INTRODUCTION

In many tumors, extracellular adenosine contributes to an immunosuppressed tumor micro-environment (TME) via activation of the A2a receptor (A2aR) expressed on lymphocytes and the A2b receptor (A2bR), highly expressed on myeloid cells. Relative to other tissues like the brain, immunosuppressive concentrations in the TME are much higher. Also unlike the brain, tumors contain high levels of albumin, to which many small molecule drugs bind non-specifically. AB928 is a novel and selective dual A2aR/A2bR antagonist designed to potently block the immunosuppressive effects of adenosine in the TME. A placebo-controlled (3:1) study of AB928 was conducted in healthy volunteers to study the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of the drug. This poster describes the final unplanned safety and PK/PD (A2aR coverage in blood T cells) data from this study.

Adenosine Receptor Mediated pCREB Signaling

METHODS

Phase 1 Healthy Volunteer Study: This Phase 1 healthy volunteer study consisted of single ascending dose (SAD) and multiple ascending dose (MAD) arms. In the SAD arm, we evaluated single daily doses of 10, 25, 75, and 150 mg, and two doses of 100 mg, 12 hours apart. In the MAD arm, we evaluated single daily doses of 75, 150, and 200 mg, and administered for 4 consecutive days. The study enrolled 85 participants (randomized 3:1, active:placebo) 40 each in the SAD and MAD cohorts the subjects ranged in age from 26-33. There was a slightly higher percentage of women in the SAD arm (39%) than in the MAD arm (29%). There were 123 evaluable subjects. In all dose groups, significant inhibition at peak plasma concentrations was observed. Significant inhibition was also observed 24 hours post-dose in the higher dose groups. Consistent with previously generated in vitro data, AB928 plasma levels ≥ 1 µM are associated with ≥ 90% adenosine receptor inhibition.

This study supported a starting dose of 75 mg AB928 in our dose-escalation trials for AB928 in patients. Four dose-escalation trials evalauating AB928 in combination with chemotherapy and/or PD-1 therapy have been initiated.

AB928 combination studies in oncology have been initiated in Australia and the US.

AB928 has demonstrated an excellent oral PK profile in human subjects, consistent with once-daily dosing.

AB928 was well tolerated in this study. No stopping rules were met and dose escalation continued until highest dose (200 mg) and maximal PD effects were observed at 150 mg (one dose level below targeted dose).

There was no evidence of the physiological effects associated with other adenosine receptor antagonists targeted in the brain.

Assessing pCREB levels on whole blood CD8+ T cells following ex vivo stimulation with 5 µM NECA provides an excellent measure of the PD effects of AB928 in human subjects. In all dose groups, significant inhibition at peak plasma concentrations was observed. Significant inhibition was also observed 24 hours post-dose in the higher dose groups.

CONCLUSIONS

AB928 Phase 1 study supported a starting dose of 75 mg AB928 in our dose-escalation trials for AB928 in patients. Four dose-escalation trials evaluating AB928 in combination with chemotherapy and/or PD-1 therapy have been initiated.

AB928 was well tolerated at single and multiple oral doses. The final data was available on the 12th of June 2018. Across the SAD and MAD cohorts the subjects ranged in age from 26-33. There was a slightly higher percentage of women enrolled across the entire study (62%).

AB928 combination studies in oncology have been initiated in Australia and the US.

In our dose-escalation studies of AB928, AB928 will be evaluated at doses of 75, 150 and 200 mg.

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Final Results of the Phase 1 Study in Healthy Volunteers of AB928, a Dual Antagonist of the A2aR and A2bR Adenosine Receptors

Being Studied as an Activator of Anti-Tumor Immune Response


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