O-glycan array to test the binding activity of NEO-201 to 94 different O-glycan structures (Figure S2).

Phase IIa combining NEO-201 with Pembrolizumab in adults with chemo-resistant solid tumors

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Introduction

NEO-201 is a humanized IgG1 monoclonal antibody (mAb) which binds to Core 1 and/or extended Core 1 O-glycans expressed by human solid and hematological malignancies as well as by human neutrophils. NEO-201 reacts against colon, pancreatic, non-small cell lung, head and neck, cervical, uterine and breast cancer, but it does not bind to most normal tissues. NEO-201 kills tumor cells expressing its target antigen via antibody dependent cell mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC). NEO-201 also binds to circulating regulatory T cells (Tregs) and kills them by CDC in vitro. The low response rates and resistance to PD-1/PD-L1 blockade in solid cancers may, in part, be due to the suppressive activity of Tregs in the tumor microenvironment (TME). Based on these data, we hypothesize that combining NEO-201 with pembrolizumab for the treatment of solid tumors may overcome resistance to checkpoint inhibitors by depleting Tregs.

Clinical Trial Objectives

Primary objectives:

- Determine the safety of the combination of NEO-201 at recommended phase 2 dose (RP2D) with pembrolizumab
- Determine Objective Response Rate and Progression Free Survival.

Secondary objectives:

- Characterize the pharmacokinetics of NEO-201 in combination with pembrolizumab.
- Explore the effects of the combination on functions and phenotypes of immune subsets, modulation of serum levels of cytokines and soluble factors.

Eligibility Criteria

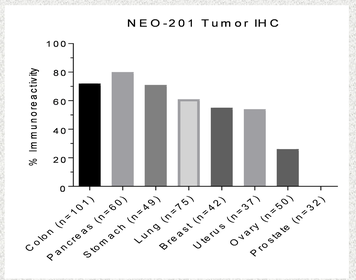
The Clinical Trial NCT03476681 is open and recruiting patients at National Institutes of Health (USA).

Eligibility criteria include the following:

A. Subjects must be over 18 years old and have histologically or cytologically confirmed recurrent, locally advanced unresectable or metastatic Non-Small Cell Lung Cancer, Cervical Cancer, Head and Neck Squamous Cell Carcinoma, Uterine Carcinoma who have progressed during or after front-line standard of care treatment, including chemotherapy and/or targeted therapy.

B. At least 10% of tumor cells expressing NEO-201 target antigen on immunohistochemistry.

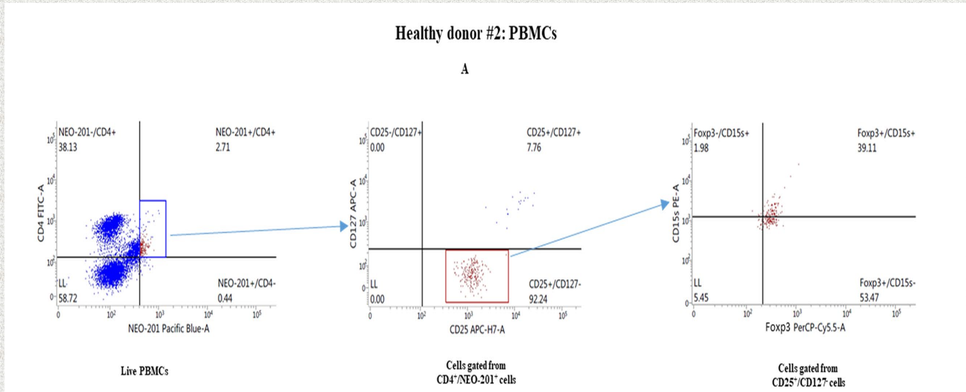
C. Patient is not a candidate for potentially curative surgery or radiation



Rationale

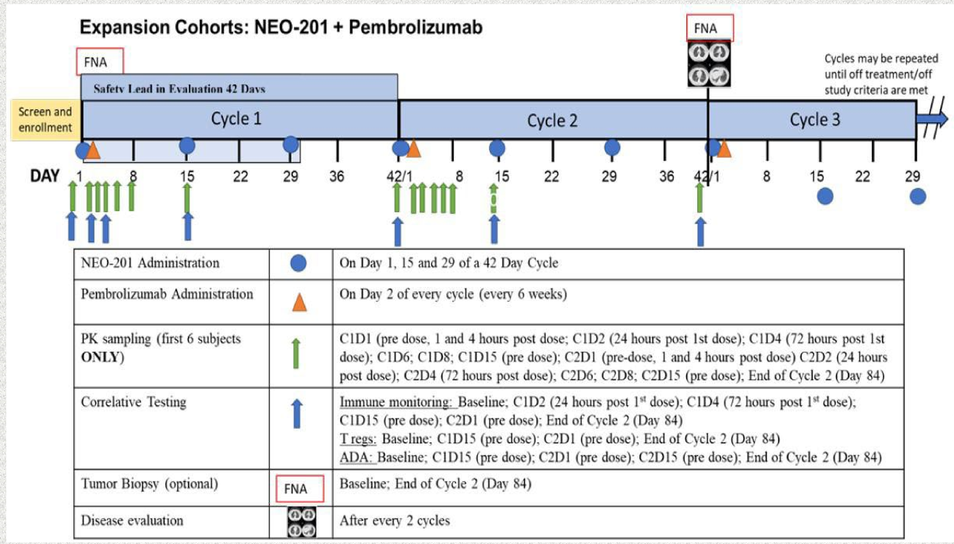
NEO-201 targets human immunosuppressive T regulatory cells in human PBMCs

Phenotypic analysis of human PBMCs as determined by flow cytometry



$CD4^+$/NEO-201^+ subset in human PBMCs from healthy donors has Tregs phenotype

Schema of Treatment: Safety Lead-In Course



Given that NEO-201 has not been previously administered with pembrolizumab, a safety lead-in will be conducted in three to six subjects who will receive NEO-201 at 1.5 mg/kg IV every 2 weeks, and pembrolizumab 400 mg IV every 6 weeks. The safety lead-in course will be 42 days in length and consist of 1 dose of pembrolizumab and 3 doses of NEO-201.
Once safety is established, 21-31 subjects would be enrolled in each of the four disease groups.

Schema of Treatment: Expansion Cohorts

Up to 228 subjects will be screened and, if eligible, treated with NEO-201 at 1.5 mg/kg every 2 weeks in combination with Pembrolizumab, given 1 day after the NEO-201, at 400 mg IV every 6 weeks.

The sample size for the expansion cohorts are calculated based on the desirable ORR (Simon minimax two-stage phase II design) for each cohort (Table 1). Allowing for an additional 5 subjects to replace potentially in-evaluable subjects, the maximum accrual on this study will be 126 subjects.

Safety lead-in successfully completed
Expansion cohorts currently enrolling

Table 1: Enrollment to two-stage design per expansion cohort

Disease Cohort	Initial Stage	Acceptable Response Rate % (N/Total)	Second Stage	Sufficiently interesting Response Rate
NSCLC	12	20% (≥1/12)	21	14.3% (≥3/21)
HNSCC	16	25% (≥2/16)	31	19.4% (≥6/31)
Endometrial	16	25% (≥2/16)	31	19.4% (≥6/31)
Cervical	13	25% (≥1/13)	20	15% (≥3/20)

Table 2: Correlative Testing During Expansion Cohorts

Test/assay	Collection point
Immune- monitoring	Baseline, 24 hrs, 72 hrs post dose 1, C1D15 pre dose, pre dose 2, Day 84 (end of cycle 2)
Tregs	Baseline, C1D15 pre dose, pre dose 2, Day 84 (end of cycle 2)
PK	Pre, 1h, 4h, 24h, 72h, C1D6, C1D8
Immunohistochemistry (IHC)	Baseline
ADA	Baseline, C1D15 pre dose, pre dose 2, C2D15 pre dose, day 84 (end of cycle 2)

Conclusion

There is a growing consensus that Tregs in TME promote tumorigenesis and progression and inhibit checkpoint inhibitor therapies by suppressing anticancer immunity.
Accumulation of Treg cells in the TME is associated with poor clinical prognosis in cancer patients. Removal of Treg cells could restore strong anti-cancer immune responses. One strategy to remove Treg cells is to use mAbs to target and eliminate them.
NEO-201 is a mAb that targets solid and blood tumors expressing core-1 and/or extended core 1 O-glycans as well as human neutrophils and human Tregs. Based on these data, we hypothesize that combining NEO-201 with pembrolizumab for the treatment of solid tumors may overcome resistance to checkpoint inhibitors therapies by depleting Tregs.

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