#2061: POLB 001, AN ORAL P38 MAPK INHIBITOR, REDUCES CYTOKINE RELEASE SYNDROME (CRS) IN A MOUSE MODEL OF IMMUNOTHERAPY-INDUCED CRS

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INTRODUCTION

Cancer immunotherapies such as CAR T cell therapies and bispecific antibodies are highly effective treatments for patients with hematological malignancies. These immunotherapies are frequently associated with systemic toxicities such as cytokine release syndrome (CRS). CRS not only impacts patient survival and performance status, but also complicates the administration of immunotherapies and restricts availability to specialist tertiary centres with access to high-dependency units. CRS is thought to arise from on-target effects of immunotherapy involving undue amplification of specific inflammatory responses[1]. Treatment of CRS includes anti-pyretic or anti-cytokine therapies such as tocilizumab (anti-IL-6R), anakinra (anti-IL-1RA), and corticosteroids[2]. No prophylactic treatments are currently approved.

POLB 001 is an oral p38 MAPK inhibitor in development for the prevention of immunotherapy-induced CRS. Here we test the capacity of POLB 001 to prevent CRS in a previously optimized mouse model of CRS.

AIM

To evaluate the effect of POLB 001 on the development of CRS in a well-characterized animal model, using adalimumab as an established positive control.

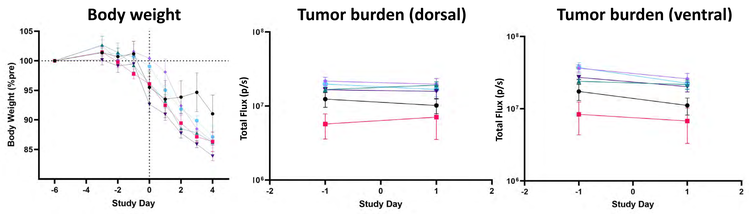
METHOD

Female NSG-MHC I/II DKO mice were irradiated & humanized with PBMCs (15 x 10^6 cells) on day -6. Tumor induction was performed on day -1 (IV 2 x 10^6 Raji-luc cells). CRS was induced with IV anti-CD28 on day 0. Groups were treated SC BID from day -2 to 3, adalimumab (5mg/kg) was administered once IV prior to CD28 on day 0. To determine differences between groups for CRS scores, cytokine levels and immune cell populations, a One-Way ANOVA was fitted to the data and comparisons of interest were made using a Bonferroni test to adjust for multiple testing, using a two-sided 5% significance interval. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

TREATMENT GROUPS

- G1: Vehicle
- G2: α-CD28 + Vehicle
- G3: α-CD28 + POLB 001 Low (2 mg/kg BID)
- G4: α-CD28 + POLB 001 Medium (10 mg/kg BID)
- G5: α-CD28 + POLB 001 High (25 mg/kg BID)
- G6: α-CD28 + Adalimumab (5 mg/kg)

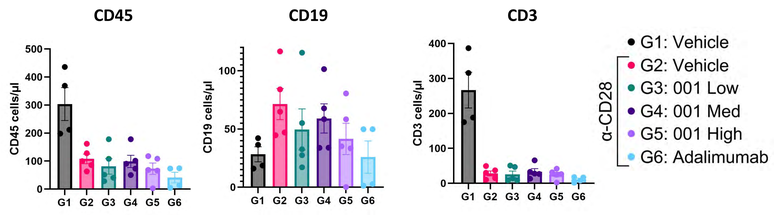
RESULTS – BODY WEIGHT AND TUMOR BURDEN



Body weight was measured daily & tumor burden at day -2 and 2.

All groups had significant weight loss over the course of the study. There was no observed treatment effect of POLB 001 or Adalimumab on body weight or tumor burden.

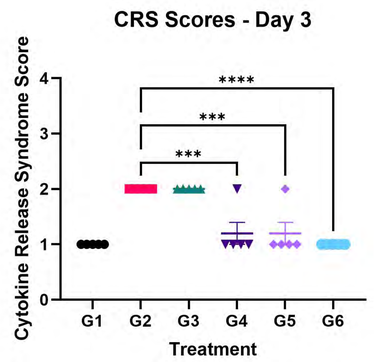
RESULTS – EFFECTS ON IMMUNE CELL POPULATIONS



Day 3 Peripheral immune cells were analysed by flow cytometry.

CRS significantly reduced levels of CD45 and CD3 cells. There was no observed treatment effect of POLB 001 or Adalimumab on CD45, CD19 or CD3 cell levels. POLB 001 had no significant effect on T cell expression of CD27 and CD62L (data not shown).

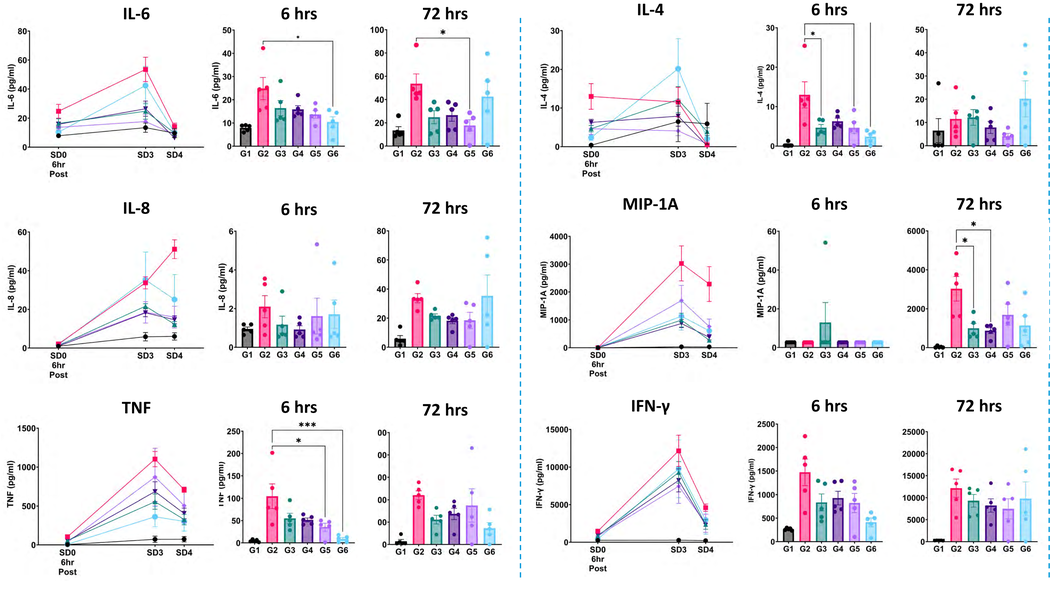
RESULTS – CRS SCORE



Clinical CRS symptoms were measured daily.

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).

RESULTS – ANTI-CD28-INDUCED CRS



Levels of cytokines in serum were determined by Luminex prior to anti-CD28 challenge (day 0) and at 6hrs, 72 hrs and c. 96 hrs post challenge.

POLB 001 statistically reduced IL-6 (high-dose), IL-4 (low- and high-dose), IL-8 (all doses – day 4), MIP-1α (all doses) and TNF (high-dose). There was a non-significant trend for reduced production of all other cytokines. Adalimumab significantly reduced IL-4 and MIP1α; there was a non-significant trend for reduced IL-6, IFN-γ and TNF. POLB 001 was superior to Adalimumab in reducing production of all cytokines except TNF, however it is likely Adalimumab bound TNF was not detectable by Luminex.

CONCLUSIONS

Key Take-Aways

- POLB 001 reduced clinical CRS scores in a dose-dependent fashion
- POLB 001 significantly reduced peak serum levels of IL-4, IL-6, IL-8, MIP1-α, and TNF and showed nonsignificant reductions in all other cytokines tested
- High and medium dose POLB 001 were comparable to Adalimumab in CRS scores and demonstrated a trend of superior cytokine inhibition

Next Steps

POLB 001 has also been successfully tested in a LPS challenge trial in healthy volunteers. The results of this animal study support further development of POLB 001 in a Phase 2 clinical study as prophylaxis for immunotherapy-induced CRS. Trial planning activities are ongoing.

REFERENCES AND ACKNOWLEDGEMENTS

1. Shimabukuro-Vornhagen A et al. Cytokine release syndrome. *Journal for ImmunoTherapy of Cancer 2018*; 6:56

2. Lee D.W. at al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant 2019*; 25(4): 625-638

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Footnotes: Immunotherapy described herein refers to cancer immunotherapy; bispecific antibodies refer to T cell engaging bispecific antibodies for hematological malignancies.