Background

Human papillomavirus (HPV) is a contagious cause of anogenital and oropharyngeal cancers developing from persistently infected and subsequently transformed basal keratinocytes of mucosal epithelium. More than 90% of cervical cancers and pre-cancerous cervical intraepithelial neoplasia (CIN) are linked to infections with high-risk HPV, with more than 50% of cancers linked to HPV16. At least 25% of women with high-grade CIN lesions progress to in situ or invasive cancer, if untreated. Current treatments for high-grade CIN can remove abnormal tissue but do not address underlying HPV infection, and 15% of women treated develop residual or recurrent high-grade CIN or cervical cancer. Long-term efficacy may require induction of tumor-specific T cell responses combined with alleviated local immune suppression and increased tumor immune cell infiltration. Multimodal mRNA-based immunotherapies that deliver both antigens and immunomodulators in a single drug product represent a promising new approach for treatment of CIN and cervical cancer that can address current disease as well as the underlying cause (HPV infection). Here we report on pre-clinical efficacy of NTX-0250, a nanoparticle-formulated, multi-component mRNA drug that co-delivers a novel HPV16 antigen design with two potent immunomodulators.

Methods

To test efficacy, we utilized the well-established, clinically relevant, C3.43 tumor model (5). C3.43 is a progressive subclone of C3, HPV16-transformed B6 mouse embryo cell line that expresses HPV16 E6 and E7 antigens under the natural promoter. Therapeutic efficacy of NTX-0250 was assessed in mice with large (>120mm³) C3.43 tumors. HPV16-specific T cells were assessed by flow cytometry on peripheral blood mononuclear cells (PBMCs). Mechanistic studies were performed by post-treatment tumor microenvironment characterization. To assess translational potentiability of NTX-0250, induction of HPV-specific T cell responses in cynomolgus monkeys was measured by flow cytometry and IFNγ ELISPOT on PBMCs.

Results

In tumor challenged mice, administration of NTX-0250 induces complete regression of large tumors resulting in long-term, tumor-free survival of 100% of treated animals (figure 1A). Complete responses are accompanied by strong tumor immune infiltration of CD8+, CD4+ APCs and NK cells and upregulation of IFNγ in the tumor microenvironment (figure 1B). In cynomolgus monkeys, administration of NTX-0250 induces strong HPV16-specific responses (figure 2).

Conclusions

Here we report for the first time robust pre-clinical efficacy of a multimodal, mRNA-based therapeutic combining antigen- and immunomodulator-encoding mRNAs in a novel nanoparticle formulation. NTX-0250 treatment resulted in complete regression of large established murine tumors and robust induction of HPV-specific T cell responses in non-human primates.

REFERENCES

1. https://www.who.int/health-topics/cervical-cancer#tab=tab_1