LOCAL IMMUNOTHERAPY WITH INTASYL™ SELF-DELIVERING RNAi TARGETING CTLA-4 PROVIDES ROBUST TUMOR CONTROL IN VIVO

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Background Immune checkpoint inhibition (ICI) of CTLA-4 with ipilimumab has proven effective in improving clinical responses for patients with advanced melanoma or other approved indications in combination with nivolumab. However, systemic treatment with ipilimumab is associated with serious adverse events (SAEs) for many (>25%) patients that can be life-threatening and/or result in discontinuation of treatment. As such, balancing efficacy with associated toxicities remains a challenge in treating patients with ipilimumab.

Local intratumoral (IT) immunotherapy may enhance local activity and decrease systemic toxicity. Additionally, by using the tumor as its own vaccine, IT immunotherapy can ignite tumor-specific immune responses well beyond the local site of administration. While clinical testing of IT antibody therapies is underway, the high molecular weight properties of therapeutic antibodies may limit their local diffusion and retention time within tumors.

RNAi therapy is an emerging modality well-positioned to optimize local clinical application of ICI. We have previously demonstrated that self-delivering RNAi (INTASYL) therapeutic compounds built on proprietary INTASYL™ technology silence targets with high specificity and without need for specialized formulations or drug delivery systems and provide robust antitumor efficacy to both directly-treated and to non-directly treated distal tumors when delivered IT in vivo.

Here we present proof-of-concept (POC) in vivo data showing IT efficacy of a novel INTASYL targeting murine CTLA-4 (mCTLA-4; 27790) in two syngeneic mouse tumor models.

Methods CTLA4 mRNA silencing was validated in CHO K1 cells expressing murine CTLA-4 in vitro by RT-qPCR. For in vivo efficacy, Hepa1-6 or CT26 cells were implanted subcutaneously into the flanks of C57BL/6 or BALB/c mice, respectively. When tumors reached threshold volume (150 mm³), animals were randomized into treatment groups; treatments were administered on Days 1, 4, 7, 10 and 13. Vehicle (PBS), a chemically identical non-targeting control (NTC) INTASYL, or INTASYL 27790 at two dose concentrations were administered IT; anti-CTLA-4 monoclonal antibody (mAb; clone 9D9) was administered intraperitoneally (IP). Tumor volumes and body weights were recorded longitudinally.

Results mCTLA-4-targeting INTASYL 27790 provided concentration-associated silencing of mCTLA-4 in vitro. When administered IT, mCTLA-4-targeting INTASYL 27790 elicited robust dose-associated antitumor efficacy in both in vivo tumor models compared with vehicle- or NTC-treated tumors, comparable to that observed under systemic IP treatment with anti-CTLA4 mAb.

Conclusions These data show IT INTASYL targeting mouse CTLA4 elicits robust on-target dose concentration-associated antitumor efficacy in two syngeneic tumor models in vivo and provide POC for targeting CTLA-4 IT with INTASYL.

Ethics Approval Animal studies were performed at Pharma Models LLC, Marlborough, MA 01752, under standard protocol approved by their IACUC.