Abstract OTU-002 Figure 2

Conclusion We have demonstrated that immunogenicity to anti-TNF is determined by HLA variants. Pre-treatment genetic testing might allow the use of individual risk profiles and targeted use of immunomodulatory therapies to deliver more durable, safe and cost-effective anti-TNF therapy.

OTU-003 ETROLIZUMAB AS INDUCTION THERAPY IN MODERATE TO SEVERE CROHN'S DISEASE: RESULTS FROM BERGAMOT COHORT 1

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10.1136/gutjnl-2018-BSGAbstracts.106

Introduction Etrolizumab (etro), a humanised anti- $\beta 7$ monoclonal antibody was evaluated in patients (pts) with moderate to severe Crohn's Disease (CD) to determine safety and efficacy. Results of the Phase III BERGAMOT (NCT02394028) exploratory induction cohort are presented.

Methods Eligible pts with moderate to severe CD (refractory/intolerant to anti-TNF α agents, immunosuppressants, and/or corticosteroids) were assigned (2:2:1) etro 105 mg SC Q4W, etro 210 mg at wks 0, 2, 4, 8, and 12, or placebo (pbo) during a 14-wk induction period. Endpoints included CDAI remission (CDAI <150), CDAI-100 and -70 responses, PRO2 remission (weighted combined score ≤ 11 , based on pt report of liquid/very soft stool frequency [SF] and abdominal pain [AP]), symptomatic remission (unweighted SF ≤ 3 and AP ≤ 1), and endoscopic improvement ($\geq 50\%$ reduction from baseline SES-CD) at wk 14.

Results 300 pts (73% aTNF-experienced) with moderate to severe CD (mean CDAI [SD], 315.6 [60.0]; mean SES-CD [SD], 14.1 [7.3]; median faecal calprotectin [range] 918 [30–15 451] $\mu\text{g/g}$; median C-reactive protein [range], 9.75 [0.2–148.0] mg/L) received etro 105 mg (n=120), etro 210 mg (n=121), or pbo (n=59).

Symptomatic remission was seen in a greater proportion of pts receiving etro 105 mg and 210 mg compared with pbo at

wks 6, 10, and 14. More pts achieved endoscopic improvement with etro 105 mg and 210 mg compared with pbo at wk 14 (table 1).

CDAI remission at wk 14 was greater with etro 105 mg and 210 mg compared with pbo: 23.3% (17.6, 30.2), 28.9% (22.7, 36.1) and 16.9% (10.4, 26.4) respectively. PRO2 remission was achieved at wk 14 in 28.3% (22.1, 35.5), 28.9% (22.7, 36.1), and 20.3% (13.1, 30.2) of pts, respectively.

The frequency of adverse events with etro was comparable with pbo; no deaths, anaphylaxis or progressive multifocal leucoencephalopathy occurred.

Abstract OTU-003 Table 1 Symptomatic remission and endoscopic improvement

	Pbo n=59	Etro 105 mg n=120	Etro 210 mg n=121
% (90% CI)			
Symptomatic remission			
Wk 6	8.5 (4.2–16.4)	15.0 (10.4–21.1)	25.6 (19.7–32.6)
Wk 10	8.5 (4.2–16.4)	15.8 (11.1–22.1)	27.3 (21.2–34.4)
Wk 14	11.9 (6.6–20.5)	20.8 (15.4–27.5)	24.8 (18.9–31.8)
Endoscopic improvement			
Wk 14	3.4 (1.1–9.7)	21.0 (15.6–27.8)	17.4 (12.4–23.7)

Conclusion Treatment with etro was well tolerated and resulted in clinically meaningful endoscopic improvement in pts with moderate to severe CD. Rapid symptomatic remission was observed as early as wk 6 and sustained through wk 14. Enrolment into induction cohorts and the maintenance phase is ongoing.

OTU-004 SHALLOW WHOLE-GENOME SEQUENCING PREDICTS THE FUTURE CANCER RISK OF LOW-GRADE DYSPLASTIC LESIONS IN ULCERATIVE COLITIS

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10.1136/gutjnl-2018-BSGAbstracts.107

Background The management of low grade dysplasia (LGD) in ulcerative colitis (UC) is uncertain due to the variable risk of progression to colorectal cancer (CRC). Chromosomal copy number alterations (CNAs) occur in colonic epithelial cells of UC patients who have developed CRC. The burden of CNAs in precursor LGD relative to high-grade dysplasia (HGD) and CRC has not been defined, and the correlation between LGD CNA burden and future HGD/CRC risk is unknown.

Shallow whole-genome sequencing is a novel, cost-effective technique for high resolution CNA assessment in formalin-fixed, paraffin-embedded tissue.

Methods We identified 19 UC proctocolectomy specimens with HGD/CRC, and analysed 77 neoplastic regions (36 LGD, 34 HGD and 7 CRC). We then analysed 13 'progressor' patients with 27 LGD lesions who subsequently developed HGD/CRC a median 427 days later (IQR 213–777), and 22 'non-progressor' patients with 26 LGD lesions who remained

HGD/CRC-free >5 years later. The two patient groups are matched for age, gender, disease duration and LGD location.

Histological diagnosis was confirmed by two blinded pathologists. Shallow whole genome sequencing (0.1x) was performed using a standardised pipeline for epithelial cell enrichment, DNA extraction, library preparation, next generation sequencing and bioinformatic analysis.

Results A median 12% of the genome of LGDs from proctocolectomy specimens showed CNAs (IQR 4%–32%), compared to 23% in HGD/CRC (IQR 19%–42%, $p=0.003$). Similarly, the number of CNA events was greater in HGD/CRC compared to LGD ($p<0.001$). Multiple CNAs involving key driver genes were more frequent in HGD/CRC compared to LGD (adjusted p -values <0.05), including 8q gain (*MYC* loss, OR 17.2), 4q loss (OR 4.59) and 18q loss (*DCC/SMAD4* loss, OR 4.15).

Abstract OTU-004 Figure 1 Both the maximal total CNA burden and number of CNA events are greater in LGD of progressor than in LGD of non-progressors ($p<0.01$) as shown in the two violin plots.

Abstract OTU-004 Figure 2

The Kaplan-Meier plot demonstrates that patients in this cohort bearing LGD with the 25% greatest CNA burden are significantly more likely to develop future CRC/HGD than the remaining 75% of patients (HR 5.1, $p=0.001$).

Conclusions LGD lesions demonstrate a surprising diversity in CNA burden, with some LGD lesions bearing CNA profiles indistinguishable from HGD/CRC. Shallow whole-genome sequencing has potential translational utility, by stratifying patients with LGD lesions according to risk of progression to HGD/CRC.

OTU-005

TARGETING EXPANDED GUT HOMING EFFECTOR T CELL LINEAGES IN GI-GVHD: A NEW THERAPEUTIC PARADIGM

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10.1136/gutjnl-2018-BSGAbstracts.108

Introduction Acute graft versus host disease may affect the gastrointestinal track (aGI-GvHD) in up to 60% of haematopoietic stem cell transplant (HSCT) recipients who develop GvHD resulting in significant morbidity. Half of these patients will develop steroid refractory disease which is associated with high mortality (up to 90%) due to lack of safe and efficacious therapies. Here we test the hypothesis that the integrin $\alpha 4\beta 7$ /Madcarn-1 pathway is clinically important in the pathogenesis of human aGI-GvHD.

Methods Prospective experimental study, recruiting HSCT recipients with aGI-GvHD ($n=10$) and controls [IBD ($n=36$) and non-IBD controls ($n=32$)]. Samples collected included peripheral blood and distal colonic biopsies. The $\beta 7$ +CD4 +compartment was phenotyped with a multiparametric flow cytometry panel. MADCAM-1 and S100A8 (the calprotectin subunit, biomarker of intestinal damage) expression in the gut were tested with RT-PCR. Clinical data on aGI-GvHD patients treated with vedolizumab were prospectively collected.

Results Within the effector memory population (CD3 +CD4 +CD45RA-CD45RO+CCR7-) there was significant enrichment of $\beta 7$ +effector memory cells in both inflammatory conditions (IBD: $24\% \pm 2.7$, aGI-GvHD: $29\% \pm 6.5$ vs. controls: $17\% \pm 1.1$, both $p<0.05$). Analysis of each individual subtype of the effector T cell lineages demonstrated that $\beta 7$ expression was especially enriched in Th1 (CXCR3 +CCR6-), Th17 (CCR6 +CXCR3-) and Th1/17 (CXCR3 +CCR6+) ($p=0.0034$). MADCAM-1 expression in aGI-GvHD is upregulated in comparison to non-IBD controls [fold change: 2 (0, 5), $p=0.006$] and at similar levels to patients with UC [2 (0, 9)]. Levels of MADCAM-1 expression correlated to the expression of the calprotectin subunit S100A8 [$r=0.90$, 95% CI(0.34, 0.99), $p=0.014$]. Six patients with steroid refractory aGI-GvHD patients were treated with vedolizumab, a monoclonal antibody targeting $\alpha 4\beta 7$. Five patients had a sustained clinical improvement (75% median reduction in clinical score, $p=0.03$) up to 6 months of follow up. These results compare favourably to other patients with steroid refractory aGI-GvHD treated at our centre with other second line treatments.

Conclusions For the first time, we show that aGI-GvHD is associated with significant expansion of gut homing effector lineages, most notably Th1 and Th17 cells. Interestingly the ligand for the $\alpha 4\beta 7$ integrin (Madcarn-1) is also highly expressed in gut tissue from aGI-GvHD patients, supporting further the therapeutic targeting of this gut homing pathway. Our promising clinical data on vedolizumab use have the potential to change the landscape of treatment in this condition.