TPS2693 A Phase 1 Dose-escalation and Expansion Study of an Intratumorally Administered Dual STING Agonist (ONM-501) Alone and in Combination with Cemiplimab in Patients with Advanced Solid Tumors and Lymphomas

Foldi, Julia, MD/PhD[1], Villaruz, Liza C., MD[1], Beane, Joal D., MD[5], McArthur, Heather, MD[3], Wagner, Patrick, MD[4], Gandhi, Chintan, MD[7] Luke, Jason J., MD[1], Jonathan, Euodia[6], Ostrander, Brian MS[6], Krishnan, Kartik, MD/PhD[6], Piha-Paul, Sarina A., MD[2]

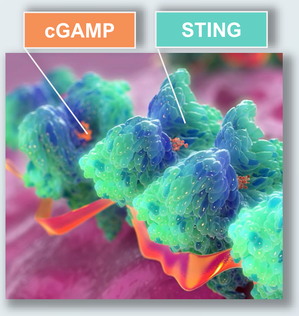
[1]Department of Hematology/Oncology, Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, PA
[2]Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX
[3]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX
[4]Department of Surgery, Division of Surgical Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA
[5]Department of Surgery, Division of Surgical Oncology, The James Cancer Hospital and Solove Research Institute Wexner Medical Center, The Ohio State University, Columbus, OH
[6]OncoNano Medicine Inc, Southlake, TX
[7]BRCR Medical Center Inc., BRCR Global, Tamarac, FL

BACKGROUND

STING - a Compelling Immuno-Oncology Target

The Stimulator of Interferon Genes (STING) pathway has garnered significant interest as a potential target for anticancer interventions due to its role in driving the production of pro-inflammatory cytokines and activating robust tumor-specific cell killing. Cyclic dinucleotides such as cGAMP, the endogenous STING agonist, are not ideal clinical candidates for exogenous routes of delivery. Early trials showed limited efficacy with unadulterated cGAMP due to rapid enzymatic degradation and clearance rates, cell membrane impermeability, and off-target toxicity. Thus, there is a need for improved methods for delivery and activation of the STING pathway. ONM-501 is comprised of a STING-activating pH-sensitive PC7A polymer conjugated with cGAMP. At physiologic pH, ONM-501 forms a micelle capable of preventing degradation of cGAMP. In the acidic tumor microenvironment, ONM-501 effects STING agonism through a multi-faceted mode of action: 1) endocytosis of nanoparticles and pH-activated micelle dissociation and payload release in endolysosomes enhances intracellular delivery of cGAMP 2) the combination of cGAMP canonical binding, and PC7A polymer noncanonical binding on STING protein yields synergistic STING activation and 3) stabilization of the STING poly-condensate by PC7A polymers delays STING degradation and prolongs STING activation. In pre-clinical models, these factors combine to help generate a stronger and more prolonged innate immune response that more effectively translates to a robust adaptive immune response. Herein, ONM-501 is being investigated in this first-in-human Phase 1 trial as an intratumorally-delivered monotherapy and combination therapy with the anti-PD1 antibody, cemiplimab, for patients with solid tumors and lymphomas.

ONM-501 – Mechanism of Action



ONM-501 is a dual-activating STING agonist comprised of:

1. **OMNI™:** proprietary bioactive pH-sensitive polymer tailored to bind to a non-canonical site that activates STING
   - Polyethylene glycol (PEG)
   - Poly (methyl methacrylate) (PMMA)
2. **cyclic GMP-AMP (cGAMP):** endogenous STING agonist, loaded into micelles as payload.

ONM-501 affects STING agonism through:

- Endocytosis of nanoparticles
- pH-activated micelle dissociation and payload release in endolysosomes enhancing intracellular delivery of cGAMP

- Combination of cGAMP canonical binding and PC7A polymer noncanonical binding on STING protein yielding synergistic STING activation

- Stabilization of the STING poly-condensate by PC7A polymers delaying STING degradation and prolongs STING activation

STUDY OBJECTIVES

Primary Objectives

1. **Part 1 – Monotherapy and Combination Therapy Dose Escalation**
   - To determine the maximum tolerated dose (MTD), minimum effective dose (MED) and/or recommended dose for expansion (RDE) of intratumoral ONM501 as a monotherapy and in combination with cemiplimab
   - To evaluate the safety and tolerability of intratumoral ONM-501 as a monotherapy and in combination with cemiplimab
2. **Part 2 – Dose Expansion Cohorts**
   - To establish the optimal RDE and schedule of intratumoral ONM-501 in combination with cemiplimab
   - To further evaluate the safety and tolerability of intratumoral ONM-501 in combination with cemiplimab

Secondary Objectives

Secondary objectives are to characterize the plasma pharmacokinetics (PK) and systemic or intratumoral pharmacodynamics (PD) of ONM-501 monotherapy and in combination with cemiplimab; and in Part 2 to evaluate the preliminary antitumor activity of ONM-501 in combination with cemiplimab in terms of Objective Response Rate (ORR) and Duration of Response (DOR) using RECIST v 1.1, as well as Progression Free Survival (PFS) and Overall Survival (OS) in homogenous indication-specific expansion cohorts.

STUDY DESIGN

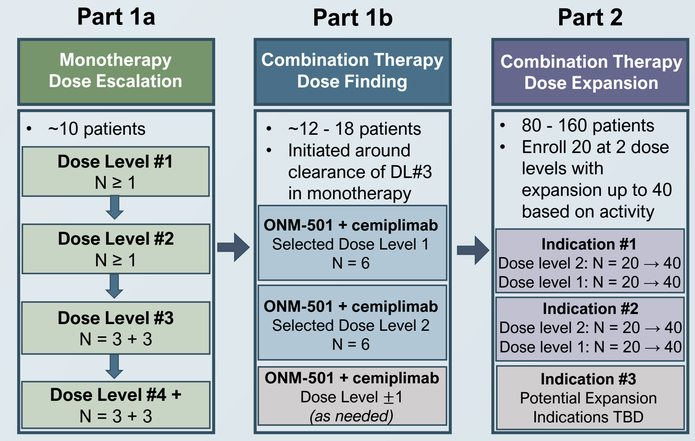
NCT06022029 is a first-in-human, open-label, multi-center global clinical trial. Adult patients with solid tumors or lymphomas that are **advanced, non-resectable, recurrent, or progressing** and have **a minimum of one injectable lesion are eligible for this study.**

Study Treatment:

ONM-501 is administered intratumorally once per week for three weeks (21 days), followed by three weeks without injection.
- ONM-501 starting dose 600 µg

Cemiplimab is administered intravenously during combination therapy arms according to standard administration protocol, once every three weeks
- 350 mg over 30 minutes every three weeks

Figure 1. ON-5001 Study Design



KEY ELIGIBILITY CRITERIA

Inclusion

- Patients aged ≥ 18 years with histologically confirmed advanced, nonresectable, or recurrent and progressing solid tumors or lymphomas
- Measure disease per RECIST v 1.1 criteria
- A minimum of one injectable lesion, accessible for intratumoral injection
- ECOG PS 0-1
- Adequate organ function

Exclusion

- Other malignancy active within the previous 2 years except for basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast that has completed curative therapy
- Brain metastases that are untreated or in the posterior fossa or involve the meninges. Other stable or previously treated progressing brain metastases may be permitted on a case-by-case basis
- High bleeding risk as determined by the investigator
- Major cardiovascular event within 6 months prior to study drug administration

STUDY ENDPOINTS

Table 1. Primary and Secondary Endpoints

Primary Endpoints	Secondary Endpoints
➢ Safety: • Dose limiting toxicities (DLTs) • Treatment Emergent Adverse Events (TEAEs) including Severe Adverse Events, and TEAEs leading to discontinuation or death • Maximum Tolerated Dose (MTD) • Minimum Effective Dose (MED)	➢ Pharmacokinetics (PK): • cGAMP and PC7A polymer ➢ Pharmacodynamics (PD): • Plasma IL-6, IL-12, IP-10, IL-1β, TNFα ➢ Immunohistochemistry of CD8, CD4 T-cells in pre and post treatment biopsies ➢ Antitumor activity based upon RECIST v 1.1

STUDY SITES

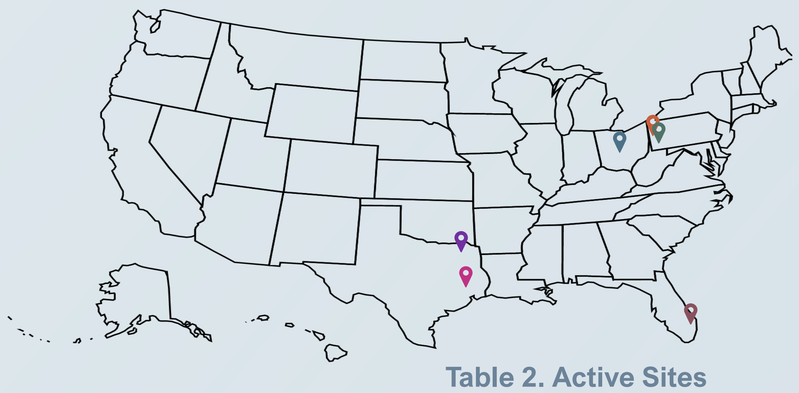


Table 2. Active Sites

Active Study Sites		
MD Anderson Cancer Center Houston, Texas	University of Pittsburgh Medical Center Hillman Cancer Center Pittsburg, Pennsylvania	Ohio State University Comprehensive Cancer Center Columbus, Ohio
University of Texas Southwestern Medical Center Dallas, Texas	Allegheny Health Network Pittsburgh, Pennsylvania	BRCR Global Tamarac, Florida

COMING SOON…

ADDITIONAL SITES

We are opening the combination escalation and dose expansion cohorts to additional sites in the United States and Australia:

Table 3. Additional Sites

Country	Additional Sites
United States	5 to 10
Australia	5 to 10

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