Abstract

PD1-Fc-OX40L is a first-in-class biologic derived from the Agonist Redirected Checkpoint (ARC)™ platform developed by Shattuck Labs. The ARC platform was developed to solve a fundamental challenge in cancer immunotherapy, which was to develop combination therapeutics that could block immune checkpoints (such as PD-1), while simultaneously activating Tumor Necrosis Factor (TNF) SuperFamily Receptors (such as OX40, 4-1BB, GITR and CD40).

Pre-clinical development and characterization has been completed, and demonstrated that PD1-Fc-OX40L is a potent immune agonist both in vitro and in vivo. The ARC binds immobilized PD-L1, PD-L2, and OX40 at 2.08, 1.76, and .246 nM affinities, respectively, and binds the respective ligands/receptor on cells in vitro and ex vivo. High binding affinity on both sides of the construct translated to potent stimulation of OX40 signaling and PD1:PD-L1/L2 blockade, in multiple in vitro assays, including improved potency as compared to pembrolizumab, nivolumab, talisizumab and combinations of those antibodies. Furthermore, when activated human T cells were co-cultured with PD1-L1 positive human tumor cells, PD1-Fc-OX40L was observed to concentrate within the immune synapse, which enhanced proliferation of T cells and production of IL-2, IFNγ and TNFα, leading to efficient killing of tumor cells. The therapeutic activity of PD1-Fc-OX40L in established murine tumors was superior to PD1 blocking, OX40 agonist, or combination antibody therapy. Importantly, all agonist functions of PD1-Fc-OX40L are dependent on Fc receptor cross-linking, due to the inherent trimeric and hexameric structure of PD1-Fc-OX40L.

The human drug product of PD1-Fc-OX40L, SL-279252, has completed both pre-clinical and non-clinical development, and a phase I trial in human cancer patients will begin by early 2019.

Summary

- ARCS are a novel class of bi-functional biologics capable of targeting type-I and type-II membrane proteins, and can target all checkpoint molecules and the entire family of TNFR superfamily receptors.
- >180 ARCs have been synthesized/characterized by Shattuck to date.
- PD1-Fc-OX40L can link checkpoint-blocking and T cell co-stimulation signals in the same microenvironment, at the time in which T cells are engaging cognate tumor antigens.
- PD1-Fc-OX40L has completed NHP GLP tox studies, is on track for a Nov 2018 IND submission, and is anticipated for first-in-man treatment Q1 2019.

Figure 1. ARC Platform. Advantages, examples of Type I/Type II target combinations, and relevant disease indications.

Figure 2. PD1-Fc-OX40L Mechanism of Action. (A) Immune suppressive signaling via PD-L1/PD-L2 can be blocked by the (B) PD1 domain of the ARC, while (C) simultaneously agonizing T cells via OX40L. At the same time T cells encounter tumor antigens – a MOA that the separate administration of two distinct antibodies cannot recapitulate.