AUPM-170: First-in-Class, Oral Immune Checkpoint Inhibitor of PD-L1/2 and VISTA


ABSTRACT

Highly durable clinical responses observed with antibodies to immune checkpoint receptors such as PD-1 and VISTA have redefined our understanding of cancer therapy and provided insights into the role of these receptors in immune responses. While these antibodies thus improve clinical activity, they also lead to which AUPM-170, a novel oral small molecule, could be a potential alternative. Here we report the first clinical small molecule, AUPM-170, which has shown promise in preclinical studies and is being tested in humans. AUPM-170 exhibits specificity against PD-L1 and PD-L2 and has the potential to rescue IFN-γ production in CAR-T treated patients. It is also being evaluated for its ability to inhibit the expression of VISTA in tumor cells. AUPM-170 has been shown to rescue IFN-γ production in T cells treated with PD-L1/2 inhibitors. The preclinical studies add value to the development of AUPM-170 as a potential alternative to antibodies in the treatment of cancer.

OBJECTIVES

Small molecule immune checkpoint antagonists with the ability to block multiple immune checkpoint pathways: Candidates are designed and selected for the ability to disrupt the PD-L1/PD-L2/CTLA4/VISTA pathway plus one or more related pathways.

RESULTS

AUPM-170 does not inhibit other immune checkpoints

AUPM-170 inhibits the establishment of lung metastases in murine tumors

AUPM-170 exhibits anti-tumor efficacy in mice

AUPM-170 inhibits the growth of C576 colon carcinoma

AUPM-170 does not exhibit MC-38 anti-tumor efficacy in immune deficient SCID-BgH mice

Toxicology summary of AUPM-170


AUPM-170 targets both PD-L1 and PD-L2

AUPM-170 rescues IFN-γ expression in human T cells from PD-L1, PD-L2 or VISTA inhibition

Pharmacokinetic profile of AUPM-170

Short exposure results in sustained PD in vitro in human T cells

SUMMARY

We have identified AUPM-170, a novel dual-antagonist of PD-L1 and VISTA. AUPM-170 exhibits superior efficacy compared to the VISTA-mediated inhibition of T cell proliferation and IFN-γ production. AUPM-170 has been shown to 

- Durable DMF profile including oral bioavailability
- PD profile consistent with immune modulation in vivo
- Anti-tumor activity in multiple syngeneic tumor models

AUPM-170 exhibits flexible, oral administration and antagonism of PD-L1 and VISTA which may provide for improved or expanded clinical benefit in cancer patients.