A MULTICENTRE PHASE 1B STUDY OF NG-641, A NOVEL TRANSGENE-ARMED AND TUMOUR-SELECTIVE ADENOVIRAL VECTOR, AND PEMBROLIZUMAB AS NEOADJUVANT TREATMENT FOR SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Background Despite multimodal management strategies, outcomes for patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) remain poor. Immune checkpoint inhibitors have demonstrated promise as a neoadjuvant strategy to reduce relapse rates1; however, the immunosuppressive SCCHN tumour microenvironment (TME) has limited the efficacy of immunotherapy to date. This ‘cold’ TME is characterised by an absence of T-cell activation/inflammation2 and high levels of stromal fibroblast activating protein (FAP),3 indicative of immunosuppressive cancer-associated fibroblasts (CAFs). Novel approaches to ameliorate this immunosuppressive TME are required to realise the full benefit of immunotherapy in SCCHN.NG-641 is a next-generation blood-stable and transgene-armed Tumour-Specific Immuno Gene Therapy (T-SIGn) adenoviral vector that selectively replicates in epithelial tumour cells. NG-641 encodes four immunostimulatory transgenes: a FAP-directed bi-specific T-cell activator antibody to target CAFs, interferon alpha 2 to promote innate and adaptive immune responses, and C-X-C motif chemokine ligands 9 and 10 to induce T cell infiltration.4 Together, these transgenes are designed to locally re-programme the immunosuppressive TME and promote functional anti-cancer immune responses while minimising systemic immune-related toxicities. This mechanism of action is particularly suited to SCCHN and should complement anti-PD-1 inhibitors. We, therefore, designed a study to assess neoadjuvant treatment with NG-641 and pembrolizumab in locally advanced SCCHN.

Methods The mode-of-action transgene (MOAT) study is a multicentre, open-label, dose-escalating, phase 1b study of NG-641 as monotherapy or with pembrolizumab. Patients are eligible if they have newly diagnosed or recurrent locally advanced SCCHN and have definitive surgery planned within 8 weeks of screening. In Part A, patients will receive three doses of intravenous NG-641 monotherapy prior to surgery (figure 1). Once NG-641 transgene expression is confirmed in excised tumour tissues, Part A will close and NG-641 dose-escalation can continue in Part B. Patients will then receive a single dose of pembrolizumab given ~5 days after NG-641 to minimize toxicity and take advantage of the mechanism of NG-641 prior to PD-1 blockade. The primary objective is to characterise the safety and tolerability of NG-641 ± pembrolizumab in SCCHN; secondary objectives are to identify a recommended dose of NG-641 plus pembrolizumab and to assess treatment outcomes, including pathological tumour responses and overall survival. Pharmacodynamic outcomes will be assessed following NG-641 ± pembrolizumab, including characterising immune/inflammatory biomarkers in both tumour and blood. The study is to be conducted at 4 sites in the UK; up to 36 patients will be enrolled.

ACKNOWLEDGEMENTS This study was funded by PsiOxus Therapeutics Ltd.

TRIAL REGISTRATION This trial is registered as NCT04830592 on clinicaltrials.gov.

REFERENCES

ETHICS APPROVAL This study was approved by a central United Kingdom Research Ethics Committee (South Central - Oxford A Research Ethics Committee); approval reference 20/SC/0425, Integrated Research Application System ID 290504. All participants must provide informed consent prior to enrolment.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.437