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ONM-501 - A polyvalent STING agonist for oncology immunotherapy

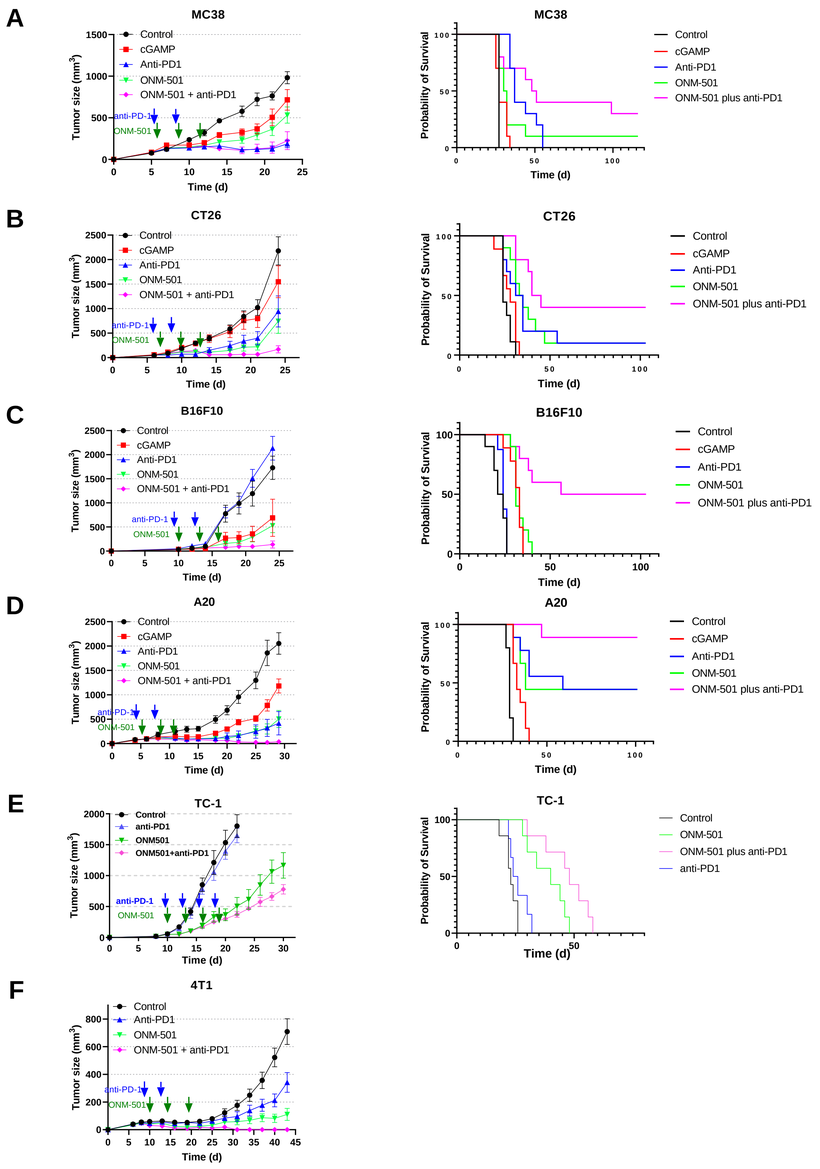
Suxin Li[1], Jian Wang[1], Jonathan Wilhelm[1], Qingtai Su[2], Gaurav Bharadwaj[2], Jason Miller[2], Wei Li[1], Katy Torres[1], Zirong Chen[2], Ruolan Han[2], Tian Zhao[2], Jinming Gao[1,2]

[1]Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX 75390
[2]OncoNano Medicine, Inc., Southlake, TX 76092

Introduction

The stimulator of interferon genes (STING) plays a central role in innate immune response against infection and cancer. Several cyclic di-nucleotide (CDN) and non-CDN small molecule STING agonists have demonstrated effectiveness against cancer in preclinical animal models, however their clinical trials showed limited therapeutic efficacy. ONM-501, a dual-activating STING agonist employs PC7A, a synthetic polymer that induces polyvalent STING condensation and prolongs innate immune activation has been recently developed. ONM-501 encapsulates the endogenous STING agonist cGAMP with the PC7A micelles offering dual 'burst' and 'sustained' STING activation. The mechanism and effectiveness of intratumorally delivered ONM-501 as an immunotherapy against solid tumors has been demonstrated in preclinical models.

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

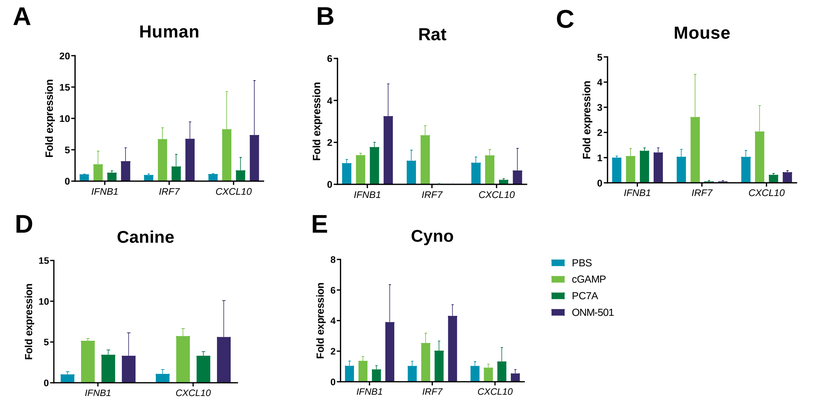


The mean tumor volume and Kaplan-Meier survival curves demonstrate ONM-501 has antitumor efficacy both as a monotherapy and in combination with anti-PD1 in MC38 colorectal model **(A)**, CT26 colon tumor model **(B)**, B16F10 melanoma tumor model **(C)**, A20 B cell lymphoma **(D)**, TC-1 E6/E7 HPV-related tumor model **(E)**, and 4T1 triple negative breast tumor model **(F)**. (Note: the survival curve data of ONM-501 treatment in 4T1 tumor model is not available because the mice were sacrificed on Day 42)

Schematic illustration of ONM-501

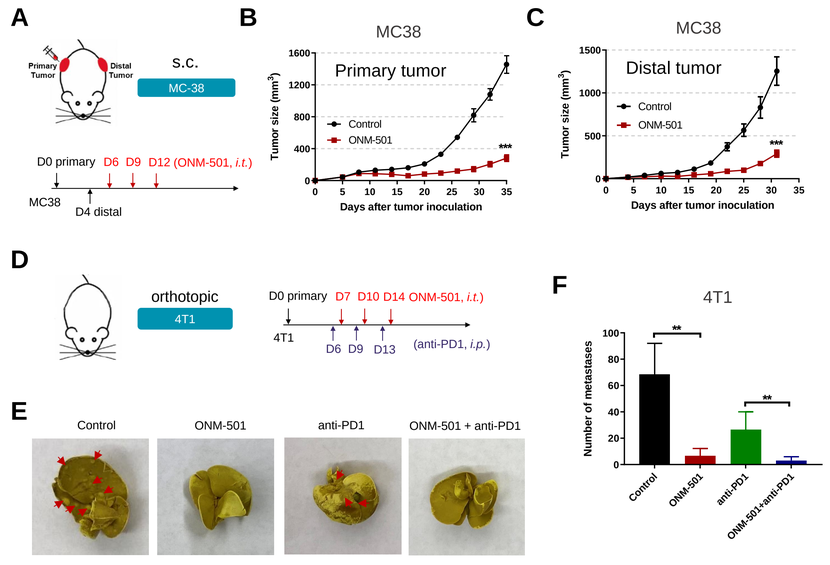
ONM-501 encapsulates endogenous cGAMP with PC7A. PC7A is a synthetic polymer that induces polyvalent STING condensation and prolongs innate immune activation

ONM-501 induces STING activation across different species



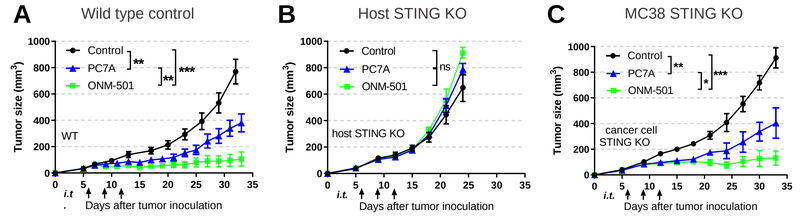
Analysis of *IFNB1*, *IRF7*, and *CXCL10* gene expression in human PBMC **(A)**, Sprague Dawley rat PBMC **(B)**, C57BL/6 mouse PBMC **(C)**, canine (beagle) PBMC **(D)** and cynomolgus monkey PBMC **(E)** were performed by TaqMan RT-qPCR after 24 h treatment with PBS, 2'3'-cGAMP, PC7A, and ONM-501. Fold expression was compared to *GAPDH* housekeeping gene (*n=5*).

ONM-501 provides systemic abscopal effect in animal studies



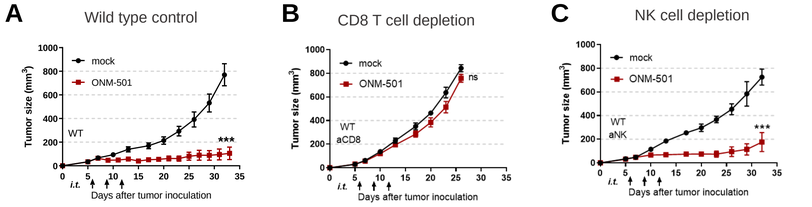
Tumor model and dose regimen for ONM-501 treatment in MC38 tumor model **(A)**; ONM-501 inhibits both MC38 primary tumor growth **(B)** and distal tumor growth **(C);** Dose regimen for ONM-501 treatment as monotherapy or in combination with anti-PD1 antibody in 4T1 metastatic tumor model **(D)**; ONM-501 treatment significantly reduces 4T1 lung metastasis **(E, F)**.

ONM-501 mediated anti-tumor efficacy is host STING dependent



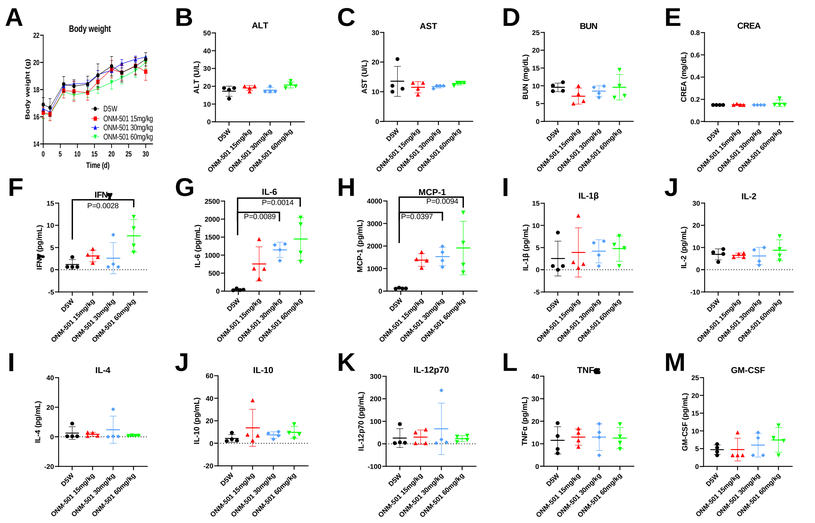
Treatment by PC7A NP and ONM-501 shows completely blocked anti-tumor efficacy in host STING-KO mice with WT MC38 cells **(B)**, but not in WT mice with both WT **(A)** and STING-KO MC38 cells **(C)**.

ONM-501 mediated anti-tumor efficacy is CD8 T cell dependent



Tumor growth curves were measured in wild type mice (inoculated with wild type MC38 cells) with control **(A) ,** anti-CD8 blockade **(B)**, and with anti-NK1.1 blockade **(C)**. Blockade of CD8 T cells completely abolished the anti-tumor efficacy **(B)** whereas blockade of NK cells showed minimal effect **(C)**.

The pilot maximum tolerable dose studies demonstrate ONM-501 was well tolerated with no noticeable adverse effects



No body weight differences were observed **(A)** , no significant changes in ALT, AST,BUN and CREA **(B-E)** no significant changes in, IL-1b, IL-2, IL-4, IL-10, IL-12p70, TNFα or GM-CSF **(I-M)** at all timepoints**,** acute increases in IFNγ, IL-6 and MCP-1 at 6h (**F-H**) and 24h (not shown), which return to control levels at D30 (data not shown). Histology of major organs showed no signs of toxicity in all groups (data not shown)

Summary

ONM-501 demonstrated pronounced anti-tumor efficacy in a panel of syngeneic tumor models. The anti-tumor effect was mediated by host STING and dependent on CD8+ T cells but not NK . These results support further evaluation of ONM-501 as a clinical candidate for the potential treatment of solid tumors.

References

[1] Li S, et al. Nature Biomedical Engineering. 2021;5: 455-466.
[2] Bennett Z, et al. Seminars in Immunology. 2021; p.101580.

Acknowledgment

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