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ABSTRACTS COLLECTION

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Pharmacology Poster Session

P183.

Preliminary Safety and Efficacy of Itolizumab, A Novel Targeted Anti-cd6 Therapy, In Newly Diagnosed Severe Acute Graft-versus-host Disease: Interim Results from The Equate Study

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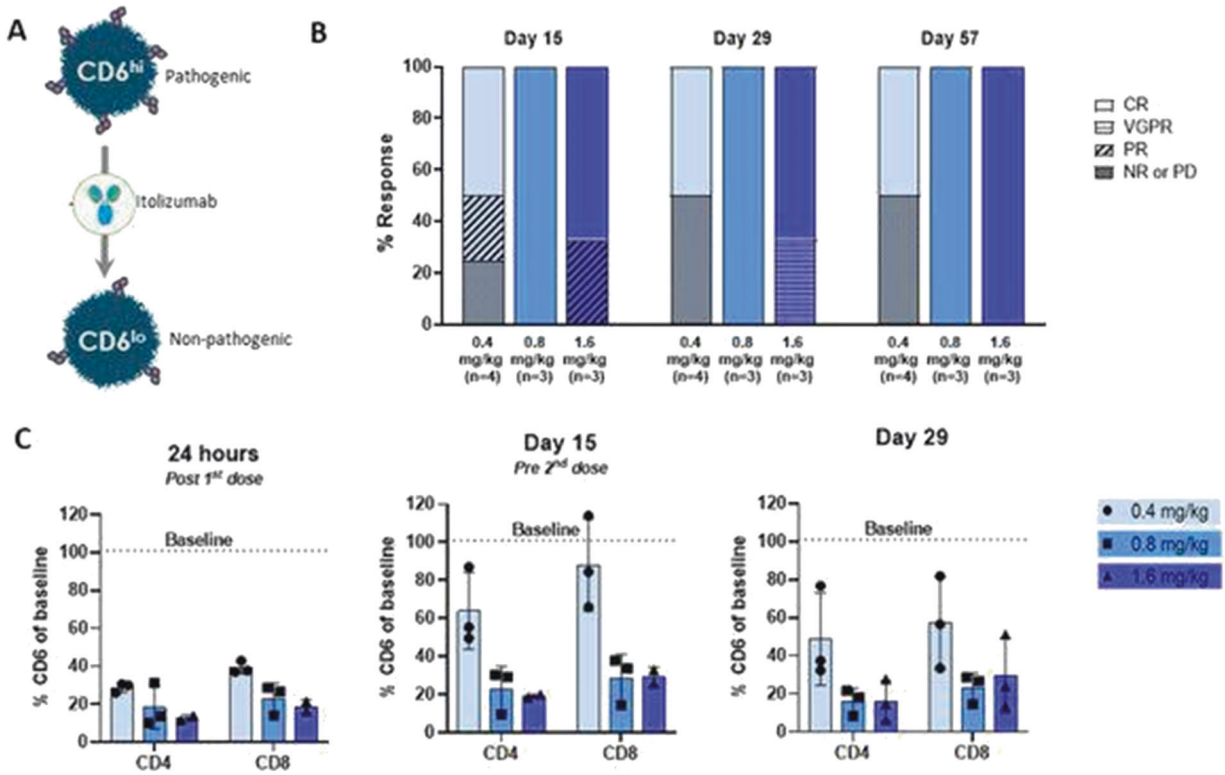
Background: CD6 is a co-stimulatory receptor predominantly expressed on T cells. CD6high CD4+ T cells were recently shown to drive Th1/Th17 immune responses in inflammatory bowel disease and may have a similar role in acute graft-versus-host disease (aGHVD). The CD6 ligand, activated leukocyte cell adhesion molecule (ALCAM), is expressed on antigen presenting cells, as well as epithelial and endothelial cells of aGVHDtarget organs (e.g. skin, GI tract). Previous studies in patients receiving allogeneic hematopoietic cell transplants showed that ex vivo depletion of donor CD6+ T cells lowered the incidence of aGVHD, providing a rationale for therapeutically targeting CD6 in aGVHD. Itolizumab is a humanized IgG1 monoclonal antibody that binds CD6 and blocks interaction with ALCAM to inhibit T cell activity and trafficking that is being evaluated as treatment for aGVHD.

Methods: Here we present interim study results from EQUATE (as of 2020 Nov 13), an ongoing US-based Phase 1b/2 study of itolizumab in combination with steroids for newly diagnosed severe aGVHD (Grade III-IV). Phase 1b



A. The expression levels of CD6 are increased on T_{eff} cells (such as Th1, Th2 and Th17 cells) and are associated with autoreactivity and pathogenic phenotype. Itolizumab reduces CD6 expression, and low CD6 expression is associated with a low inflammation, non-pathogenic phenotype. B. Response to itolizumab was observed as early as Day 15 and was sustained at the 2 higher doses through Day 57. CR, complete response; VGPR, very good partial response based on Martin Consensus 2009 Criteria; PR, partial response; NR, no response; PD, progressive disease. C. Cell surface CD6 levels on CD4 T cells of subjects are presented as % of baseline. Itolizumab dose-dependently reduced the surface levels of CD6 on CD4+ and CD8+ cells by 24 hours following the first dose. CD6 trended toward baseline levels by Day 15 (pre 2nd dose) at the lowest dose of itolizumab (0.4 mg/kg) but not at the 2 higher doses (0.8 and 1.6 mg/kg).

involves an open-label, dose-escalation study evaluating doses from 0.4 to 2.4 mg/kg (IV Q2 weeks through Day 57).

Results: Ten subjects have completed treatment through Day 57: 0.4 mg/kg ($n = 4$), 0.8 mg/kg ($n = 3$), and 1.6 mg/kg ($n = 3$). All subjects received corticosteroids at an initial dose of 1-2 mg/kg/day. Baseline characteristics include mean age of 48, 90% male, 90% white, 80% with peripheral blood graft source, 80% with HLA matched donor, mean time to GVHD onset of 43 days, and 100% with GI involvement.

Across dosing cohorts, all subjects experienced at least 1 adverse event (AE), with hypomagnesemia ($n = 3$) and peripheral edema ($n = 3$) being the most common. Most AEs were mild to moderate in severity. One mild infusion reaction AE was noted. Serious AEs that are not unexpected for severe aGVHD on systemic immune suppression were noted in 5 subjects, including recurrent GVHD ($n = 1$), sepsis ($n = 2$; 1 was considered a DLT) and fever ($n = 1$). COVID-19 ($n = 1$) and disseminated nocardia ($n = 1$) were also reported. Across cohorts, the overall response rate (ORR; complete response [CR] + partial response [PR] + very good partial response [VGPR]) was 80% at Day 29, with 70% of subjects experiencing CR and 10% experiencing VGPR. ORR was sustained through Day 57. At Day 57, 7 subjects had tapered steroids by ≥80% (Fig 1B). Immunologically, itolizumab dose-dependently decreased CD6 levels on T cells within 24 h of first dose, which was maintained throughout the treatment period, particularly at 0.8 and 1.6 mg/kg (Fig 1C).

Conclusions: In summary, the preliminary safety and high response rates of itolizumab with steroid therapy in newly diagnosed severe aGVHD is encouraging. Its early risk-benefit profile supports continued study and evaluation in future randomized controlled trials.

Clinical Trial Registry: NCT03763318

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Technologies and Cambium Oncology. He has served on scientific advisory boards of Pharmacyclics, Novartis, CRISPR, Kite, Partners, Amgen, Verastem, Kalytera, Syndax, Johnson and Johnson and CareDx. He is also the founding editor of ImmunoMedicine. Daanish Hoda - Owns stock in Aprea Therapeutics Mark Schroeder is a consultant for Janssen, GSK, and Sanofi Genzyme. Nosha Farhadfar has research funding from CSL Behring and on an advisory board of Incyte. Cherie T. Ng, Lisette M. Acevedo, Maple Fung, Joel Rothman, Stephen Connelly, and Krishna R. Polu are employees of Equillium. Corey Cutler is a consultant for Jazz, Janssen, CareDx, Generon, Mesoblast, Syndax, Omeros, Genzyme and Incyte.

P184.

Evaluation of a Limited Sampling Strategy in the Therapeutic Drug Monitoring of Busulfan

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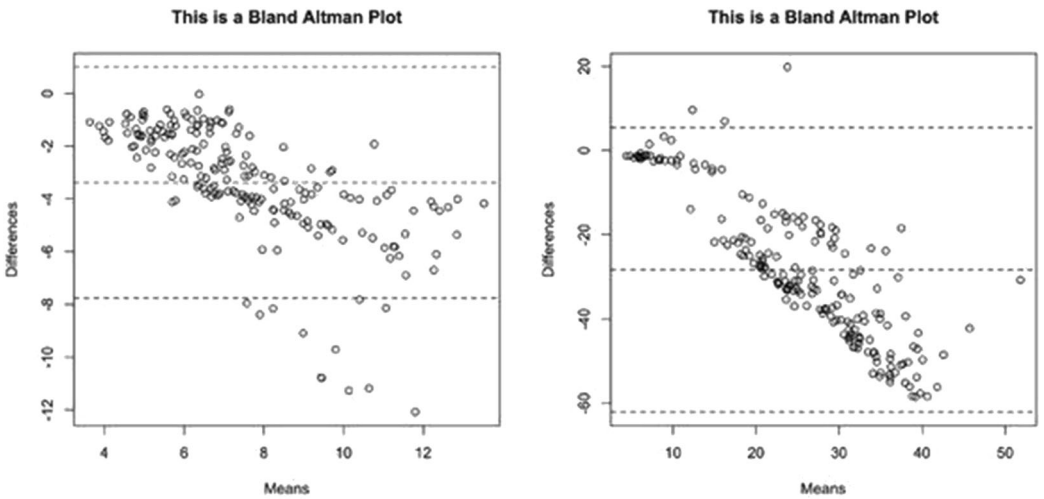
Background: Busulfan (Bu) is one of the most frequently used chemotherapies in conditioning regimens before hematopoietic stem cell transplantation (HSCT). Bu exposure is measured as the area-under-the-concentration-time-curve (AUC), which depends on Bu clearance (Cl). Standard sampling strategy (SSS) for Bu therapeutic drug monitoring (TDM) involves using multiple blood samples to measure the AUC, and this method is very labor-intensive, inconvenient, and costly. One of the strategies to simplify TDM is to use a limited sampling strategy (LSS) to reduce the number of samples per patient. Several studies have investigated the use of LSS with different approaches and conflicting results. Therefore, we planned to evaluate the accuracy of an LSS of Bu using two samples compared to the SSS using 5–6 samples.

Methods: We retrospectively studied patients who received HSCT at Sultan Qaboos University Hospital (SQUH), Oman, from 2003 to 2020. Patients from all age groups and pre-transplant diagnoses were included. Bu was administered intravenously either 6-hourly (QID) or once daily (OD) depending on transplant indication. Bu plasma concentration was measured by liquid chromatography- tandem mass spectrometry API3200®. The SSS involved five samples at 0, 2, 3, 4, and 6 h (QID) or six samples at 0, 3, 6, 12, 18, and 24 h (OD). This was compared to an LSS using two samples collected at 2 and 6 hours (QID regimen) and 3 and 6 hours (OD regimen). The agreement between the sampling strategies was investigated by the Bland–Altman (BA) plot.

Results: Two-hundred and two patients were included (102 males and 100 females). The median age was 16 years (IQR 6-28). Forty-eight percent were transplanted for malignant diseases, and 52 % had inherited blood disorders or immunodeficiency syndromes. A total of 502 doses (210 in the QID regimen and 292 in the OD regimen) were analyzed for SSS and LSS. In the QID regimen, the median AUC using SSS was 3220 ng/ml*h (IQR: 2799–3647), and the median clearance (Cl) was 5.63 ml/min/kg (IQR: 4.69–6.75). In comparison, the median AUC using LSS was 2057 ng/ml*h (IQR: 1672-2473), and the median Cl was 8.72 ml/min/kg (IQR 6.90-11.59). Using the BA plot,



Bland-Altman plots for the agreement between clearances estimated using SSS and LSS in the QID (left) and OD (right) regimens.

the mean difference in clearance between the SSS and LSS was −3.38 ml/min/kg (BA limits: −7.76 and +1.01). In the SDD regimen, the median AUC using SSS and LSS was 7022 ng/ml*h (IQR: 4149-7532) and 1371 ng/ml*h (IQR: 1074–1820), respectively, while the corresponding Cl was 10.99 ml/min/kg (IQR: 8.52–15.70) and 50.97 ml/min/kg (IQR: 34.01-74.27), respectively. The mean difference in Cl between the two strategies on the BA plot was -45.14 ml/min/kg (–127.21 to –36.92) (Figure 1).

Conclusions: Bu AUC and Cl estimated using two concentration-time points were significantly different than the standard 5- or 6-samples. The difference between SSS and LSS was more pronounced with the SDD with a fivefold higher Cl observed with LSS compared to SSS. Bu is known to have high inter-individual and intra-individual variability in PKs, and this might preclude the use of an LSS for PK determination especially in a heterogenous patient population.

Clinical Trial Registry: Not applicable.

Disclosure: Nothing to declare.

P185.

The Impact of Letermovir Prescribing on the Rate of Cytomegalovirus Reactivation Following Allogeneic Stem Cell Transplantation

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Background: Letermovir is licensed for prophylaxis against CMV reactivation following allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult CMV-seropositive (R+) patients. Treatment is routinely recommended for 100 days post-transplant. Given that CMV reactivation/disease is one of the most clinically significant complications post-transplant, letermovir prophylaxis offers the possibility of improved outcomes in this group. This study assessed rates of CMV reactivation to day+100 and day+168 and CMV management costs at 3 UK transplant centres.

Methods: All adult R+ patients who received letermovir prophylaxis at University Hospital of Wales (UHW), Queen Elizabeth Hospital Birmingham and Bristol Haematology and Oncology Centre between 31/07/2019-31/10/2020 were included in the study. Data previously reported on 124 R+ UHW patients were used as the comparator for reactivation to day+100 (Ibrahim et al. 2014) and letermovir marketing authorisation (MA) data (Marty et al. 2017) for reactivation between day+100 and day+168. Additional data from 38 UHW R+ patients transplanted in the 18 months prior to introducing letermovir were used to compare costs of CMV management.

Results:

Table 1: Baseline characteristics and CMV reactivation rates

Parameter	Letermovir cohort (n = 60) n (%)	Pre-letermovir cohort (n = 124) n (%)
Age, median (range) y	55 (16-74)	56 (19-72)
Gender – Male, n (%)	32 (53)	64 (51)
CMV status, n (%)		
R+/D+	35 (58.3)	66 (53)
R+/D-	24 (40)	58 (46)
R+/Equivocal	1 (1.7)	0 (0)
Intensity, n (%)		
RIC	46 (76.7)	109 (88)
Myeloablative	14 (23.3)	15 (12)
Donor type, n (%)		
Unrelated	44 (77.3)	84 (68)
Sibling	10 (16.7)	40 (32)
Haplo-identical	4 (6.7)	0 (0)
Cord	2 (3.3)	0 (0)
CMV reactivation rate day+100, n (%)	10 (16.7)	97 (78.2)

A total of 60 patients received letermovir prophylaxis of whom 49(81.7%) reached day+100 while 32(53.3%) had reached day+168 at data cut off. No patient discontinued letermovir due to intolerance. Three patients discontinued letermovir early: 1 each at day+21 and day+71 (patient error) and day+88 (diarrhoea due to aGvHD). All subsequently reactivated at day+56, 85 and 123, respectively.Ten(16.7%) patients reactivated before day+100 at a median of 23(5-98) days, accounting for 5(14%) and 5(21%) of the R+/D+ and R+/D- cohorts, respectively. 6/10(60%) reactivating patients were subsequently treated. Of the 40 patients who received letermovir to day+100 without CMV reactivation, 13(33%) had subsequent late reactivation at a median of 141(123-163) days post-transplant, 10 R+/D+ and 3 R+/D-. Notably, of the 27 patients who did not reactivate beyond day+100, 4 (15%) inadvertently continued for an additional 14(6-38) days due to having excess supply at home. Following introduction of letermovir, CMV reactivation rates prior to day+100 reduced from 78.2% to 16.7% and post day+100 was 30% which was comparable to the 26% reported in the MA data. Mean estimated CMV management costs (list drug prices plus

inpatient bed days) to day+168 in the letermovir group was £14,622 compared to £11,142 in the 38 R+ patients treated before introduction of letermovir. Despite the increased drug expenditure, bed days were reduced from a mean of 7.4 days (0-63) to 1.1 days(0-22).

Conclusions: Letermovir prophylaxis reduced CMV reactivation, treatment requirement and hospitalisation up to day+168 post-transplant but increased overall expenditure. Further studies are needed to assess optimal duration of letermovir therapy and impact on quality of life.

Disclosure: Nothing to declare.

P186.

Pharmacokinetic Analysis of Baricitinib in Phase 1-2 Study for Treatment Refractory Chronic Graft-Versus-Host Disease

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Background: Allogeneic hematopoietic stem cell transplantation (HCT) is often complicated by chronic graft-vs-host disease (cGVHD). Baricitinib, a JAK-1/2 inhibitor approved for rheumatoid arthritis (RA), may mediate an anti-inflammatory, anti-fibrotic and immunomodulatory effect in patients with cGVHD. Noncompartmental analysis (NCA) and exposure-response models were used to characterize the pharmacokinetic (PK) profile of baricitinib and its relationship to available clinical endpoints in a phase I/II trial for treatment refractory cGVHD after allogeneic HCT.

Methods: Twenty treatment-refractory cGVHD patients (median prior treatments: 4; range: 2-7), 19 (95%) with skin sclerosis and all with severe NIH score started therapy with 2 mg/day baricitinib PO before intra-patient dose escalation to 4 mg/day PO beginning Cycle 4, Day 1 (C4D1). PK sampling encompassed only the first 4 hours of C1D1 and C4D1 doses. Exposure parameters (C_{max}, $AUC_{0\text{-}4hr}$, C_{4hr}) on C1D1 and C4D1 were computed using NCA. Relationships between baricitinib PK and co-administered posaconazole, fluconazole, prednisone, creatinine clearance, race, sex, body weight, and age were examined. Logistic regression was used to characterize the relationship with binary response at 3 months and the likelihood of experiencing the most common treatment emergent adverse event (TEAE) along with other baseline/demographic variables. Using a proportional odds model, associations between dose interruptions, reductions, or discontinuations and baseline/demographic variables were analyzed.

Results: While comparable to RA patients, this cohort of cGVHD patients demonstrated a nonsignificantly higher C1D1 C_{max} (69.6 [sd 33.8] nM) relative to healthy volunteers (45.7 [sd 16.7] nM) given 2 mg, which warrants further analysis. First dose C_{max} is also significantly higher ($p = 0.01$) in patients treated with prednisone and normal renal function. While both azoles are CYP3A4 inhibitors, only fluconazole resulted in higher C1D1 C_{4hr} ($p = 0.029$). None of these drug interactions are considered to be clinically meaningful. Worsening renal function is significantly ($p = 0.047$) associated with increasing C1D1 $AUC_{0\text{-}4hr}$ (*Figure 1*).

ORR at 3- and 6- months were 60% and 65%, respectively. Best ORR at any time was 90% (95%CI 85-100%). No DLT was observed with 2 mg; 16/20 (80%) pts reached dose-escalation to 4 mg. Three pts required dose-reductions due to neutropenia (2), and refractory myalgias (1). Common TEAEs included upper respiratory infection (13), neutropenia (6), hypophosphatemia (12), and hypertriglyceridemia (5).

No significant exposure-response relationships were found with respect to binary response at 3 months; grade of most frequent TEAEs; or dose interruptions, reductions, or discontinuations.

Table 1: NCA summary of means and %CVs.

	C1D1 – 2 mg		C4D1 – 4 mg	
	Mean	%CV	Mean	%CV
$AUC_{0\text{-}4hr}$ (hr*ng/mL)	65.0	34.2	168.2	32.1
C_{4hr} (ng/mL)	18.8	36.2	43.0	39.0
C_{max} (nM)	69.6	33.8	161.4	26.5
T_{last} (hr)	3.9	11.8	4.0	3.6
T_{max} (hr)	2.1*	60.9	1.8	59.6

median

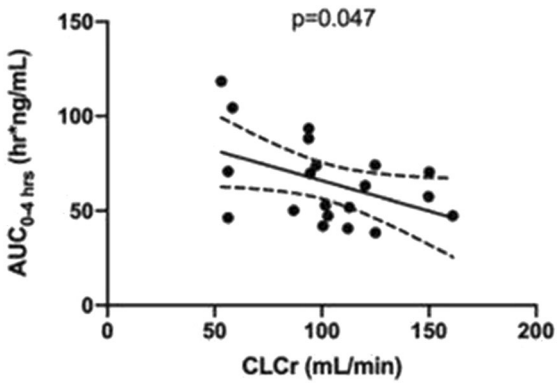

Figure 1: Creatinine clearance vs. baricitinib (C1D1) $AUC_{0\text{-}4hrs}$.

Conclusions: In cGVHD patients, renal function was significantly associated with baricitinib AUC. Drug interactions unlikely with prednisone and fluconazole. Exposure-response analysis did not identify safety concerns with respect to TEAE.

Clinical Trial Registry: www.clinicaltrials.gov (Identifier: NCT02759731)

Disclosure: Nothing to declare.