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

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 # 1155

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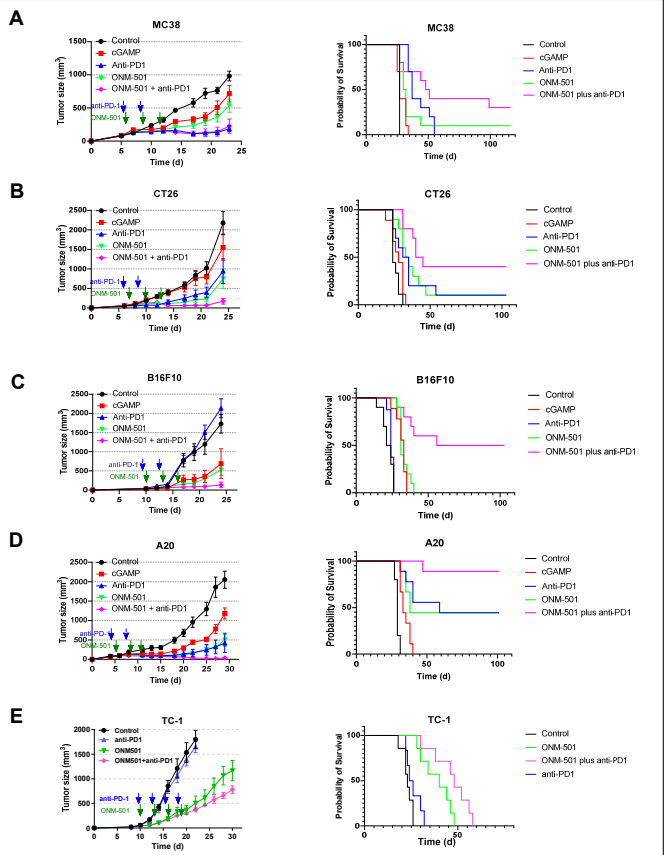
Introduction

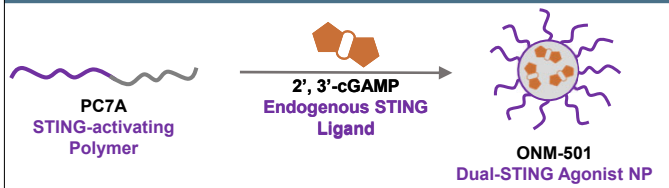
The Stimulator of Interferon Genes (STING) plays a crucial role in the innate immune response. Several small molecule STING agonists have demonstrated effectiveness against cancer in preclinical models. In clinical trials, however, they showed limited therapeutic efficacy. We developed ONM-501, a dual-activating 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 within 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 PD and safety evaluation in rats and primates.

ONM-501 shows anti-tumor efficacy in multiple syngeneic tumor models as monotherapy and in combination with anti-PD1



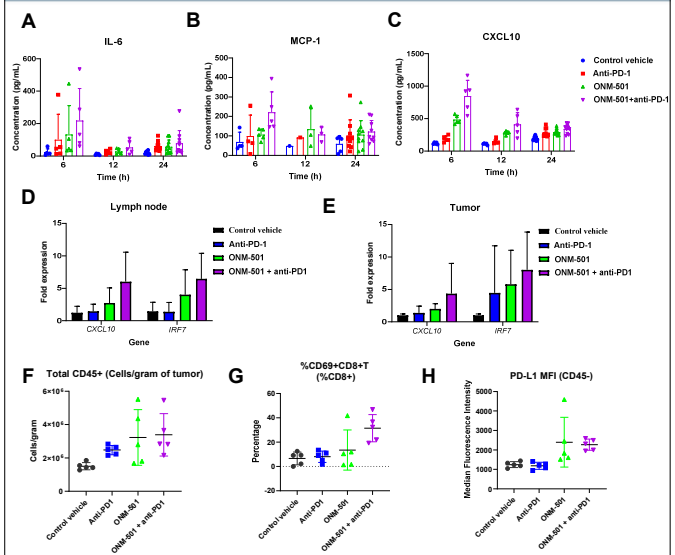
ONM-501 demonstrated single-agent tumor growth inhibition and survival improvement in both aPD1-sensitive MC38 **(A)** CT26 **(B)** and A20 **(D)** models and aPD1-resistant B16F10 **(C)** and TC-1 **(E)** models. The combination of ONM-501 and aPD1 demonstrated markedly improved therapeutic outcomes compared with monotherapies in all 5 models including durable remission/long-term survival over 100 days in 3/10, 4/10, 5/10 and 8/10 animals in MC38, CT26, B16F10 and A20 models, respectively

Schematic illustration of ONM-501



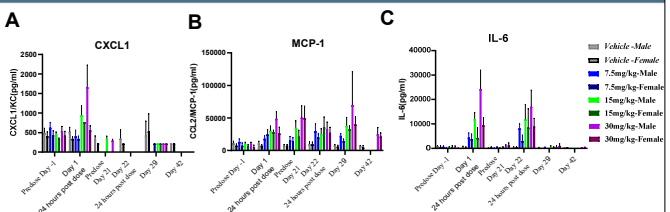
ONM-501 encapsulates endogenous cGAMP within PC7A micelles. PC7A is a pH-sensitive synthetic polymer that induces polyvalent STING condensation and prolonged innate immune activation

ONM-501 induces STING activation and TIL increases in B16F10 syngeneic tumor model as monotherapy and in combination with anti-PD1



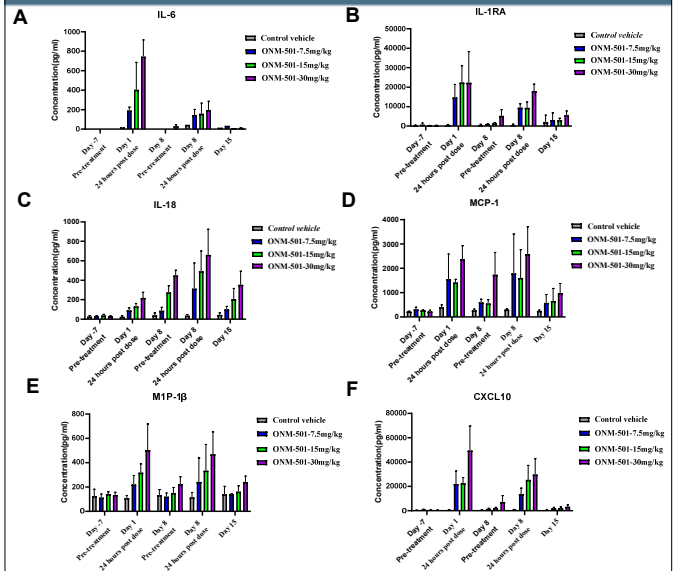
Increased circulating cytokines IL-6 **(A)**, MCP-1**(B)** and CXCL10 **(C)** were observed at 6-24h after IT injected 50μg ONM-501 (Q3Dx2) and/or 200μg IP-injected anti-PD1 (Q3Dx2) in B10F10 tumor-bearing mice. qPCR analysis of *CXCL10 and IRF7* gene expression in draining lymph nodes **(D)** and tumors **(E)** showed increased expression of both genes in ONM-501 and combo group 24h after last dose. Flow cytometry analysis of tumor tissue showed increased CD45+ total lymphocyte infiltration **(F)**, increased percentage of CD69+ (activated) CD8+T cell population **(G)** and increased PD-L1 expression in CD45- (tumor) cells **(H)** with ONM-501 monotherapy and combo therapy with anti-PD1.

ONM-501 induces dose-dependent cytokine response in rats



In a 4-week repeat-dose GLP-compliant toxicology study in rats with 4-week recovery period, 4 x QW SC injections of 7.5-30mg/kg ONM-501 was administered in naïve male and female SD rats. Dose-dependent and reversible increases in circulating levels of CXCL1**(A)**, MCP-1 **(B)** and IL-6 **(C)** were observed in both sexes following dosing, consistent with the STING-activating activity of ONM-501.

ONM-501 induces dose-dependent cytokine response in non-human primates



In a 2-week repeat-dose toxicology study, 2 x QW SC injections of 7.5-30mg/kg ONM-501 was administered in naïve cynomolgus monkeys. Dose-dependent and reversible increases in circulating levels of IL-6 **(A)**, IL-1RA **(B)**, IL-18 **(C)**, MCP-1 **(D)**, MIP-1ß **(E)** and CXCL10 **(F)** were observed following dosing, consistent with the STING-activating activity of ONM-501.

ONM-501 demonstrates a strong safety profile in preclinical models

The highest tolerated SC doses in different species

Species	Mice	Rats	Monkeys
MTD (**HED**) (mg/kg) in single-dose studies	74 (**6**)	45 (**7.3**)	30 (**9.7**)
HNSTD (**HED**) (mg/kg/dose) in 2-week QW dosing studies	-	30 (**4.8**)	30 (**9.7**)
HNSTD (**HED**) (mg/kg/dose) in 4-week, QW dosing GLP studies	-	30 (**4.8**)	(TBD)

MTD: maximum tolerated dose; HNSTD: highest non-severely toxic dose; HED: human equivalent dose; QW: once weekly

The toxicity profile of ONM-501 was evaluated in mice, rats and monkeys in several toxicology studies using SC injection as a surrogate for IT injection in healthy animals. The highest tolerated doses in each species and their human equivalent doses are summarized in the table.

The average efficacious IT dose of ONM-501 in mice is ~0.001mg/dose/(mm³ of tumor), assuming similar activity with the same local drug concentration, the estimated efficacious dose in a minimally injectable human tumor of 10mm in diameter would be ~0.5mg/dose, or 0.007mg/kg/dose in a 70 kg adult, indicating a large potential therapeutic window and safety margin in the proposed first-in-human clinical study of ONM-501.

Summary

ONM-501 demonstrated marked anti-tumor efficacy as a monotherapy and in combination with anti-PD1 in multiple immune "hot" and "cold" murine syngeneic tumor models. The in vivo PD analysis confirmed STING activation, enhanced tumor lymphocyte infiltration and tumor PD-L1 upregulation by ONM-501. Toxicology studies in rats and primates demonstrated PD activity consistent with STING activation and 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.

Acknowledgment

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