Tumor-targeted T-Cell Activation via an Investigational PD-L1 x CD137 Bispecific Molecule

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Background
Blockade of the PD-1/PD-L1 axis can improve outcome in a variety of cancers. Yet, many patients, including subsets of patients with PD-L1+ tumors, do not benefit. The magnitude of immune activation promoted by PD-1/PD-L1 axis blockade can be further enhanced through concomitant T-cell co-stimulation such as that achieved through PD-L1 agonism; however, clinical applications of such an approach may be limited by toxicity associated with the systemic effects of PD-L1 agonists. Here we characterize PD-L1 and CD137 tumor expression supporting the development of a PD-L1 x CD137 bispecific molecule that provides PD-1 axis blockade coupled with tumor-targeted CD137 co-stimulation.

Methods
In situ hybridization (ISH) and multicolor flow cytometry was performed to characterize PD-L1 and CD137 expression in tumor biopsies. A PD-L1 x CD137 bispecific molecule (PD-L1 x CD137) was constructed based on PD-L1 blocking mAbs and CD137-engage mAbs and was evaluated for binding to respective antigens. Its functional activity was evaluated in CD3 or SDF-driven T-cell activation systems, MLB assays and tumor microenvironment models. Antitumor activity in vivo was evaluated in combination with tumor targeted anti-CD3 based bispecific DART® molecules.

Results
ISH revealed expression of PD-L1 in a significant proportion of surgically resected carcinomas; noteworthy, many such tumors contained CD137+ immune infiltrate adjacent to PD-L1+ cells. Moreover, ex vivo co-incubation of tumor and immune cells in the presence of PD-L1-based bispecifics or Fc-enhanced antibodies further induces PD-L1 and CD137 expression. PD-L1 + CD137 blocks and binds PD-L1, reversing PD-1-mediated T-cell inhibition equivalently to the effect of approved PD-L1 benchmark mAbs. It also binds CD137, but absent clustering supported by PD-L1+ cells, fails to induce CD137 signaling, in the presence of PD-L1-expressing cells, however, PD-L1 x CD137 drives CD137 activation and immune cell co-stimulation. Robust T-cell activation and cytokine secretion was induced by PD-L1 x CD137, with significantly greater activity than that observed with the combination of PD-L1 blocking and CD137 agonistic mAbs. Notably, when combined with tumor targeted immunotherapies, PD-L1 x CD137 supports enhanced activation of effector cells and anti-tumor activity.

Conclusions
These ex vivo data show that an investigational PD-L1 x CD137 bispecific can switch on CD137 co-stimulation in a PD-L1-dependent fashion. While tumor adaptive resistance via PD-L1 induction promotes tumor immune escape, PD-L1 x CD137 can exploit the checkpoint up-regulation by contributing a co-stimulatory signal in addition to checkpoint blockade. PD-L1 x CD137 provides a potential therapeutic approach to overcome limitations of existing PD-1/PD-L1-targeting strategies either as monotherapy or in combination with complementary immune based therapeutic modalities, such as CD3 based bispecifics or Fc-enhanced mAbs.

Rationale
PD-L1 and CD137 Expression in Non-small Cell Lung Cancer and Adjacent Normal Tissue

PD-L1 x CD137 Enhances Activation of Primary T Cells

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PD-L1 x CD137 Inhibits Tumor Growth in Combination with Redirected T-Cell Killing

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PD-L1 x CD137 in Non-human Primates

PD-L1 x CD137 Transiently Expands T Cells and NK Cells in Vivo

PD-L1 x CD137 Exploits Tumor Immune Adaptive Resistance and Enhanced T-cell Activation

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Conclusions
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