POLB 001, AN ORAL P38 MAPK INHIBITOR FOR THE PREVENTION OF CYTOKINE RELEASE SYNDROME

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INTRODUCTION

Cytokine Release Syndrome (CRS) is a potentially severe adverse effect of cancer immunotherapies including CAR T cell therapies and T cell-engaging bispecific antibodies (BsAbs) which carry black box warnings for CRS, and management of CRS requires close monitoring and can be severe if not recognised and treated promptly. Monitoring & management of patients with CRS places significant strain on the healthcare infrastructure. Initial dosing typically requires inpatient admission, or outpatient care only where patients can remain near the clinical setting with adequate care-giver support. Availability of a convenient and effective prophylactic could reduce healthcare utilisation and enable an expansion in outpatient delivery. Due to expansion into new indications and earlier lines of treatment, use of CRS-inducing immunotherapies is expected to rise. Strategies to mitigate the impact of CRS are required.

POLB 001 is an oral p38 MAPK inhibitor in development for prevention of immunotherapy-associated CRS. POLB 001 has previously been evaluated in two Phase 1 trials: a first-in-human SAD/MAD PK/PD study and an LPS challenge study, both in healthy subjects, in which it demonstrated potent ability to decrease TNF, IL-6 and IL-8, along with clinically meaningful reduction of CRP and body temperature.

AIMS

To investigate the *in vitro* and *in vivo* effects of POLB 001 on cytokine release syndrome and T cell phenotype and function.

METHODS

In vitro: PBMCs or PBMC-derived negatively selected CD3+ T cells were co-cultured with human RPMI 8226 tumour cells at a ratio of 10:1 or 5:1, respectively. RPMI 8226 cells were stained with CMFDA prior to killing assays. Cells were treated with two commercially available BCMAxCD3 bispecific antibodies (1 nM) and POLB 001 (0.5 - 50 nM). Tumour cell death and immune cell phenotypes were measured by flow cytometry using propidium iodide and standard staining techniques.

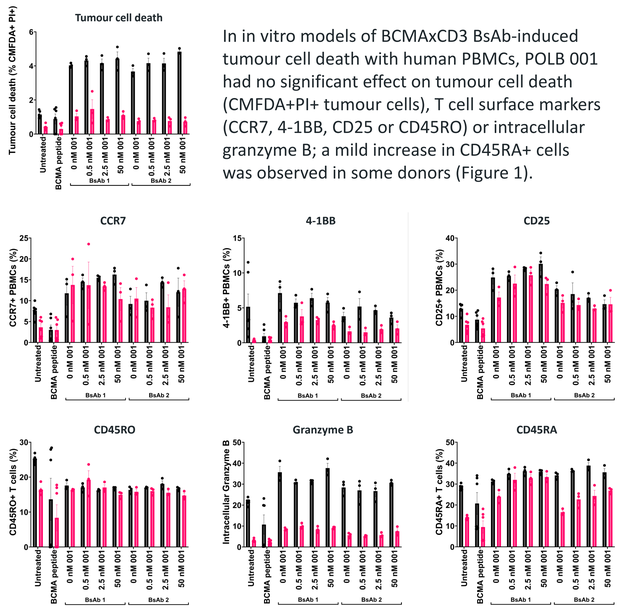
In vivo: NSG-MHC I/II DKO mice (Jackson labs) were irradiated at 100 cGy & humanised with PBMCs ($15x10^6$ or $10x10^6$ cells/mouse). After 5 days, tumour induction was performed by injecting $2x10^6$ Raji-Luc cells/mouse. A CD28 agonist or CD19xCD3 bispecific antibody was used to induce CRS. Mice were treated prophylactically with either vehicle or POLB 001. An additional group was included in the CD28 induced CRS model which was treated with an anti-TNF antibody. Serial serum samples were obtained for Luminex cytokine analysis and flow cytometry. CRS scores were measured as follows: 0 = normal activity, 1 = normal activity, hunched +/- piloerection, 2 = hunched with reduced activity but will still move around the cage without continued stimulation, 3 = rarely moving, or not moving unless being stimulated, 4 = moribund (non-responsive to touch). Tumour burden was measured by IVIS (data not shown).

Statistical analyses: For data at individual timepoints, a one-way ANOVA was fitted to the data and comparisons were made using a Bonferroni/Tukey test to adjust for multiple testing for each timepoint, using GraphPad Prism 11.0.1.

Clinical: POLB 001 is being investigated in a non-randomised, single-arm, multicentre, open label phase 1/2 trial in patients with multiple myeloma eligible to receive the bispecific T-cell engager antibody, teclistamab, within its licensed indication (Figure 5).

RESULTS

In vitro BCMAxCD3 cell killing assay



In in vitro models of BCMAxCD3 BsAb-induced tumour cell death with human PBMCs, POLB 001 had no significant effect on tumour cell death (CMFDA+PI+ tumour cells), T cell surface markers (CCR7, 4-1BB, CD25 or CD45RO) or intracellular granzyme B; a mild increase in CD45RA+ cells was observed in some donors (Figure 1).

In vivo CD19xCD3 induced cytokine secretion

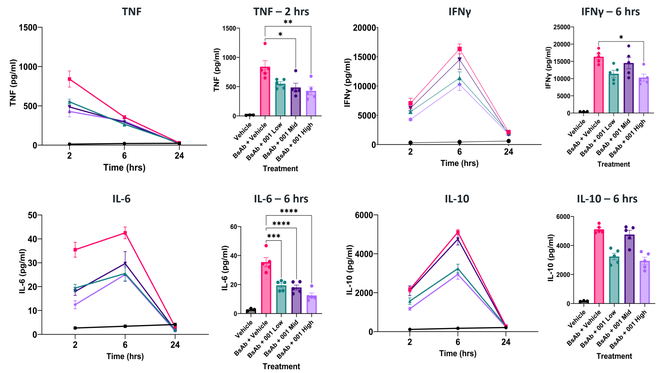


Figure 2 (above): Plasma cytokine profiles following CD19xCD3 challenge

In an in vivo CD19xCD3 BsAb-induced CRS model, POLB 001 reduced levels of all cytokines tested (TNF, IFNγ, IL-6, IL-10) at all timepoints, with significant decreases of peak levels ($p \leq 0.05$) (Figure 2).

Figure 1 (left): Tumour cell death and cell markers for tumour cell killing

● Donor 7
● Donor 8

In vivo anti-CD28 induced cytokine secretion

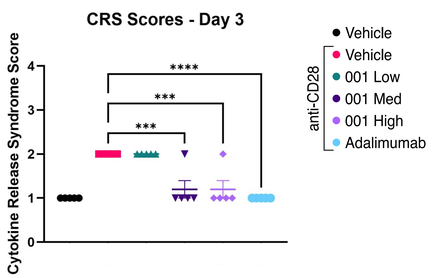
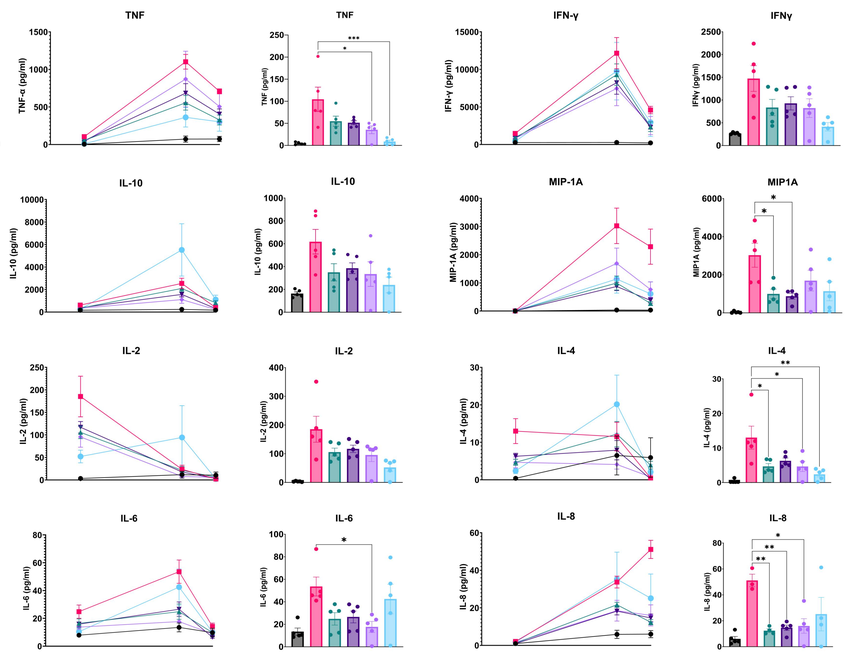


Figure 3 (above): Clinical CRS symptoms measured daily

In an in vivo CD28-induced CRS model, CRS clinical score was measured on Day 3, following CD28-induced CRS induction on day 0. Medium- and high-dose POLB 001 ($p<0.001$) and adalimumab ($p<0.0001$) significantly prevented CRS symptoms at day 3. CRS symptoms were also prevented at low dose POLB 001 on day 4 ($p<0.05$, data not shown) (Figure 3).

Peak levels of all cytokines tested were reduced; TNF, IFNγ, MIP1A, IL-2, IL-4, IL-6, IL-8, IL-10 (IL-6 & IL-4, $p<0.05$, IL-8 & MIP1A, $p<0.01$, IL-2, IL-10, TNF & IFNγ, non-significant) (Figure 4). There was no significant difference in tumour burden across groups.

Figure 4 (right): Levels of cytokines in serum determined by Luminex prior to anti-CD28 challenge



Ongoing TOPICAL Clinical Trial

TOPICAL (Trial Of Prevention of Immuno Cytokine Adverse Events in MyeLoma) is a Phase 1/2, single arm, open label, non-randomised clinical trial investigating the safety and efficacy of POLB 001 in preventing cytokine release syndrome in multiple myeloma patients receiving teclistamab. POLB 001 is an orally administered p38 MAPK inhibitor in development for cancer-immunotherapy associated CRS.

- The study design is depicted in figure 5 (Study visit windows not shown)
- A safety review of the initial patients will be conducted to select the recommended dose
- POLB 001 can be administered in a healthcare setting or at home
- Approximately 30 patients will be enrolled
- The study is being conducted in the United Kingdom by Accelerating Clinical Trials Ltd (ACT). Chief Investigator: Dr Emma Searle. The Christie NHS Foundation trust, Manchester

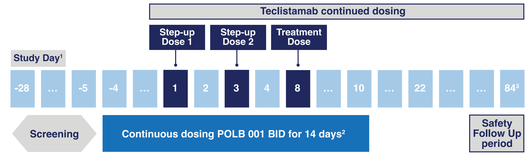


Figure 5: Dosing schedule in single arm, multi-centre, open label Phase 1/2 trial in patients with multiple myeloma receiving teclistamab

Primary Endpoint: To make a preliminary assessment of the safety of POLB 001 in multiple myeloma patients following initiation of teclistamab treatment

Secondary Endpoints; (1) to define early efficacy signals of CRS Prevention **(2)** to document the pharmacokinetics and pharmacodynamics (PK/PD) profile of POLB 001 in patients with relapsed or refractory multiple myeloma (RRMM)

Exploratory Endpoints: To explore the effect of POLB 001 on circulating cytokine profiles in patients receiving teclistamab

CONCLUSIONS

- POLB 001 did not affect BsAb-induced tumour cell-killing in an *in vitro* model
- POLB 001 reduced key CRS-associated cytokines and did not impair BsAb induced tumour cell death
- POLB 001 dose-dependently reduced clinical CRS scores and significantly reduced peak serum levels of TNF, MIP-1A, IL-4, IL-6, and IL-8 in a humanised mouse model of CD28 induced CRS
- POLB 001 significantly reduced peak serum levels of TNF, IFNγ, and IL-6 in a CD19xCD3 in vivo model of CRS

Next Steps

A Phase 1/2 trial of POLB 001 in teclistamab-treated patients with multiple myeloma is ongoing

REFERENCES/ACKNOWLEDGEMENTS

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