1104 A SAFE AND HIGHLY POTENT PD-1-IL-2 FUSION (AWT020) THAT DECOUPLES THE EFFICACY AND TOXICITY OF IL-2 THERAPY

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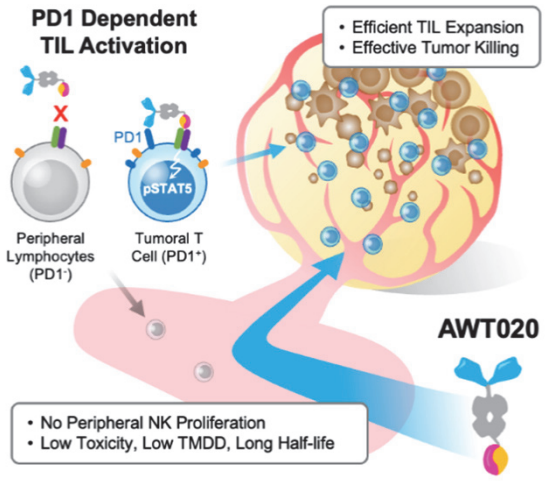
Background Interleukin 2 (IL-2) is a pivotal immune agonist for tumor immunotherapy that has demonstrated its clinical efficacies in melanoma and renal cell carcinoma. Nevertheless, its pleiotropic effect has led to severe side effects and its anti-tumor activity is compromised by its activation of regulatory T cells. In contrast, the PD-1 blockade-based cancer immunotherapy has good safety profiles by targeting and sustaining the activity of tumor-antigen specific T cells within cancer tissues. To take advantage of the complementary antitumor activity of PD-1 monoclonal antibody (mAb) and IL-2, a bifunctional fusion protein composed of PD-1 mAb and IL-2c mutein (AWT020) is designed to enhance the therapeutic efficacy while reducing the IL-2 related toxicity (figure 1).

Methods The in vitro activity of AWT020 was verified using STAT5 signaling assays and human PBMC proliferation assays. A mouse surrogate of AWT020 (mAWT020) was tested in multiple syngeneic tumor models including colon carcinoma models (MC38 and CT26), melanoma model (B16F10), and breast carcinoma model (EMT6). The tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AWT020 were accessed in cynomolgus monkeys.

Results AWT020 stimulated much greater pSTAT5 activation and proliferation in PD-1$^+$ T cells than PD-1$^-$ T cells. The high specificity of AWT020 on PD1+ T cells not only minimizes the systematic toxicity but also improved the anti-tumor efficacy. In PD-1 resistant B16F10 and EMT6 models, mAWT020 achieved >90% TGI, while in CT26 tumor, mAWT020 treatment achieved 70% complete response (CR). In MC38 model, mAWT020 achieved 100% CR with a single dose at 0.3 mg/kg. Cell phenotyping studies showed that mAWT020 specifically and significantly expands tumor-infiltrating CD8$^+$ T cells but has minimal effects on peripheral T cells and NK cells. Global gene expression profiling studies showed that mAWT020 significantly elevated expression levels of Cd3d, Cd3e, Cd8a, Il2rα, Cxcr3, Cxcr6, Zap70, Lck, and Pdcd1 inside tumor tissues, indicating a specific expansion and activation of T cells. Single dose study at up to 10 mg/kg in cynomolgus monkeys showed that AWT020 was well tolerated, with good exposure and long half-life.

Conclusions The high target specificity of AWT020 significantly mitigates the IL-2 related adverse side effects and allows it to be dosed at a much higher level compared to IL-2 therapy, achieving full blockade of PD-1 and optimal activation of intratumoral CD8$^+$ T cells.

Ethics Approval The protocol of animal studies has been reviewed and approved by IACUC.



Abstract 1104 Figure 1 MOA of AWT020
AWT020 is highly specific to tumor infiltrated T cells

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