**FORTITUDE – A phase 1 study of NG-350A, a novel tumour-selective adenoviral vector expressing an anti-CD40 agonist antibody: monotherapy dose escalation results**

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**Background**

1. Stimulating CD40 has been considered a promising mechanism to drive antitumour immunity and to reverse immunosuppressive ‘cold’ TMEs to ‘hot’ immune-inflamed environments.
2. NG-350A is a novel transgene-armed T-SIGn vector (Tumor-Specific ImmunoGene Therapy (T SIG), expressing a fully human IgG2 anti-CD40 Ab

**Results – Monotherapy dose escalation**

**Exposure and demographics**

- At data cut-off (May 2021), 35 patients had been treated with NG-350A monotherapy (20 IV, 15 IT).

**Safety and tolerability**

- No dose-limiting toxicities (DLTs) occurred at either IT Dose Level 1 (DL1) or IT Dose Level 2 (DL2).

**Objective**

- To assess the safety and pharmacodynamic effects of NG-350A, including TCR repertoire, in patients resistant to prior anti–PD-1/PD-L1 therapy.

**Methods**

**FORTITUDE (NCT03252311)** is a phase 1/2 open-label dose-escalation study of NG-350A with or without pembrolizumab in patients with metastatic or advanced epithelial tumours. In phase 1, monotherapy received either intratumoural (IT) or intravenous (IV) delivery, according to the design in Figure 1.

**Figure 1. FORTITUDE Phase 1Dose Escalation Design**

- **Percentage of patients with TCR repertoire changes**
- **In patients administered NG-350A IV, blood samples were taken for cytokine assessments at D1, 3, 5, 8, 11, 14, 17, 20, 24, 27, and 34.

**Pharmacodynamics and serum cytokine profile**

- **Dose-dependent increases in IL-12 (100 pg/ml and >5x baseline) were detected in patient cohorts treated with NG-350A IV Dose Level 2 and IV Dose Level 3 (100 pg/ml and >5x baseline) were detected in patient cohorts treated with NG-350A IV Dose Level 3.**

**TCR repertoire**

- **TCR repertoire in blood was assessed for 4 patients following NG-350A administration.**

**Table 3. Specific cytokines/sterokine responses following NG-350A administration**

- **As shown in Figure 3, similar increases in these cytokines were not observed with IT dosing or with the empty vector (enadenotucirev).**

**Discussion**

- **In this phase 1 trial, NG-350A was well-tolerated with most AEs consistent with anti-CD40 agents.**
- **Few AEs consistent with the known key side-effects of systemically dosed anti-CD40 Ab were observed.**
- **IV dosing of NG-350A led to higher and more sustained elevations in IL-12, IL-17A than typicable with traditional anti-CD40 Abs.**
- **Cytokine levels were markedly higher following IV than IT dosing, suggesting IV dosing led to more extensive viral replication in the tumour and higher levels of T-cell activation.**
- **The pattern of elevations observed suggest innate immune cell stimulation and Th1/Th17 type T-cell activation, consistent with the mechanism of action of CD40 agonists.**
- **NG-350A also led to the expansion of T cell clones in blood.**
- **Further experiments will assess the specificity of new clones to tumour and viral vector antigens.**

**References**


**Acknowledgements**

**NG-350A** is a novel transgene-armed T-SIGn vector that selectively replicates in tumour cells and expresses an anti-CD40 agonist antibody.

**References**


**References**