Abstract #CT213

A multicenter phase 1a/b study of NG-350A, a tumor-selective anti-CD40-antibody expressing adenoviral vector, and pembrolizumab in patients with metastatic or advanced epithelial tumors (FORTIFY)

Tom Lillie,[1] Mark O'Hara,[2] Christian Ottensmeier,[3] Eileen Parkes,[4] Lee Rosen,[5] David Krige,[1] Marya Chaney,[6] Jo Carter,[1] Vladimir Evilevitch,[1] Matthew Thomas,[1] Aung Naing[7]

[1]PsiOxus Therapeutics Ltd, Abingdon, Oxford, UK; [2]University of Pennsylvania Abramson Cancer Center, Philadelphia, PA, USA; [3]Liverpool Head and Neck Centre, Institute of Systems, Molecular and Integrative Biology, University of Liverpool & Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, UK; [4]Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, Headington, Oxford, UK; [5]UCLA Division of Hematology-Oncology, Santa Monica, CA, USA; [6]Merck & Co., Inc, Kenilworth, NJ, USA; [7]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

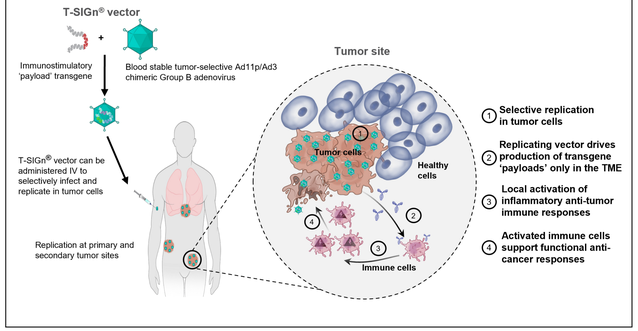
Background

- The efficacy of immune checkpoint inhibitors is often limited by the immunosuppressive tumor microenvironments (TME) seen in advanced cancers
- Stimulating CD40 is a promising mechanism to overcome treatment resistance; however, on-target toxicity including cytokine release syndrome (CRS) and liver enzyme elevations limits systemic dosing and efficacy[1–3]

T-SIGn® platform vectors

- T-SIGn (Tumor-Specific Immuno Gene) vectors are designed to drive sustained re-programming of immunosuppressive tumors by selectively expressing immunotherapeutic proteins (**Figure 1**)
  - This approach allows tumor localised production of combination therapeutics, helping convert tumors from a "cold" to "hot" phenotype without inducing systemic immune-related toxicities

Figure 1. T-SIGn vectors combine systemic IV delivery with localized activity

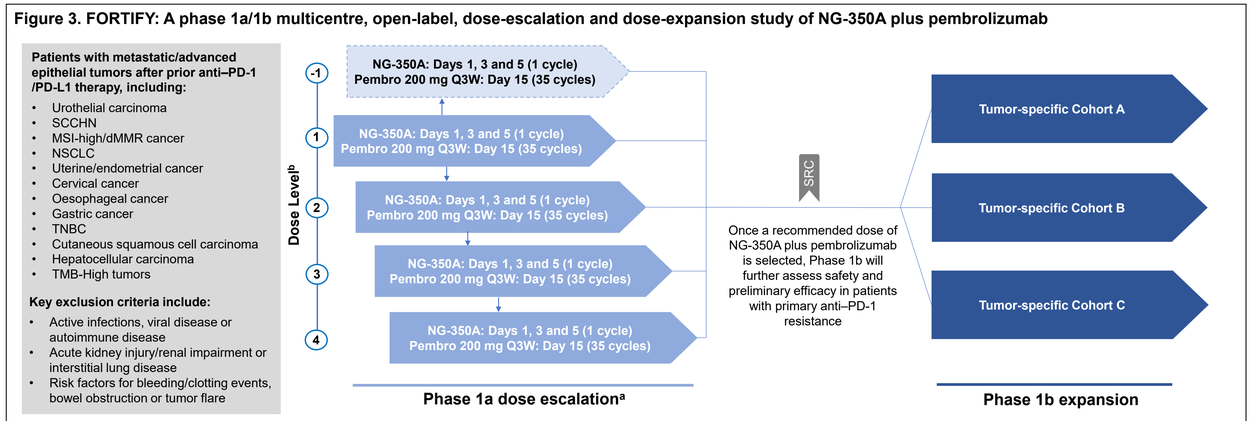


- Phase 1 trials of the unarmed T-SIGn vector enadenotucirev demonstrated a manageable toxicity profile when given IV as a monotherapy or with programmed death-1 (PD-1) checkpoint inhibitors[4-6]

NG-350A

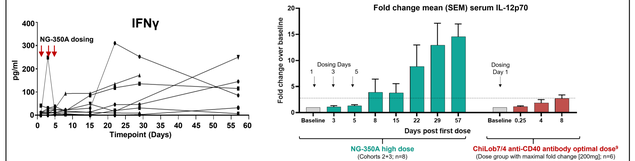
- NG-350A is a novel T-SIGn vector that expresses a fully human agonistic IgG anti-CD40 antibody to promote innate and adaptive immune responses
- The action of NG-350A is designed to re-program "cold" TMEs to allow functional anti-cancer immune responses while avoiding systemic toxicity
- Data from an ongoing first-in-human study (FORTITUDE; NCT03852511) have shown promising tolerability and translational results for NG-350A[7]
  - Prominent, sustained and dose-dependent elevations in IL-12, IFNγ, IL-17a, IL-2 and IFNα2 were observed with IV NG-350A, consistent with the mechanism of action (MoA) of anti-CD40 in stimulating TME re-programming (**Figure 2**)
  - No toxicity consistent with systemic exposure to anti-CD40 agonists was observed, with no Grade ≥3 CRS or liver toxicity

Figure 3. FORTIFY: A phase 1a/1b multicentre, open-label, dose-escalation and dose-expansion study of NG-350A plus pembrolizumab



[a]Bayesian optimal interval design. [b]Starting dose to be determined based on the FORTITUDE study. Abbreviations: dMMR; deficient mis-match repair; MSI=microsatellite instability; NSCLC=non-small cell lung cancer; pembro=pembrolizumab; SCCHN=squamous cell carcinoma of the head and neck; SRC=safety review committee; TMB=tumor mutation burden; TNBC=triple negative breast cancer; Q3W=every three weeks

Figure 2. NG-350A induces sustained increases in inflammatory cytokines



Data shown from evaluable patients from IV Cohorts 2 and 3 of FORTITUDE (1 x 10^{12} on D1 then either 3 x 10^{12} or 6 x 10^{12} on D3 and 5).

Pembrolizumab

- Pembrolizumab is a potent PD-1 checkpoint inhibitor that is approved for the treatment of a range of advanced malignancies
  - PD-1 blockade can enhance the activation and infiltration of effector T cells[8]
- Pembrolizumab and NG-350A have complementary immunostimulatory MoAs, with the potential to reverse immunosuppressive TMEs resistant to monotherapy

FORTIFY study design

- The FORTIFY (NCT05165433) study design is shown in **Figure 3**
- Patients will receive three doses of IV NG-350A in cycle 1, followed by fixed-dose pembrolizumab for up to 35 cycles
- Key study objectives are shown in **Table 1**
- Pharmacodynamic outcomes will be assessed using tumor tissues and blood
  - Analyses of tumor tissue (serial biopsies at baseline and Day 15 of cycles 1-3 [cycles 1-2 only in phase 1b]) will explore virus replication, transgene expression and immune/inflammatory responses
  - Analyses of serial blood samples will explore cytokine production and changes in peripheral immune cell subsets
- Tumor imaging will be performed every 8 weeks and assessed per RECIST 1.1 and iRECIST

Table 1. Key study objectives

Co-primary
– To characterize the safety and tolerability of NG-350A in combination with pembrolizumab in patients with metastatic or advanced epithelial tumors
– To determine the recommended dose of NG-350A in combination with pembrolizumab for further development
Secondary
– To explore the preliminary anti-tumor activity of NG-350A in combination with pembrolizumab in patients with metastatic or advanced epithelial tumors

Enrolment and study sites

- Up to 30 patients will be enrolled in phase 1a
- Enrolment is due to begin shortly
- Five sites are currently included in the study, with further Investigators sought

The Clatterbridge Cancer Centre NHS Foundation Trust
Oxford University Hospitals NHS Foundation Trust
University of Pennsylvania Abramson Cancer Center
UCLA Medical Center
MD Anderson Cancer Center

References

1. Vonderheide RH. *Clinical Cancer Res.* 2007;13:1083–8. **2.** Li DK and Wang W. *Oncol Lett.* 2020;20:176. **3.** Fibert EL, Björck PK et al. *Cancer Immunol Immunother.* **4.** Machiels J-P, Salazar R et al. *J Immunother Cancer* 2019;7:20. **5.** Garcia-Carbonero R, Salazar R et al. *J Immunother Cancer.* 2017;5:71. **6.** Fakih M, Wang M et al. *Ann Oncol* 2019;30:V231. **7.** Naing A, Rosen L et al. *Ann Oncol.* 2021;31:S853–4. **8.** Curran MA, Montalvo W et al. *Proc Natl Acad Sci USA.* 2010;107:4275–80. 9. Johnson P, Challis R et al. *Clin Cancer Res.* 2015;21:1321–8.

Acknowledgments

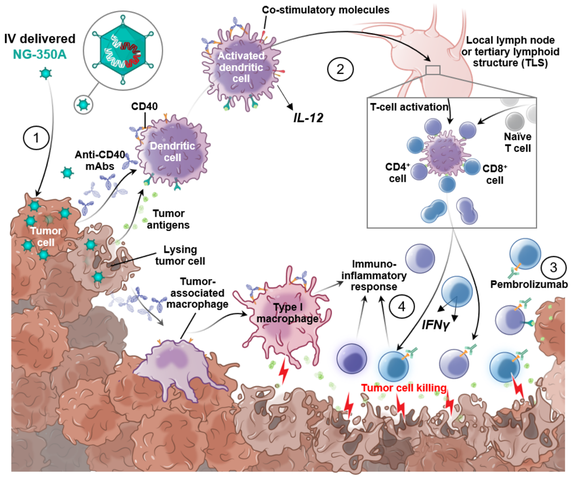
- This study was sponsored by PsiOxus Therapeutics Ltd, in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Editorial assistance was provided by Lola Parfitt of PsiOxus Therapeutics Ltd.

Disclosures

- MT is an employee of PsiOxus Therapeutics Ltd.

- NG-350A is a novel transgene-armed vector that selectively replicates in tumor cells and expresses an agonistic anti-CD40 antibody
- In a phase 1 trial, IV NG-350A drove sustained and dose-dependent cytokine responses consistent with the activity of CD40 agonists, without evidence of CD40-mediated toxicity
  - These data provided initial evidence that NG-350A can drive local immunological tumor changes while avoiding systemic toxicity
- Given the complementary MoA of NG-350A and pembrolizumab we designed a study to further assess the safety, tolerability and preliminary efficacy of combination therapy
- The FORTIFY study will assess NG-350A plus pembrolizumab for advanced cancers that have previously been treated with an anti–PD-1/L1 agent
  - Co-primary objectives are to assess safety and tolerability and to determine a recommended dose
  - Anti-tumor activity and pharmacodynamic effects of NG-350A on tumor re-programming will be assessed

NG-350A + pembrolizumab: proposed MoA



1. **NG-350A replicates only in tumor cells; anti-CD40 produced in the TME**
2. **Anti-CD40 activates dendritic cells and macrophages, leading to IL-12 production and anti-tumor CD4+ and CD8+ T cell activation**
3. **Pembrolizumab blocks PD-1 on T cells to prevent negative regulation by tumor cells**
4. **Activated and functional T-cells secrete IFNγ and drive immuno-inflammatory responses and tumor cell killing**