474 INTRATUMORAL CTLA-4-TARGETING INTASYL™ SELF-DELIVERING RNAI ENHANCES TUMOR CONTROL IN COMBINATION WITH SYSTEMIC ANTI-PD-1 ANTIBODY THERAPY IN VIVO SUGGESTING A STRATEGY TO MITIGATE IRSAES

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Background Combination immune checkpoint inhibition (ICI) of CTLA-4 and PD-1 provides superior therapeutic efficacy compared to each monotherapy in approved cancer indications. However, systemic anti-CTLA-4 and anti-PD-1 combination antibody therapy triggers immune related severe adverse events (irSAEs) that may be life-threatening and/or result in discontinuation of treatment. Managing irSAEs remains a challenge in realizing the full potential of anti-CTLA-4 plus anti-PD-1 combination ICI.

Local intratumoral (IT) administration of ICI represents a potential strategy to maintain efficacy while mitigating systemic irSAEs by limiting systemic exposure. However, the biophysical properties of antibodies make them ill-suited for local application.

RNAi is an emerging therapeutic modality well-suited for local application of ICI. We have previously demonstrated that compounds built on INTASYL™, Phio's proprietary self-delivering RNAi technology, silence their intended mRNA targets with precision specificity and without need for specialized formulations or drug delivery systems, providing robust antitumor efficacy when administered intratumorally in vivo.

Here we present proof-of-concept in vivo efficacy data supporting a novel approach to combination ICI; providing local CTLA-4-silencing via IT INTASYL in combination with systemic anti-PD-1 antibody therapy.

Methods CT26 cells (5e05) were implanted subcutaneously into bilateral flanks of BALB/c mice (N = 12/group). When tumors reached threshold volume (150 mm^3), animals were randomized into treatment groups; treatments were administered on Days 1, 4, 7, 10 and 13. Mice were administered IT vehicle (PBS; Group 1) or IT mCTLA-4-targeting INTASYL 27790 (Group 3; 2 mg/dose) to the left flank tumor only; anti-PD-1 (clone RMP1–14) was administered intraperitoneally (IP; Group 2 and Group 3). Tumor volumes and body weights were recorded longitudinally. N=4/group were euthanized on Day 15 for ex vivo immunophenotypic analyses.

Results Treatment with IP anti-PD-1 as monotherapy provided a small but significant inhibition of mean tumor growth. Adding IT INTASYL targeting mCTLA-4 in combination significantly enhanced tumor control (p = 0.0001) for treated tumors, inducing complete regression (CR) in 38% of treated tumors in comparison to 0% CR in mice treated with IT PBS or IP anti-PD-1 alone. The combination was well tolerated without significant impact on weight gain over the course of the study. Ex vivo analyses confirmed on-target activity and immunomodulatory effects.

Conclusions Here we present proof of concept efficacy data supporting IT CTLA-4-targeting self-delivering RNAi as a strategy for combination ICI with systemic anti-PD-1 inhibition. This approach may serve to limit irSAEs and realize the full potential efficacy of combination ICI targeting CTLA-4 and PD-1.

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