Phase I clinical trial of NEO-201, an anti-tumor-associated CEACAM-5/6 monoclonal antibody in solid tumors

Christopher Browning Cole[1], Maria Pia Morelli[1], Massimo Fantini[2], Maria Fergusson[1], Sharon A. Mavroukakis[2], Anjum Zaki[2], Kwong Y. Tsang[2], Philip M. Arlen[2], and Christina M. Annunziata[1]

[1]Women's Malignancies Branch National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. [2]Precision Biologics, Inc., Bethesda, MD, USA

Abstract 2531

Background: NEO201 is a humanized IgG1 monoclonal antibody generated against tumor-associated antigens from colorectal cancer that binds specifically to tumor-associated CEACAM-5 and CEACAM-6 variants and exerts anti-tumor activity through antibody dependent cellular cytotoxicity and complement dependent cytotoxicity. Here we present outcomes from a phase I trial of NEO-201 in advanced solid tumors (NCT03476681).

Methods: In a 3+3 dose escalation trial, NEO-201 was administered intravenously every two weeks in a 28-day cycle. The primary objective was to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of NEO-201 in patients with advanced solid tumors. The secondary objective was to assess the preliminary antitumor activity after every 2 cycles, and exploratory objectives assessed pharmacokinetics (PK) and the effect of NEO-201 administration on immunologic parameters and possible relationships with response. Of 17 patients enrolled, 11 had colorectal, 4 had pancreatic and 2 had breast cancer.

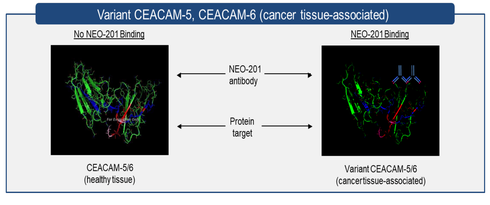
Results: Dose limiting toxicities (DLTs) included grade (Gr) 4 febrile neutropenia and prolonged neutropenia, each in 1/6 patients at dose level (DL) 2 (2 mg/kg), and Gr 3 febrile neutropenia in 1/6 patients at DL 1.5 (1.5 mg/kg). Most common Gr 3/4 toxicities were neutropenia (94%), white blood cell decrease (59%), lymphocyte decrease (29%), and febrile neutropenia (24%). Protocol was modified to allow administration of G-CSF (filgrastim), and based on safety and PK data, the RP2D was established as 1.5mg/Kg. The best response observed was stable disease (SD) in 4/9 evaluable patients with colorectal cancer. Minor CA-19-9 reductions were observed in two pancreatic cancer patients at DL 1.5. Analysis of soluble factors in serum revealed that a high level of soluble (s) MICA at baseline was correlated with a downregulation of NK cell activation markers and progressive disease (PD). Unexpectedly, flow cytometry showed that NEO-201 also binds to circulating regulatory T (Treg) cells and treatment is associated with a reduction in these cells especially in patients with SD.

Conclusion

NEO-201 was safe and well tolerated at the MTD of 1.5 mg/kg. sMICA and NK activation markers may be biomarkers of response. Reduction in Treg cells suggests that the combination of NEO-201 with immune checkpoint inhibitor should be tested in future clinical trials.

Background

TAA derived mAb NEO-201 selectively binds tumor tissue



Dose Escalation

Dose Escalation Schedule

Cohort	Dose (mg/kg)	Number of Patients
DL 1	1	4
DL1.5	1.5	6
DL 2	2	7

Demographics

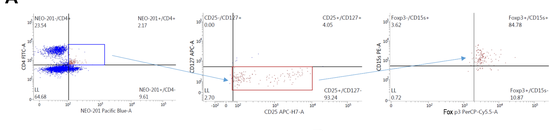
Variable	Trait	Number
TOTAL	Subjects	17
Sex	Female Male	11 6
Race	White African American Other	15 2 0
Ethnicity	Hispanic Non-Hispanic	0 17
Disease Histology	Adenocarcinoma of pancreas Colorectal cancer Breast	4 11 2

Results

Grade 3-4 AEs

Adverse Event	DL 1 (n=4)		DL2 (n=7)		DL 1.5 (n=6)		Cumulative Incidence (grade 3-4, n =17)
	Gr 3	Gr 4	Gr 3	Gr 4	Gr 3	Gr 4	
Anemia			2				2/17 (12%)
Febrile Neutropenia			2	1	1		4/17 (24%)
Sepsis				1			1/17 (6%)
Lymphocyte count decreased	1		2	1		1	4/17 (24%)
Neutrophil count decreased	2	2	1	5		5	16/17 (94%)
White blood cell decreased	1		3	2		4	8/17 (47%)
Hypertension	1						1/17 (6%)

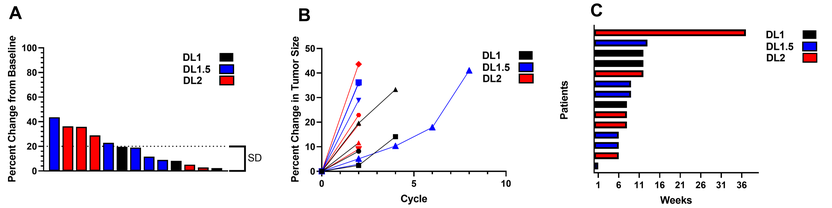
NEO-201 binds CD15s+ Treg cells in PBMCs



A. Representative Treg cells flow cytometry plot and gating

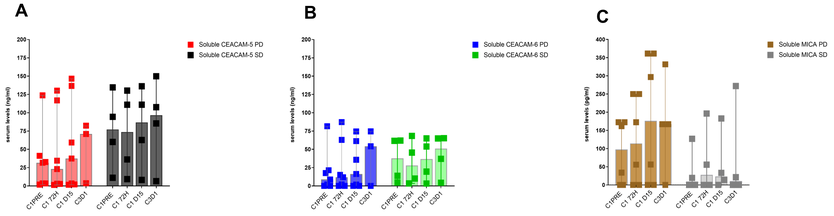
B. Treg cells numbers in PBMCs at indicated timepoints

Response and Time on Study

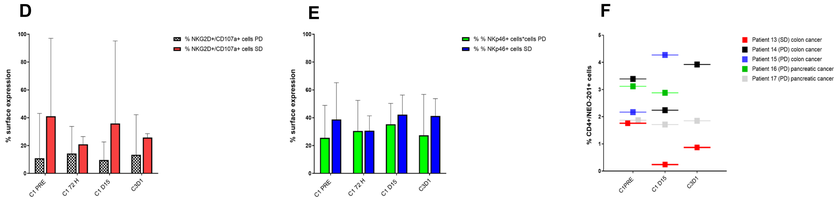


A. Best response by dose level. **B**. Tumor size change over time. **C**. Time on study.

Lower sMICA levels and higher NK cell activation in patients with SD



A-C. Median serum levels of soluble CEACAM-5 **(A),** CEACAM-6 **(B)** and MICA **(C)** grouped by response to treatment.



D-E. Percentage of NKG2D+/CD107a+ and NKp46+ NK cells from CD56+/CD16+ NK cells in subjects with stable and progressive disease at different time points by flow cytometry analysis.
F. Percentage of circulating CD4+/NEO-201+ Treg cells at different time points in subjects treated with NEO-201 DL1.5 by flow cytometry analysis.