ONM-501, A POLYVALENT STING AGONIST, EXHIBITS ANTI-TUMOR EFFICACY WITH INCREASED TUMOR T-CELL INFILTRATION IN MICE AND IS WELL TOLERATED IN RATS AND NON-HUMAN PRIMATES

Background The Stimulator of Interferon Genes (STING) plays a crucial role in the innate immune response. Several small molecule STING agonists have demonstrated effectiveness against cancer in preclinical models. In clinical trials, however, they showed limited therapeutic efficacy. We developed ONM-501, a dual-activating STING agonist that employs PC7A, a synthetic polymer that induces polyvalent STING condensation and prolongs innate immune activation. ONM-501 encapsulates the endogenous STING agonist 2',3'-cGAMP with the PC7A micelles offering dual ‘burst’ and ‘sustained’ STING activation. The mechanism and effectiveness of ONM-501 as an immunotherapy against solid tumors has been demonstrated in multiple preclinical models. Here we report in vivo efficacy and pharmacodynamic (PD) analysis of ONM-501 as a monotherapy and in combination with anti-PD1 in multiple murine tumor models and the safety evaluation in rats and primates.

Methods Anti-tumor efficacy of ONM-501 was evaluated by tumor growth inhibition and survival in tumor-bearing mice as a monotherapy or combined with anti-PD1. Immune activation and tumor microenvironment changes were evaluated by FACS analysis in tumors and draining lymph nodes and cytokine analysis in peripheral blood. STING activation was evaluated by expression of IFNB1, IRF7 and CXCL10 in tumors and draining lymph nodes using qPCR. Safety and tolerability were evaluated in rats and primates by single- and multiple-dose subcutaneous injections in naïve animals up to the highest feasible dose.

Results ONM-501 demonstrated broad anti-tumor efficacy both as monotherapy and combined with anti-PD1 in multiple models including A20, CT26, MC38 and B16F10. FACS analysis showed significantly increased tumor-infiltrating T-cells after ONM-501 mono- and combo- therapies in the B16F10 tumors. ONM-501 upregulated PD-L1 expression in tumor tissue. STING activation was confirmed by the increased IRF7 and CXCL10 mRNA levels in tumor and draining lymph nodes after monotherapy and anti-PD-1 combination. In the single- and multiple-dose toxicity studies, Sprague-Dawley rats and cynomolgus monkeys were well tolerated without severe or irreversible systemic toxicities up to the maximum feasible dose (30mg/kg). Dose-dependent increases in lymphocytes and cytokines, consistent with STING activation, were also observed.

Conclusions ONM-501 demonstrated marked anti-tumor efficacy as a monotherapy and in combination with anti-PD1 in murine syngeneic tumor models. The in vivo PD analysis confirmed STING activation, enhanced tumor T-cell infiltration and PD-L1 upregulation by ONM-501. Toxicology studies in rats and primates demonstrated a strong safety profile and large therapeutic window. The novel dual STING agonist ONM-501 is a promising therapeutic candidate for clinical evaluation in solid tumors.

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REFERENCES

Ethics Approval All animal experiments were performed with ethical compliance and approval from Institutional Animal Care and Use Committee of the University of Texas Southwestern Medical Center, Labcorp Early Development Laboratories Inc and ITR Laboratories Canada Inc.