) and 0.86 (0.78-0.94); $P = 0.02$) due to an increased risk of GF. Unexpectedly, the only other patient, disease or transplantation variable associated with an inferior outcome was male sex of the recipient. In summary, the conditioning regimen with thiotepa and fludarabine offered an excellent survival despite a considerable incidence of graft failure. The risk of graft failure needs to be assessed in the light of an expected reduced risk of long term sequels, such as infertility whit this preparation.

Disclosure of conflict of interest: None.

O161

Second allogeneic stem cell transplantation for children and adolescents following relapse after first transplantation for MDS with excess of blasts-a study of the European Working Group of MDS in childhood (EWOG-MDS)

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Allogeneic stem cell transplantation is the only curative treatment for myelodysplastic syndromes with excess of blasts (MDS-EB). It is associated with a risk of relapse in the order of 15-30%. We report the outcome of MDS-EB patients who received a second HSCT (HSCT2) for disease recurrence following first HSCT (HSCT1). Patients and transplantation procedure: Fifty-two patients (pts) registered in the EWOG-MDS 98 and 2006 studies relapsed after HSCT1 for MDS-EB (38 with primary MDS, 14 with therapy-related MDS). Preparative regimen of HSCT1 consisted of busulfan (Bu), cyclophosphamide and melphalan in 38 patients, other Bu-based regimens in 8 and other schemes in 10 pts. Median time to relapse after HSCT1 was 14.6 months (3.3-92.5), median time from relapse to HSCT2 3.5 months (0.6-90.7) and median age at HSCT2 13.3 years (5.4–25.3). Nine patients were transplanted from a matched sibling donor, 32 from a 9/10 or 10/10 matched unrelated donor (MUD), 2 from an 8/10 MUD and 9 from an alternative family donor. Stem cell source was peripheral blood (PB) ($n = 33$), bone marrow (BM) ($n = 18$) or cord blood ($n = 1$). Second conditioning regimen was based on the use of TBI in 23 pts, on treosulfan in 13 pts. The remaining 16 other pts received different regimens. Outcome: With a median follow-up time for survivors of 4.1 years (0.3-10.6) after HSCT2, the probability of overall survival (OS) and event-free survival (EFS) at 5 years were 0.29 (0.15-0.43) and 0.27 (0.14-0.40), respectively. The 5-year cumulative incidence of relapse was 0.49 (0.37-0.65), while that of transplant-related mortality (TRM) was 0.24 (0.15-0.40). Thirteen patients died due to TRM, 6 of them because of GvHD-related complications. A second relapse was recorded in 25 pts; 3 of them are alive with disease. All but one patient engrafted. Grade III–IV acute and chronic GvHD (cGvHD) was observed in in 12 pts each; cGvHD was extensive in three pts. Patients with a structural complex karyotype or a blast count above 20% at second HSCT had a trend towards worse 5-year EFS (0.13 and 0.09, respectively). There was no difference in EFS according to the type of donor employed and age at second HSCT. Patients with an early relapse before 12 months after HSCT1 had a higher risk for TRM at 5 yrs. (0.42 vs 0.15, $P = 0.05$). The cumulative incidence of relapse at 5 years was significantly lower in pts receiving PBSC in comparison with pts receiving BM (0.34 vs 0.78, $P < 0.01$), as well as in patients experiencing cGvHD in contrast to pts without cGvHD (0.08 vs 0.66, $P < 0.01$). Stem cell source and presence of cGvHD were highly correlated (no cGvHD was observed in BMT recipients). In a multivariate COX-analysis the absence of chronic GvHD remained a predictive variable for an increased risk of relapse (RR = 9.2). Conclusion: We conclude that HSCT2 can cure one out of four patients with MDS-EB relapsing after HSCT1. The association of cGVHD with a lower risk of relapse indicates the importance of a Graft-versus-leukemia effect. PBSC as stem cell source for HSCT2 might be privileged in case of adult donors.

Disclosure of conflict of interest: None.

O162

Outcomes of hematopoietic stem cell transplantation for acute lymphoblastic leukemia: a comparative study between adolescents-young adults and children. A study on behalf of the SFGM-TC

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Overall survival (OS) after Hematopoïetic Stem Cell Transplantation (HSCT) for Acute Lymphoblastic Leukemia (ALL) is lower in Adolecent and Young Adults (AYAs) than in children (1,2). AYAs seem to have higher risk diseases but same relapse rates than children (3), whereas Transplantation Related Mortality (TRM) seems to be higher in AYAs (2). This study compare, in a large cohort, OS after HSCT for ALL between AYA and children to determine factors influencing survival and TRM differences. Patients aged between 1 and 25 years who received HSCT for ALL between 2005 and 2012, reported in the SFGM-TC registry were included. 5-years OS and DFS and cumulative incidence of relapse and TRM were compared between AYAs (15-25 years old) and pediatric patients (1-15 years old). 891 patients, 494 children (1-15 years) and 397 AYAs (15-25 years) were included. Median follow-up was 45,67 months. T phenotype was found in 29.8% of AYAs and 25.1% of children, and high risk cytogenetic was more frequent in AYAs (29.8% versus 26.7% in children) but without any significant difference. HSCT was commonly done in first Complete Remission (CR) in AYAs (56.8%) and later (2^{nd} CR or more) in children (57.5%). Peripheral stem cells (PBSC) were more used in AYAs than in children (28% versus 10.3%), and cord blood were used more often in children (29.4% versus 16.4%) $P < 0.0001$. AYAs had a significantly lower 5 years-OS than children (Figure1), and lower 5 years-DFS than children. Those differences were confirmed in multivariate analysis. AYAs had greater risk of TRM than younger (18% versus 13%, $P = 0.04$) (Figure 1), whereas incidence of relapse was similar in both group (32% in AYAs and 27% in children, $P = 0.1663$). In univariate analysis, TRM was higher in case of transplantation with PBSC, but this result was not confirmed in multivariate analysis. Regarding causes of transplantation related deaths, chronic GVHD related mortality was significantly higher in AYAs (34.3% versus 23%, $P < 0.0001$), whereas organ toxicity mortality was higher in children (74.4% versus 60%, $P = 0.02$). Frequency of death due to acute GVHD or infections are similar in both group. Incidence of Chronic GVHD was higher in AYAs (32% versus 18% in younger, $P = < 0.0001$), whereas cumulative incidence of acute GVHD are similar in both group (61% in children, 62% in AYAs, $P = 0.6488$). Use of PBSC increased the incidence of chronic GVHD (HR: 1.67 (1.21; 2.32), $P = 0.0072$) in univariate analysis. AYAs patients also seem to have greater risk of TRM after HSCT due to chronic GVHD. Choice of stem cell source or treatment adhesion should be questioned in further studies. Figure 1: A: OS for AYAs (AJA) and pediatrics (PED) patients ($P = 0.0012$) B: Cumulative incidence of TRM in AYAs (AJA) and children (PED) $P = 0.0413$.

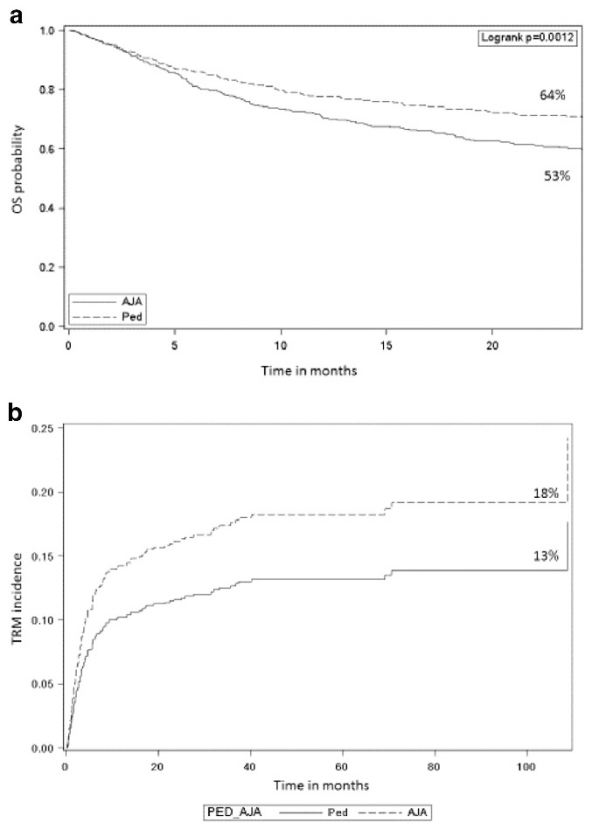
[O162]

Table 1: Results of HSCT in pediatric patients and AYA. Univariate analysis:

	Pediatric	*AYAs*	P-*value*
2 years OS	64%	53%	$P = 0.0012$
2 years DFS	60%	49%	$P = 0.0074$
Relapse incidence	27%	32%	$P = 0.1663$
TRM cumulative incidence	13%	18%	$P = 0.0413$
Acute GVHD	61%	62%	$P = 0.6488$
Chronic GVHD	18%	32%	$P < 0.0001$
Causes of death ($n = 132$)			
Acute GVHD	59,70%	76,80%	$P = 0,503$
Chronic GVHD	23%	34,30%	$P < 0.0001$
Infection	84,70%	89,20%	$P = 0.6348$
Organ toxicity	74,40%	60%	$P = 0.0205$

[O162]

Figure 1 : A:OS for AYAs (AJA) and pediatrics (PED) patients (p=0,0012) B: Cumulative incidence of TRM in AYAs(AJA) and children (PED) p=0,0413.



Disclosure of conflict of interest: None.

O163
Previously Published

O164
Haematopoietic cell transplant (HCT) in pediatric acute myeloid leukemia (AML) after similar upfront therapy with AML-nopho; a comparison of conditioning regimens

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Severe toxicity, treatment related mortality (TRM) and relapse after HCT remain unmet needs in HCT for pediatric AML. Conditioning regimen is suggested to influence these outcomes. We compared the outcomes of pediatric AML patients treated with the same upfront AML-NOPHO protocols but transplanted with different conditioning regimens. We retrospectively analysed pediatric AML patients treated with NOPHO2004/DB01 or NOPHO/DBH AML2012, transplanted between 2005-2015 in the Netherlands, Belgium and the Nordic countries. 3 Busulfan-based conditioning strategies were compared; CloFluBu: Busulfan (dosing with therapeutic drug monitoring; TDM), Fludarabin (40 mg/m2), Clofarabin (120 mg/m2), BuCy: Busulfan (TDM or 16 mg/kg), Cyclofosfamide (120 mg/kg) and BuCyMel: Busulfan (TDM or 16 mg/kg), Melphalan (140 mg/m2), Cyclofosfamide (120 mg/kg). TDM target was a cumulative Bu-exposure of 90 mg*h/L. Main outcome of interest was leukemia free survival (LFS). Other endpoints were occurrence of veno occlusive disease (VOD), acute and chronic Graft-Versus-Host-Disease (GVHD), relapse and TRM. Predictor analysis was performed using Cox Proportional Hazard Models. Risk factors considered were age, conditioning, cells source, gender and CR-status. 106 children were included (80 CR2, 24 CR1, 2 refractory), 57% male, median age 9.1 (0.8-21.5) years, transplanted with matched family donor 30 (28%), mismatchFD 3 (2.8%), MUD 54 (51%) and unrelated cord blood 18 (17%). In 69 (65%) patients Busulfan TDM was done. Median follow up was 1.9 (0.1–10) years. 37 received CloFluBu, 38 BuCyMel and 31BuCy. Estimated 3 years LFS was 64% (±5). Conditioning was the only predictor for LFS: compared to CloFluBu no difference was found with BuCyMel (HR1.3, 95%CI 0.5–3.5, $P = 0.5$), but BuCy compared worse (HR 2.6, 95%CI 1.1–6.3, $P = 0.03$; fig 1). The estimated TRM at 2 years was 10%(±3), non-significantly higher in BuCyMel (15% ± 6) compared to CloFluBu (6% ± 5) and BuCy (8% ± 5); fig 2. Relapse rate was 24% (±5) with conditioning regimen being the only predictor: compared to CloFluBu there was no difference with BuCyMel (HR 1.0, 95%CI

[O164]

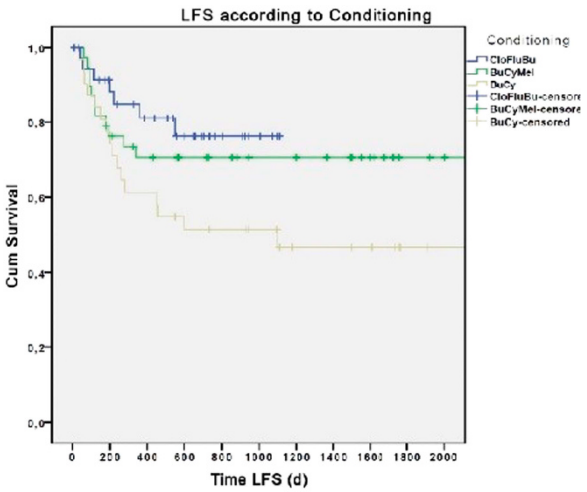

Figure 1. LFS according to conditioning

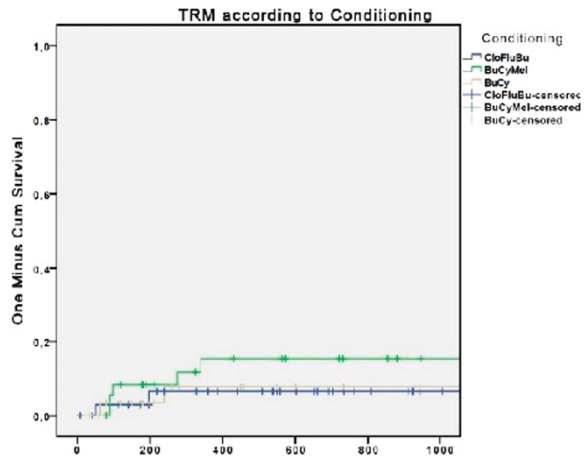

Figure 2. TRM according to conditioning

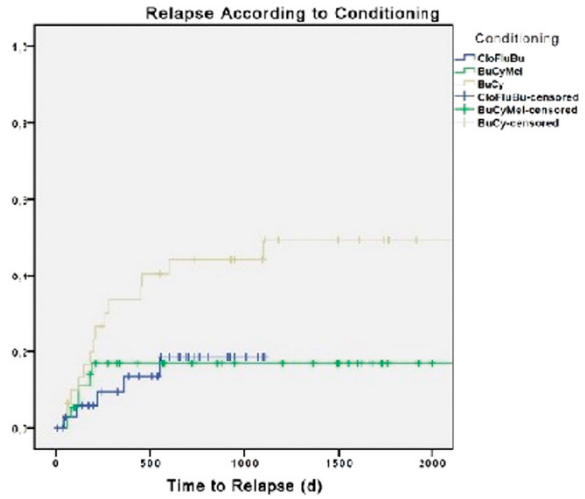

Figure 3. Relapse according to conditioning

0.3–3.3, $P = 0.99$), but BuCy compared worse (HR 3.1, 95%CI 1.1–8.6, $P = 0.03$; fig 3). Probability for aGVHD grade 2-4 was lowest after CloFluBU 18.9%, compared to 32.3% and 47.4% in BuCy and BuCyMel respectively ($P = 0.032$). For cGVHD no differences were found between groups. No VOD was noted in the CloBuFlu and the BuCy group while in the BuCyMel group, where almost 30% received VOD prophylaxis, VOD occurred twice. Conclusion LFS after BuCyMel and CloFluBu were similar, but BuCyMel was associated with increased toxicity (aGvHD, VOD). BuCy was associated with lower survival due to higher relapse probability. CloFluBu holds promise as low toxic and effective conditioning in pediatric AML-patients. Longer follow up and prospective studies are needed to confirm these results.

Disclosure of conflict of interest: None.

O165

Donor age matters in T-cell depleted haploidentical hematopoietic stem cell transplantation in pediatric patients

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Nowadays, T-cell depleted (TCD) haploidentical transplantation is increasingly used in paediatric patients with haematological malignancies otherwise incurable.For many years, donor selection has been based on KIR mismatch and KIR genotype. In unrelated and sibling transplantation setting, donor age has been associated to poor overall survival due to increased NRM. We analyzed the impact on outcome of donor age in TCD haploidentical transplantation. Ninety-four high-risk leukaemia patients that underwent first haploidentical HSCT since 2007 to 2016 have been included in the study. Graft manipulation consisted on CD3/CD19 depletion in 69 cases and TCRαβ+/CD19 depletion in the remainder cases. Both procedures were performed with a CliniMACS device (Miltenyi Biotec, Germany). Conditioning consisted on high doses of fludarabine, busulfan and thiotepa.The median time to neutrophil ($>0.5\times109$/L) and platelet recovery ($>20\times109$/L) were 13 and 10 days, respectively. Cumulative incidence of NRM was $22 \pm 5\%$ at a median time of 89 days (30- 1391 days). None patient in 1st CR died because toxicity. Univariate analysis shown that donor age was the main risk factor associated with NRM (donor $\geqslant 40$ years: $43 \pm 10\%$ vs donor < 40 years: $13 \pm 5\%$, $P = 0.006$).Twenty-five patients relapsed at a median time of 160 days (range: 23–617 days). Cumulative incidence of relapse was $28 \pm 5\%$.Cox analysis showed that the main prognostic factors of relapse were: disease status (non remission, HR: 2.86, 95% CI: 1.21–6.75, $P = 0.02$), KIR genotype (genotype A, HR: 3.05, 95% CI: 1.3–7.12, $P = 0.01$) and chronic GvHD (non chronic GvHD, HR: 3.99, 95% CI: 1.16–13.75, $P = 0.03$).The probability of DFS was $50 \pm 6\%$. The median follow-up for survivors was 4 years (9 months-11 years).Donor age ($<$ 40 years: $59 \pm 7\%$ vs $\geqslant$ 40 years: $35 \pm 8\%$, $P = 0.02$), KIR genotype (genotype B: $59 \pm 6\%$, vs genotype A: $13 \pm 8\%$; $P = 0.0001$), disease status (remission: $57 \pm 6\%$ vs not in remission: $26 \pm 9\%$, $P = 0.001$), disease phase (1st CR: $96 \pm 4\%$ vs $\geqslant$1st CR: $35 \pm 6\%$, $P = 0.0001$), chronic GvHD (yes: $70 \pm 10\%$ vs no: $43 \pm 6\%$, $P = 0.005$) and the number of NK cells at day +30 after transplant (above median: $70 \pm 8\%$, vs below median: $31 \pm 8\%$; $P = 0.004$) were found associated to DFS in univariate analysis. In conclusion, simple criteria such as donor age should be considered as donor selection criteria also in depleted haploidentical setting.

Disclosure of conflict of interest: None.

O166

Solid organ transplantation (SOT) after haematopoietic stem cell transplantation (HSCT) in pediatric patients. a multicentric retrospective EBMT study; on behalf of Paediatric Disease Working Party (PDWP)

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Solid organ transplantation (SOT) is a rare possible therapeutic approach to cure severe complications that may occur after hematopoietic stem cell transplantation (HSCT). Aim of this retrospective multicentric EBMT study is to analyze the incidence of SOTs performed after either allogeneic or autologous HSCT in pediatric patients (pts). A questionnaire including information about HSCT and SOT procedures has been sent to 249 pediatric EBMT centers. 78 centers (31%) answered and 20 (25.6%) accepted to participate, carrying out the data. We evaluated SOTs performed in HSCT recipients between 1984 and 2016. In this survey, a total number of 44 SOTs was collected: 20 were liver, 12 lung, 6 heart and 6 kidney. HSCT characteristics of children given SOT after HSCT are reported in Table 1. The majority of pts ($n = 15$) received

[O166]

Table 1 HSCT characteristic of children who received SOTs.

	LIVER	LUNG	HEART	KIDNEY	TOTAL
	n=20 (45%)	n=12 (27%)	n=6 (14%)	n=6 (14%)	n=44
Age at HSCT, median (range)	4,74 (0,60-15,99)	7,84 (0,95-17,28)	7,47 (1,64-13,33)	9,08 (4,12-17,12)	
Age at SOT, median (range)	6,57 (1,06-16,33)	13,73 (4,21-20,41)	19,89 (13,14-31,30)	8,25 (5,25-22,79)	
Type of underlying disease					
Malignant	12(60%)	7(58.3%)	6(100%)	4(66.7%)	29
Non malignant	8(40%)	5(41.7%)		2(33.3%)	15
Type of HSCT					
Allogenec	16(80%)	12(100%)	2(33.3%)	5(83.3%)	35
Autologous	4(20%)		4(66.7%)	1 (16.7%)	9
TBI: yes	4 (20%)	3(25%)	5(83.3%)	3(60%)	15
no	16(80%)	9(75%)	1(16.7%)	2(40%)	28
Bus: yes	5(25%)	7(58.3)	1(16.6%)	1(16.6%)	14
no	15(75%)	5(41.7%)	5(83.4%)	5(83.4%)	30
Type of donor :					
Related donor	7(43.7%)	7(58.3%)	2	4(80%)	20
Unrelated donor	9(56.3%)	5(41.7%)		1(20%)	15
Haploidentical					
aGVHD:					
absent	12(60%)	4(33.3%)	6(100%)	4(66.6%)	26
grade I-II	1 (20%)	5 (41.7%)		1(16.6%)	7
grade III-IV	7(20%)	2(16.6%)		1(16.6%)	10
Unknown		1(8.3%)			1
cGVHD: yes	3(15%)	10(83.3%)			13
no	17(85%)	2(16.7%)	6(100%)	6(100%)	31

Legend: HSCT=hematopoietic stem cell transplantation; SOT= solid organ transplantation; TBI=total body irradiation; Bus=Busulphan; aGVHD=acute graft versus host disease; cGVHD= chronic graft versus host disease

SOT 4-12 years (yrs) after HSCT, while 13, 8 and 7 underwent SOT 12-18, 18 and 1-4 yrs later, respectively. The indications for SOT were Graft versus Host disease (GvHD) in 13 pts (29.5%), underlying disease in 10 (22.7%), either acute ($n=2$), chronic ($n=13$) or acute/chronic ($n=1$) toxicity in 16 pts (36.3%). Three of these latter children underwent SOT due to toxicity combined with GvHD. Organ failure resulted in SOT in 4 pts (9%), while in 1 patient (2.2%) the reason is unknown. In 30 (68.1%) cases the donor of the solid organ was a cadaver, while in 4 cases the donor was the same of the HSCT. Overall, 39 pts received immunosuppressive therapies (IST) after SOT and, at last follow-up, IST are still ongoing in 95% of them. Details about indications and outcome of different SOTs are reported in Table 2. To the best of our knowledge, this is the first survey collecting SOTs performed in pediatric patients receiving HSCT. In comparison to recent published studies1,2, we collected a large number of SOT evaluating only EBMT pediatric centers (44 SOT in 20 centers). In our experience, GvHD and toxicity represent the major indications for SOT. Cardio-toxicity secondary to radiotherapy is the major indication for heart transplantation, while lung transplant, as reported in adults, is mostly offered to patients experiencing chronic GvHD (obliterans bronchiolitis). Considering an overall survival at last follow-up (>10 yrs) of 75% (100% for kidney, 83% for lung, 67% for heart, 65% for liver transplantation), our data indicate that SOT may be a therapeutic option in very selected patients given HSCT, also during pediatric age.

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O167
Previously Published

O168
Haematopoietic stem cell transplant in children with cytidine triphosphate synthase 1 (CTPS1) mutation

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CTPS1 encodes for CTP synthase 1 which is responsible for the catalytic conversion of Uridine Triphosphate to Cytidine Triphospate. This is important in the biosynthesis of

[O166]

Table 2. Indications of different SOTs and outcome of these patients

	LIVER	LUNG	HEART	KIDNEY	TOTAL
	n=20 (45%)	n=12 (27%)	n=6 (14%)	n=6 (14%)	n=44
Indications for SOT					
GVHD	4(20%)	9(75%)	0	0	13(29.5%)
Underlying disease	7(35%)	0	0	3(50%)	10(22.7%)
Organ failure	4(20%)	1(8.3%)	0	0	5(11.3%)
Toxicity	2(10%)	0	6(100%)	2(33.3%)	10(22.7%)
GVHD and Toxicity	2(10%)	1(8.3%)	0	0	3(6.8%)
Transplant Organ complications	0	1(8.3%)	0	1 /16.4%)	2(4.5%)
Other	1(5%)	0	0	0	1(2.2%)
Major complications after SOT					
No complications					
Infections	9(45%)	3(25%)	2(33.3%)	4(66.6%)	18(41%)
Graft rejection	0	5(42%)	0	1(16.6%)	6(14%)
Organ failure	1(5%)	1(8.3%)	1(16.6%)	1(16.6%)	4(9%)
Infections and graft rejection	4(20%)	1(8.3%)	2(33.3%)	0	7(16%)
other	2(10%)	1(8.3%)	0	0	3(7%)
	4(20%)	1(8.3%)	0	0	5(11%)
Survival at last follow-up					
Alive	13(65%)	10(83%)	4(66.6%)	6(100%)	33(75%)
Dead	7	2	2	0	11(25%)
Lost at follow-up	0	0	0	0	0
Age at the last follow up (survivors) , median (range)	14,65 (4,09-4,77)	17,27 (11,46-31,36)	30,06 (21,39-37,07)	25,17 (6,58-4,16)	
Age at time of death, median (range)	7,35 (1,19-16,17)	21,57 (21,40-1,74)	23,02 (13,17-32,87)		

phospholipids and nucleic acids and plays a key role in cell growth, development, and tumorigenesis. Loss of function of CTPS1 has been associated with combined immunodeficiency. We report the outcome of HSCT in the only 8 patients with mutations in CTPS1 identified to date, who were transplanted in two UK centres, Newcastle and Manchester. 4 unrelated patients from Newcastle and 4 patients from 2 families in Manchester are reported. Median age at presentation was 7 months (range birth–7 years). Patients presented with recurrent sino-pulmonary infections in 5/8, chronic diarrhoea in 3/8, EBV-driven CNS lymphoma in 2/8 (pre-treated with EBV-specific T cells), pneumonitis post VZV infection and EBV-driven HLH in one. Positive family history in a sibling was present in 6/8. Median age at transplant was 8 years (range 15 months–17 years). Stem cell sources were all matched unrelated - PBSC (5/8), BM (2/8), cord blood (1/8). Conditioning was fludarabine (7/8) with treosulfan (3), melphalan (3), and busulfan (1). One received treosulfan and cyclophosphamide. 7/8 received alemtuzumab. CD34+ cell dose range was 0.4–12 × 106/kg. Neutrophil and platelet engraftment achieved by D+13 (median). Skin GvHD was seen in 6/8 with grade I-II in 3 patients. Skin GvHD grade III was seen in 3 patients, one following cord transplant with no serotherapy, which was resolved with steroid, ATG and ECP. The other 2 developed grade III skin and gut GvHD, which were resistance to treatment. Transplant related mortality was seen in 3/8 patients due to EBV encephalitis, severe gut GvHD or progressive multifocal leukoencephalopathy. Patients who survived (5/8) had median 10 years follow up, with 75-100% donor T cell chimerism, normal lymphocyte subsets (5/5), normal post vaccine responses (4/5) and no EBV-related complications. Mutations in CTPS1 have only been described recently1. Patients cannot handle Herpes virus infections and develop life-threatening complications. HSCT is curative with an overall survival 5/8 (62.5%) in this small series. Surviving patients have normal immunity with a median 10 years follow up. Early diagnosis of patients before significant sequalae develops will likely lead to improved survival.

Disclosure of conflict of interest: None.

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O169

Treatment of LPS-Responsive Beige-Like Anchor Protein (LRBA) deficiency by allogeneic hematopoietic stem cell transplantation: A joint IEWP-EBMT-ESID-PIDTC study

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Augmentation of regulatory T cell function in LPS-responsive beige-like anchor protein (LRBA)-deficient individuals by regular CTLA4-Ig (abatacept) infusions potentially induces remissions. However, not all symptoms such as life-threatening multi-organ autoimmunity and immunodeficiency, chronic enteropathy, cytopenias, hypogammaglobulinemia, and lymphoproliferation are responsive, and patients remain dependent on CTLA4 substitution. Furthermore, steroids, sirolimus, hydroxychloroquine, and other immunosuppressants are used but may not prevent long-term deterioriation of this potentially fatal disease. Hematopoietic stem cell transplantation (HSCT) was shown to be successful, but may not fully correct the defect either, as LRBA is widely expressed in non-hematopoietic tissues. Previous reports of HSCT in LRBA deficiency suggest that transplant-related mortality (TRM) may be higher than in other inborn errors (2 of 4 patients), raising the question of whether the disease status at HSCT or other disease-related factors were involved. To better understand the role for HSCT as a potentially curative treatment for LRBA deficiency, we collected the international HSCT experience from the EBMT Inborn Errors Working Party, ESID, and the PIDTC networks. To date, we have collected data from a total of 12 patients who underwent HSCT for LRBA deficiency out of a total cohort of 66 patients. Survival is 67% (8 of 12); all deaths were due to TRM (pre-existing infections, graft failure, multi-organ failure, thrombotic microangiopathy) and occurred within 3 months of HSCT. Surviving patients show various, mostly favourable degrees of remission (complete: 4; good partial: 2 (not requiring therapy); partial: 2 (need of immunosuppression for LRBA-related symptoms)) with a median follow-up of 20 months (range 3–135). HSCT course and recurrence of residual symptoms are apparently not dependent on the donor's LRBA status, type/intensity of conditioning, or chimerism. All survivors show full donor chimerism ($>$95% WBC) except one (WBC 95%, donor T cells $<$50%). Detailed data regarding donor source, transplant regimen, GvHD, and disease response will be presented. Yet, patient numbers are too small to recommend a specifically successful HSCT modality from present evidence. More data are collected to draw conclusions regarding outcome of HSCT vs other treatment options such as abatacept and other pharmacologic immunosuppressants.

Disclosure of conflict of interest: None.

O170

Update on safety and efficacy of lentiviral hematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy (MLD)

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MLD, an arylsulfatase A (ARSA) deficiency, is a fatal demyelinating lysosomal disease with no approved treatment. In 2010, we started a phase I/II clinical trial with HSC-GT in early onset MLD patients (pts), reporting initial results from the first 9 pts. The investigational medicinal product (IMP) consists of autologous HSC engineered with a lentiviral vector encoding ARSA cDNA infused after Busulfan (Bu) conditioning. Twenty-four patients have been treated: 20 in the clinical trial, 1 compassionate use and 3 hospital exemption. This is an updated ad hoc analysis of the first 21 pts with $>$12 months (m) follow up (FU) (as of Sep 15, 2016) comprising 9 Late Infantile (LI), 11 Early Juvenile (EJ) and 1 pt classified as intermediate (included in the EJ group for this analysis). Median age at treatment is 39.3 m (7.7-141.7); 8 LI and 4 EJ were treated before onset of overt disease manifestations. We compared the clinical outcome to that in a cohort of 28 untreated MLD pts followed in a natural history (NH) study ongoing at our Institute (16 LI and 12 EJ). Median IMP dose and transduction rate were 9.7x10e6 $CD34^+$ cells/kg and 93%. The first 10 pts received 14 doses of Bu with a total target AUC of 67.2 mg*h/L (Group A). Protocol was amended to reduce engraftment variability: the subsequent 11 pts received Bu in 4 doses with a target AUC of 85 mg*h/L (Group B). No treatment-related adverse events were observed after IMP infusion. The median of days of Neutrophils $<$ 500 was 25.5 in Group A and 29 in Group B. Other Grade III-IV toxicities were mucositis in 13 pts and febrile neutropenia in 10 pts. There was no treatment related mortality and no evidence of abnormal clonal proliferation. Nineteen pts are alive with median FU of 29 m (12.2–67.5); 2 EJ pts treated after onset of symptoms died due to disease progression at 7.8 m and 15 m after GT. We observed persistent engraftment of gene corrected cells. At last available FU, median proportion of gene-corrected progenitors was 52.3% (17.2-90.6). We observed a significant increase of ARSA activity in PBMC after GT ($P < 0.001$), ranging from normal to above normal levels in most pts; it was significantly higher in group B ($P = 0.030$) and in LI pts ($P = 0.037$). In all treated pts ARSA was detectable in cerebrospinal fluid. We performed an ad hoc exploratory analysis to identify differences in early deterioration of motor and cognitive function in GT treated pts as compared to the NH cohort. Progression of disease (PD) was arbitrarily defined as an increase of $\geqslant 1$ level of Gross Motor Function Classification (GMFC) and/or decrease in IQ $\geqslant 10$ points, confirmed at $\geqslant 1$ additional time points. PD occurred in 9 pts (3 LI and 6 EJ). Progression free survival (PFS) post-GT was significantly lower in pts treated while symptomatic ($P = 0.003$; 3-yr PFS: 22% vs 72.9%). We defined disability as loss of walking ability (GMFC $\geqslant 3$). Disability free survival (calculated from birth) was significantly different ($P < 0.001$) between untreated LI and GT LI pts (5-yr age: 6.2% vs 85.7%). This updated report show that GT is well tolerated. Pre-symptomatic LI pts show a sustained clinical benefit compared

to symptomatic subjects. The 4 pre-symptomatic EJ pts at present have not shown disease progression. Prolonged FU will provide additional information on the long-term safety, clinical efficacy and outcome-predictor factors of HSC-GT.

Reference

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Disclosure of conflict of interest: A. Aiuti is the principal investigator of the TIGET–MLD clinical trial of gene therapy. The MLD gene therapy was licensed to GlaxoSmithKline (GSK) in 2014 and GSK became the financial sponsor of the trial. The remaining authors declare no conflict interest.

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Fertility in long-term survivors of HSCT for primary immune deficiency: a preliminary study

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The use of alkylating agents in conditioning regimen (CR) of hematopoietic stem cell transplantation (HSCT) participates to late toxicities of the procedure including infertility. In patients treated for malignant disease, severe gonadal dysfunctions are extremely frequent after busulfan based CR but little is known in long-term survivors of HSCT for primary immune deficiencies (PID) who have not received chemotherapy prior HSCT. The aim of this observational study is to appreciate fertility in long-term survivors of HSCT for PID. Patients and methods: patients >20 years old in January 2016, who received HSCT <16 years old for PID at the immuno-hematology unit, Paris, France were included in this retrospective observational study. Medical notes were reviewed and the following information were retrieved: sex, primary diagnosis, age at HSCT, CR, age at last follow up, ovarian failure, fertility status and age at pregnancy. Of the initial cohort of 151 patients, 61 were lost for follow up before the age of 20. Ninety patients followed $>$ 20 years were included in this retrospective study. There were 38 female and 52 male. Primary diagnosis was severe combined immune deficiency ($n=$ 35), omenn syndrome ($n=$ 10), Wiskott-Aldrish syndrome ($n=$ 12), Combined immune deficiency ($n=$ 16), Lymphohistiocytosis ($n=$ 10) or others ($n=$ 7). Median age at transplantation was 0.8 years (range 0.1–16.9). Twenty patients received no chemotherapy in their CR, 23 were conditioned with a reduced intensity conditioning (melfalan and fludarabine or busulfan $\leqslant$ 8 mg/kg and cyclophosphamide), 38 with a myeloablative CR (busulfan $>$ 8 mg/kg and cyclophosphamide) and 9 patients were transplanted twice with chemotherapy based CR. Median age at last visit was 25.3 years (range 20–42.9). Twenty-two patients underwent endocrine follow up and spermogram was performed in 8 boys. Twenty-four patients became pregnant ($n=$ 13) or fathered ($n=$ 11) at a median age of 23 years (range 17–33) and gave birth to 28 children. Pregnancies were spontaneous in all patients with available data (14/14). Eight girls presented primary ovarian failure, 3 partial ovarian failure and 14 had unknown fertility status despite normal puberty development. In male, there were 6 boys with azoospermy, 2 with a normal spermogram and 33 with normal puberty but unknown fertility status. Distribution as a function of sexe and intensity of conditioning regimen are shown in the table bellow: Median age at last follow up and at transplantation were similar between the different groups. * Patients transplanted twice with alkylating chemotherapy based CR ** patient with adenosine deaminase deficiency These preliminary results of an ongoing study are preliminar and don't allow to drawn definitive conclusions. However, it shows a higher rate of pregnancy than expected in long-term survivors of patients who underwent HSCT for PID after CR containing myeloablative dose of busulfan and cyclophosphamide. Gonadal functions seem compromised in patients transplanted twice with alkylating chemotherapy. More precise longitudinal evaluation of gonadal function is needed to better define strategies to preserve fertility.

Disclosure of conflict of interest: None.

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Outcome of allogeneic hematopoietic stem cell transplantation (allo HCT) in erythropoietic porphyria (EP) — on behalf of EBMT-IEWP

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Allo HCT is a potentially curative treatment for erythropoietic porphyria (EP). However, there are no systematic data on its outcome or prognostic factors. This is a retrospective study on patients mainly registered at EBMT who underwent allo HCT for EP. The primary objective of the study is to identify the long-term survival and prognostic factors for transplant outcome. A total of 27 patients underwent allo HCT for EP (25 had erythropoietic protoporphyria (EPP), 1 had X-linked protoporphyria (XLP), and 1 had congenital erythropoietic porphyria (CEP)) from 1989-2014. Median age at transplant was 13 years (0.6-63) and 13 patients (48%) were males. Median duration of follow up was 8.8 years (range: 2–11). Unrelated, or related donor (HLA-matched/mismatched) was used in 15 (56%) and 10 patients (37%) respectively, whereas cord blood (CB) was used in 2 (7%). Bone marrow (BM) graft was used in 18 (67%) and peripheral blood stem cells (PBSC) in 7 patients (26%). Preparative regimen was busulfan or treosulfan-based in 17 patients (59%). In-vivo serotherapy (antithymothyte globulin = ATG) and ex-vivo T cell depletion was used in 62% and 24% of patients respectively. Primary and secondary engraftment failure occured in 8% and 12% respectively. Secondary graft failure occurred in 3 patients (2 patients underwent repeat allo HCT and one survived with self-reconstitution). Data of acute GVHD was available on 21 patients with 3 patients developing aGVHD and 3 patients developing cGVHD. Secondary lymphoma (PTLD) occurred in 2 patients. The cumulative incidence (CI) of 3-year non-relapse mortality (NRM) with BM and PBSC transplant were 29% (95% CI 7–50) and 71% (6-80) respectively, and it tended to be favorable among patients who received busulfan/treosulfan (27% with 95% CI of 4–51) compared to other regimens including fludarabine/low dose total body irradiation (TBI)-based regimens (60% with 95% CI of 17–100). Median survival was not reached for the whole cohort. The 5-year overall survival (OS) of BM and PBSC transplants were 76% (95% CI 56–97) and 57% (95% CI 20–94), and 5-year disease-free survival was 54% (95% CI 30–78) and 29% (95% CI 0–72) respectively. The 5-year OS tended to be favorable among patients who received busulfan/treosulfan (86% with 95% CI of 68–100) compared to other regimens (40% with 95% 22–83%) and the 5-year disease-free survival was tended to be favorable in patients who received busulfan/treosulfan (59% with 95% CI of 34–85) compared to other regimens (20% with 95% of 18–55%). Both patients ($\leqslant$7 years old)) who underwent CB transplant survived at 5-year with remission of EP. Allo HCT

is a potentially curative therapy for EP. Patients with no suitable BM or PBSC graft may benefit from cord blood transplant. BM graft may have better survival outcome compared to PBSC. Busulfan- or treosulfan-based regimen may yield more favorable survival outcome.

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O173

Single Centre Retrospective Analysis of 6 Patients with Autosomal Recessive IFN-gamma-Receptor Deficiency

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Mendelian susceptibility to mycobacterial disease (MSMD) characterizes a group of primary immunodeficiencies, which render affected individuals susceptible to weakly virulent mycobacteria. Mutations in IFNGR1 and IFNGR2, the genes encoding the components of the Interferon-γ-receptor, can- among others- cause this phenotype. Hematopoietic stem cell transplantation (HSCT) is currently the only curative option for this condition. Objective and Methods: We retrospectively analysed data on clinical presentation and outcome of HSCT in

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Table 1. The most important differences between G-CSFs in mobilization of unrelated hematopoietic stem cells donors. **all aphereses – one or maximum two aphereses in a donor*

	Lenograstim	Biosimilar filgrastim	Filgrastim	*p*-value
Mean preapheresis white blood cell count (interquartile range, G/L)	43.7 (33.8-52.5)	45.2 (36.9-52.2)	46.4 (37.3-55.4)	0.246
Mean preapheresis erythrocytes count (interquartile range, G/L)	4.70 (4.38-4.95)	4.76 (4.44-5.09)	4.79 (4.55-5.06)	0.193
Mean preapheresis thrombocytes count (interquartile range, G/L)	237 (198-267)	236 (196-276)	250 (215-285)	0.126
Mean preapheresis CD34+ count (interquartile range, cells/µl)	111 (63-136)	119 (83-157)	124 (73-162)	0.354
Mean number of CD34+ cells collected from first apheresis (interquartile range, $x10^6$/kg of recipient)	7.5 (4.5-9.2)	8.3 (5.2-9.8)	9.4 (5.5-11.0)	0.06
Mean number of CD34+ cells collected from all* aphereses (interquartile range, $x10^6$/kg of recipient)	7.7 (4.7-9.2)	8.5 (5.7-9.8)	9.4 (5.5-11.0)	0.085
Growth factor efficiency (interquartile range, mean number of CD34+ cells from first apheresis per kg per daily G-CSF dose in µg/kg)	0.68 (0.42-0.87)	0.75 (0.52-0.95)	0.77 (0.57-0.97)	0.074
Percentage of donors that needed one apheresis for collection	87%	93%	93%	**0.005**
Mean post apheresis white blood cell count (interquartile range, G/L)	40.1 (32.4-46.1)	46.2 (39.5-51.0)	46.24(38,0-55.6)	**<0.001**
Mean post apheresis erythrocytes count (interquartile range, G/L)	4.41 (4.05-4.70)	4.52 (4.18-4.83)	4.58 (4.28-4.84)	**0.013**
Mean post apheresis thrombocytes count (interquartile range, G/L)	147 (118-169)	152 (122-178)	167 (138-193)	**<0.001**

6 patients with autosomal recessive IFNGR1- ($n = 5$) and IFNGR2- ($n = 1$) deficiency subsequently transplanted in our institution between 1997 and 2016. Median age at first infections was 8 months (range 2–36). 4/6 had a positive family history with at least one sibling, who had died from mycobacterial disease in early infancy. Molecular diagnosis was established at a median age of 3,8 years (range 0.9–7.5). Infectious agents identified in this cohort included BCG, M. avium, M. kansasii, M. kanarisense, Salmonella and Listeria. HSCT was performed at a median age of 5.3 years (range 1–9.7), in 5/6 patients with grafts donated by HLA-identical family members, in one case from a matched unrelated donor. Conditioning included myeloablative combinations of busulfan, treosulfan, TBI or radioimmunotherapy with cyclophosphamide, fludarabine, melphalan or thiotepa. Overall survival (OS) is 83% (5/6) with a median follow up of 5 years (0.1 – 16). One patient died on day +51 from severe haemorrhage after diagnostic liver biopsy. One patient needed a second transplant almost 9 years after the initial attempt because of secondary graft failure and autologous reconstitution. With a follow up of 1.5 to 18 years all four long term survivors show a normalization of immune functions and have cleared mycobacterial disease with complete ($n = 3$) or mixed ($n = 1$) donor chimerism. In this single centre retrospective analysis patients with IFNGR-deficiency are diagnosed with a median delay of 3 years after onset of infections and –with one exception- have experienced at least one severe mycobacterial infection often in spite of a positive family history. In contrast to earlier publications (Roesler *et al*., 2004), which report an OS of 50% (8 patients), survival and outcome seem to have improved in recent years.

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Pharmacist day

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Biosimilar G-CSF versus filgrastim and lenograstim in healthy unrelated volunteer hematopoietic stem cell donors

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The World Marrow Donor Organization recommends original granulocyte colony stimulating factor (G-CSF) for mobilization of stem cells in healthy unrelated hematopoietic stem cell donors. We report, for the first time in one study, the comparison of a biosimilar G-CSF with two original G-CSFs (filgrastim and lenograstim) in mobilization in unrelated donors. In 2015, due to legal issues and changes in market availability, the G-CSF used in mobilization of hematopoietic stem cells in donors and patients at our institution has been first changed from lenograstim to biosimilar filgrastim and later to original filgrastim. As publications that compare biosimilars with both original G-CSFs are limited, we decided to retrospectively analyze the efficiency of mobilization with those three drugs in healthy unrelated hematopoietic stem cell donors. We included data of 313 consecutive donors (121 received lenograstim, 85 biosimilar filgrastim and 107 filgrastim) who were mobilized during the period from October 2014 to March 2016 at the Medical University of Warsaw. The primary endpoints of this study were efficiency of CD34+ cell mobilization to the circulation and results of the first apheresis. The mean daily dose of G-CSF was: 9.1 μg/kg for lenograstim, 9.8 μg/kg for biosimilar filgrastim and 9.3 μg/kg for filgrastim (p 2×106 CD34+ cells/kg of recipient). Main differences between the groups are shown in Table 1. Our data provide positive evidence for the use of biosimilar G-CSF in healthy unrelated hematopoietic stem cell donors. It is shown that the biosimilar G-CSF does not differ from the original growth factors when mobilization of the CD34+ positive cells is analyzed. Small and clinically irrelevant differences seen in the study can be contributed to differences in G-CSF dose and collection related factors. We still need to wait for the results of long term observations of the donors after biosimilar G-CSF before we can recommend its use as standard in mobilization of hematopoietic stem cells in healthy unrelated donors.

Disclosure of conflict of interest: None.

O175

Perceptions of caregivers and healthcare providers about therapies after pediatric allogeneic stem cell transplantation: barriers and facilitators for medication adherence

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Immunosuppressive therapy following pediatric allogeneic stem cell transplantation (SCT) is essential for the patient's prognostic along with the antibioprophylaxis and hygienic measures. But medication adherence is suboptimal in children and adolescents, from 52 to 73% 1,2. The patient's caregiver, who is generally the parent in pediatrics, has an important role in the care and in medication adherence. Exploring parents' perceptions about the post-transplantation therapies allows understanding the attitude of medication adherence. It will also take into account parents' needs or expectations about the healthcare system. To complete this evaluation, it seems important to explore healthcare providers' perceptions as well and compare it to caregivers' perceptions. A qualitative design was used for this research. Semi-structured interviews were conducted by a pharmacist nearby patient's caregivers and healthcare providers of a pediatric center (pediatricians, residents, nurses, nursery assistants). The interviews were based on four topics: the allogeneic SCT, the post-transplantation therapies, the caregiver's experience and the healthcare system. The prospective interviews were audio-taped, transcribed and analyzed by inductive approach. The perceptions of 15 caregivers and 21 healthcare providers were studied in the 4 predetermined topics, and another important topic emerged: family, siblings and entourage. Factors of adherence were identified about the immunosuppressive and the antibioprophylaxis therapies. The bad flavor of some syrups, the large number of medications, and the sudden transitions of care (from one hospital or ward to another, or from hospital to home) were revealed as main barriers. On the contrary, recognizing the benefits of medication is an essential facilitator of adherence. Integrating medications into the daily routine of family and support from the entourage and healthcare providers were also identified as important facilitators for medication adherence. About the healthcare system, this study revealed different expectations, needs or regrets of caregivers. Most are about how to communicate information: the needs of concretization and coordination are reported by both caregivers and healthcare providers. Moreover caregivers expressed the need to consider the whole family as an entity whereas healthcare providers focused on the parent-child couple. This original study addressed the post-transplantation therapies from both patient's caregivers and healthcare providers' point of view. Non-revealed yet in literature, barriers and facilitators of adherence were highlighted for therapies after pediatric allogeneic SCT. Moreover, similarities and differences between caregivers and healthcare providers' perceptions were underlined. These new findings

should be implemented into educational programs in a French pediatric center.

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O176

Different strategies of chemotherapy-induced nausea and vomiting (CINV) prevention in multiple myeloma patients after autologous hematopoietic stem cell transplantation: a single center experience

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Despite the improvements of pharmacological control, CINV still represents a major problem in patient undergoing hematopoietic stem cell transplantation (HSCT). We present here a comparison of two pharmacological strategies for preventing CINV in Multiple Myeloma (MM) patients who received an autologous HSCT in our Institution. This is a restrospective analysis of 46 sequential patients, median age 58yo, diagnosed with MM, who underwent an autologous HSCT following a Melphalan 200 mg/sqm condition regimen at day -1. The first 31 patients received CINV prophylaxis with palonosetron i.v and dexamethasone 8 mg die (Regimen A), whilst the following 15 were administered with fosaprepitant iv, ondansetron iv and dexamethasone 8 mg die (Regimen B). Emesis breakthroughs were treated with alizapride and metoclopramide. Nausea and vomiting were assessed through the CTCAE 4.0 score system +. Patients treated with Regimen B had received more chemotherapy cycles than Regimen A (7 vs 4) and a higher frequency of second transplantation, p ns. Overall 70% of patients reported nausea at some moment of the procedure (21% grade 1, 47% grade 2). In Regimen A the overall incidence of nausea was 65% (50% grade1, 50% grade 2) whilst in Regimen B it was 80%, all grade 2. Chi-square test showed that the Regimen B had a significant lower nausea grade 1 ($P = 0.0031$). The overall incidence of vomit was 56% (84% grade 1, 16% grade 2); in Regime A it was 58% (78% grade 1, 22% grade 2) whilst in Regimen B was 53%, not statistically different. We also analyzed the interval between -1 and +3, which is usually reported at higher risk of CINV; nausea at all grade was more frequent in with Regimen A, without any statistically significant difference. Older patients showed a trend to a higher incidence of emesis. We evidenced a trend to a better CINV control with the Regimen A. The small sample size and the retrospective nature of this analysis may prevent to assess more significant differences across the studied regimens.

Disclosure of conflict of interest: None.

O177

Busulfan pharmacokinetics (PK): is it different in patients with fanconi anemia?

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High risk of excessive toxicity related to baseline DNA fragility in patients with FA mandates reduced doses of chemotherapy in general. Different groups have shown that radiation can now be safely replaced by Busulfan (Bu) in the conditioning regimen for patients with FA including in alternative donor setting. In non-FA patients (e.g. transplant for MDS/leukemia, cord blood transplants), Bu PK has been studied extensively (at 0.8–1 mg/kg dose given every 6 hrs × 4 days); however there are no available PK data in patients with FA. We hypothesized that Bu at 0.8-1mg/kg and 0.6-0.8mg/kg given IV every 12 hours for 4 doses will achieve adequate levels stable donor engraftment without excessive toxicity in patients with FA. We report Bu PK results in patients with FA undergoing alternative donor HCT using preparative regimen of Bu (days -8 (first dose with PK), 7 (second dose), -6 (two doses), followed by fludarabine, cyclophosphamide and rabbit ATG on days -5 through -2. Thirty-seven patients with FA (median age of 8.2 years; range 4.3–44) underwent HCT between June 2009 and May 2014. First 19 patients received an initial busulfan dose of 0.8-1mg/kg/dose, while for the next 18 patients, the busulfan dose was reduced to 0.6-0.8mg/kg/dose × 4 doses IV over 2 hours. First dose Bu PK samples were drawn at the end of infusion, at 15 and 30 mins post-end of infusion, and at 3, 4, 5, and 6 hrs after start of Bu infusion. A steady state concentration (Css) target of $\leqslant$ 450ng/mL was initially established to limit toxicity. Subsequent 3 doses of Bu were reduced (if needed), based on PK results. Plasma concentration data were analyzed by standard non-compartmental analysis using WinNonlin software. Bu levels were also correlated with toxicity i.e. hyperbilirubinemia, mucositis. Bu was well tolerated without major toxicity in all but one patient. After one of the early patients developed sinusoidal obstruction syndrome (SOS), the busulfan PK goal was lowered to a Css of $\leqslant$ 350ng/mL. Median Css was 359 ng/mL (range: 243–477) after first dose in patients who received Bu dose of 0.8-1.0 mg/kg ($n = 19$), with 12 of 19 patients having Css of $>$ 350ng/mL. In contrast, patients receiving 0.6-0.8 mg/kg Bu ($n = 18$) had the median Css of 267 ng/mL (range: 194–403) with only two patients with Css over 350ng/mL ($P = 0.0003$). Patients with hyperbilirubinemia had higher estimated Bu Css (including those requiring dose change) compared to those without hyperbilirubinemia in the pediatric cohort (age < 18) ($P = 0.0328$). In contrast no significant correlation was seen with mucositis (Figure 1) or donor chimerism (data not shown). Bu PK parameter estimates are summarized in Table 1 and were comparable to patients without FA. To our knowledge, this is the first report of prospective Bu PK in patients with FA. Bu at above doses was well tolerated in almost all children with FA, and generated optimal levels to achieve our goals of stable donor engraftment while avoiding excessive toxicity (especially SOS). Overall Bu Pk profile in patients with FA is not different from non-FA patients. Dose reduction as shown in this study will lead to optimal levels necessary given the baseline increased sensitivity of patients with FA.

Disclosure of conflict of interest: None.

O178

Treosulfan-based conditioning in pediatric hematopoietic stem cell transplantation: a prospective study on treosulfan exposure and clinical outcome

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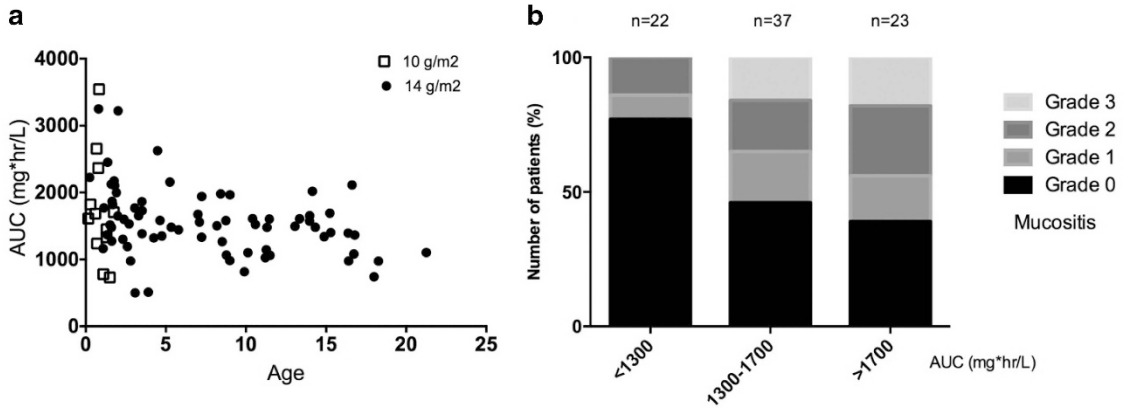

Treosulfan-based (TREO) conditioning is increasingly applied in pediatric HSCT for both malignant and non-malignant diseases due to its favourable toxicity profile. The relationship between TREO pharmacokinetics and outcome is unclear. Similar to busulfan, we hypothesized that both toxicity and efficacy are dependent on TREO systemic exposure. In this multicentre prospective observational study, we studied the pharmacokinetics of TREO in pediatric HSCT recipients and the relationship between TREO exposure and clinical outcome. Patients transplanted in the pediatric transplant units in Leiden and Rome between June 2011 and July 2016 receiving TREO-based conditioning regimen for malignant and non-malignant indications were included. Two blood samples were collected on day 1 to determine TREO area under the curve (AUC), calculated with a 2-compartment PK model.1 The relationship between AUC and outcome (i.e. mucosal, skin, hepatic and neurological toxicity until 28 days after HSCT, engraftment, chimerism and event-free survival (EFS)) was characterized using logistic regression or Cox regression. Included in the study were 82 pediatric patients of whom 83% had non-malignant diseases. The median age was 4.6 years (0.2-21.3) and 52 patients (63%) were male. Donors were HLA-identical (33%), matched unrelated (48%) or mismatched related (19%). TREO was combined with fludarabine and thiotepa (TFT: 63%) or fludarabine (TF: 33%). TREO dosages were 10 g/m2 for patients under one year (16%), and 14 g/m2 for other patients (84%). Engraftment rate was 96.3% and 82.7% for TF and TFT respectively. Seven patients (8.5%) in the TFT and one patient (1.2%) in the TF group developed grade $\geqslant 2$ GvHD. The most common toxicities grade $\geqslant 2$ (max. grade 3) were mucosal (31.7%), skin (22%) and hepatic toxicity (35.4%). Sinusoidal obstruction syndrome was not observed. Mean TREO exposure was 1579 ± 515 mg*h/L (14 g/m2) and 1744 ± 795 mg*h/L (10 g/m2), inter-individual variability was 33-56%. There is a significant negative relationship between AUC and age ($R = -0.319$, $P = 0.003$) despite the lower dose in patients under age of 1 year. High TREO exposure is associated with an increased risk of developing severe mucositis, both in the TFT and TF group. The risk of developing $\geqslant$ grade 2 mucositis is higher when AUC exceeds 1700 mg*h/L (OR 4.87; 95%CI 1.12–21.20, $P = 0.035$) compared to AUC under 1300 mg*h/L. We did not find a relationship between TREO exposure and GvHD, graft failure, chimerism (day 100 and 1 year) or EFS (median follow-up 15 months). Image Figure 1.A: The relation between treosulfan exposure and age. B: Frequency of mucositis grades for each exposure group. Here we demonstrate, for the first time, the high variability in pharmacokinetics of TREO in a large cohort of children. Moreover, there is an inverse relationship between AUC and age. TREO exposure is associated with the occurrence of moderate/severe mucositis. Together, our data indicate that age-dependent and PK guided individualized dosing of TREO may contribute to further reducing the toxicity profile. Ongoing studies will reveal whether TREO exposure is related to long-term outcome parameters, such as disease recurrence and late organ toxicity.

Disclosure of conflict of interest: None.

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O179

Monitoring voriconazole pharmacogenomics and plasma concentrations in the treatment and prevention of invasive fungal disease for hematological patients:-a single center experience

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Voriconazole has been widely used in treatment and prevention invasive fungal disease for immunodeficiency hematological patients. And the voriconazole plasma drug levels were associated with its efficacy and toxicity. The hepatic cytochrome P450 isoenzyme 2C19 plays a important role in voriconazole metabolism. However if CYP2C19 genetic polymorphism can result in voriconazole metabolism and drug plasma level in setting of Asian population especially in hematologic patients is unknown. Objective To evaluate the effect of CYP2C19 polymorphism on the voriconazole (VCZ) plasma concentration of patients with hematological disease and the value of serial monitoring voriconazole plasma concentrations in the treatment and prevention of invasive fungal disease(IFD). Between January to August 2016, 76 hematological patients who received voriconazole for the treatment or prevention of invasive fungal disease were enrolled in this study. The population CYP2C19 polymorphism of voriconazole were performed using PCR-Pyrosequencing. The trough plasma concentrations of vriconazole (C_{trough}) was determined using high-performance liquid chromatography (HPLC). Genotyping for CYP2C19 polymorphic isoenzyme variations showed that 32 subjects (43.42%) for the CYP2C19 wild-type, 43 (56.58%) for the CYP2C19 no-wild-type. 45 of 76 patients received voriconazole intravenous administration, Based on the genotype analysis, 45 subjects were identified as extensive metabolizers' groupfor EMs (CYP2C19*1/*1), poor metabolizers' group for IMs+PMs (CYP2C19 * *1/*2,*1/*3,*2/*3, *2/*2,*3/*3) , and there was a significant difference between C_{trough} values in the two groups (1.66 ± 1.86ug/mL vs 3.30 ± 2.35ug/mL, $P = 0.00$). 3. The C_{trough} of the 45 patients

were detected for 119 times totally. The medium of the C_{trough} 45 hematological patients were described. Lack of response to therapy was more frequent in patients with voriconazole levels <1.5mg/L (23.5%) than in those with voriconazole levels >1.5mg/L (21.4%)) ($P=0.87$). And the risk of adverse events was more frequent in patients with voriconazole levels >5.5mg/L (40.0%) than in those with voriconazole levels <5.5mg/L (25.0%) ($P=0.49$). Furthermore, the C_{trough} values of patients with adverse events is higher than the others (3.21 ± 2.46ug/mL vs 2.17 ± 2.14 ug/mL, $P=0.042$). The single-center study showed that the mutation of CYP2C19 was quite common in Chinese hematological patients. Patients with CYP2C19 wild-type phenotype are extensive metabolizers, their C_{trough} of voriconazole are significantly lower than patients with CYP2C19 non-wild-type phenotype (poor metabolizers). Appropriate concentrations of voriconazole can improve the efficiency of therapy and safety outcome.

Disclosure of conflict of interest: None.

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