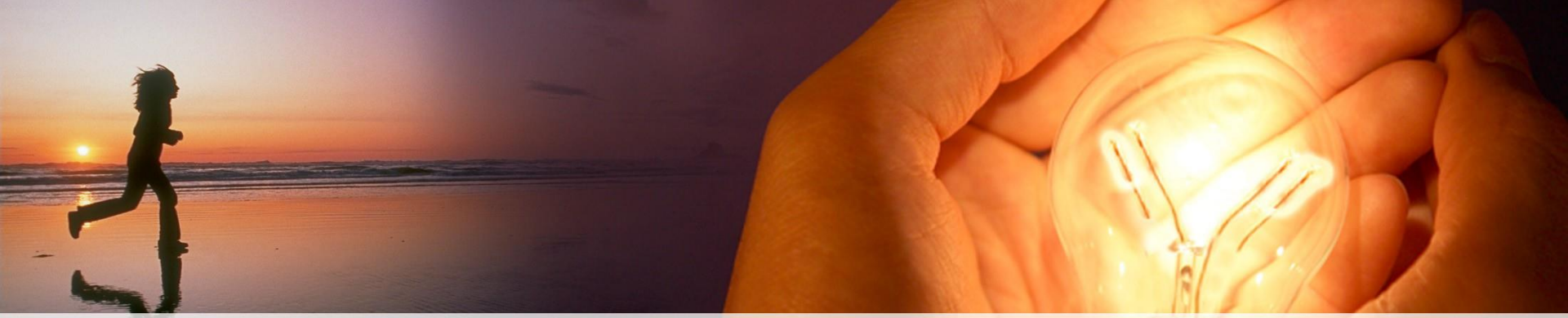


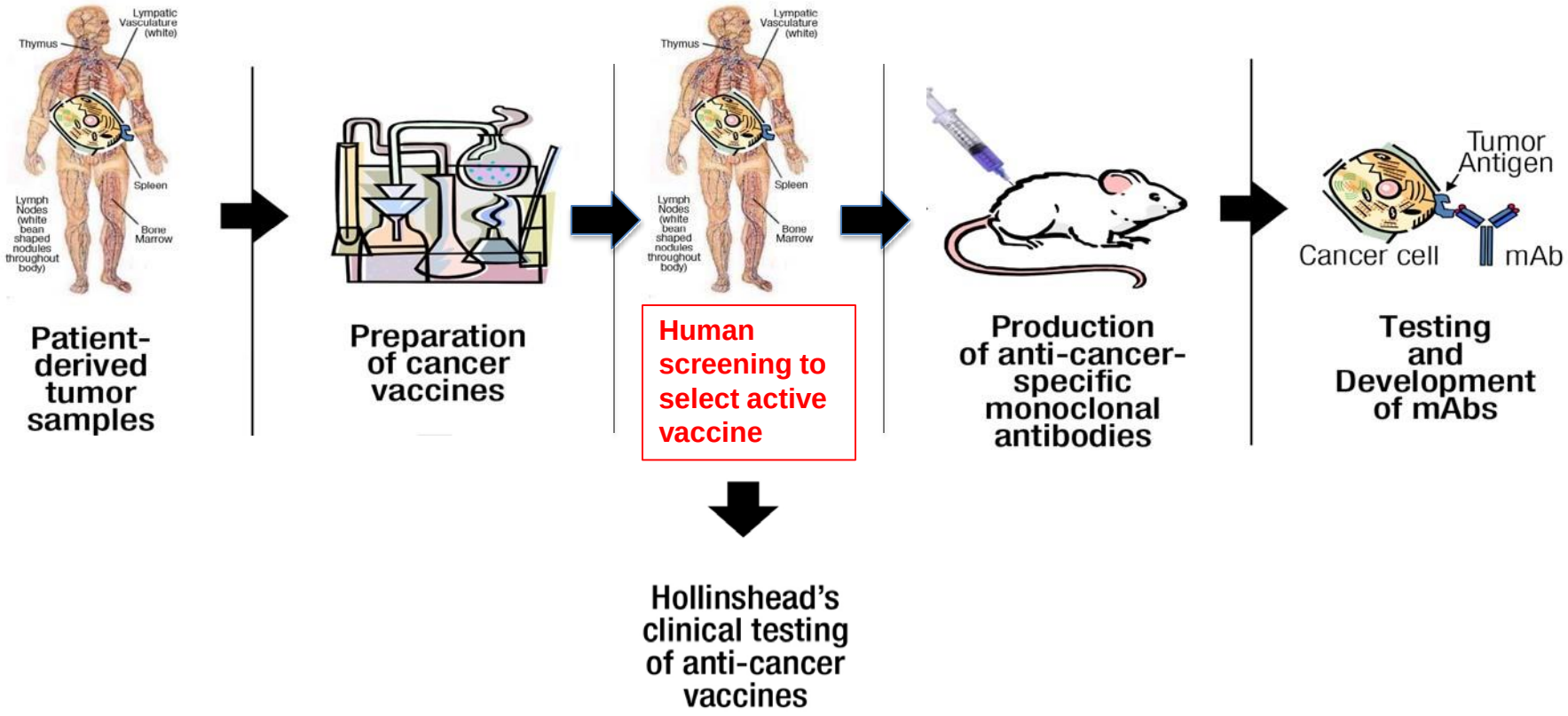
PRECISION BIOLOGICS

Novel Targets Of Neoantigens In Monoclonal Antibodies

Philip M. Arlen, M.D.

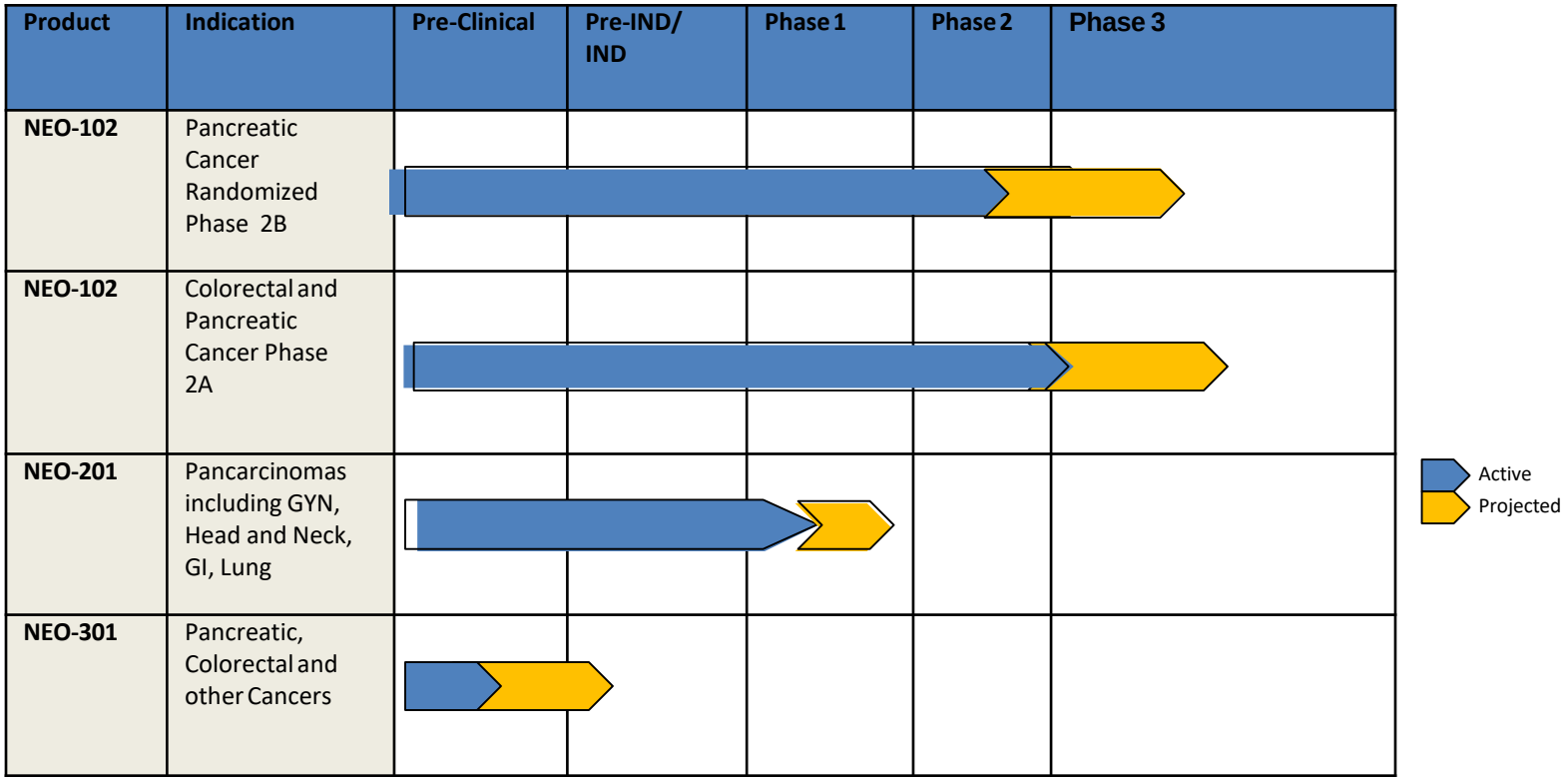
October, 2019

Only Human Derived & Human Tested Neo-antigen Platform to Create Novel Therapeutics



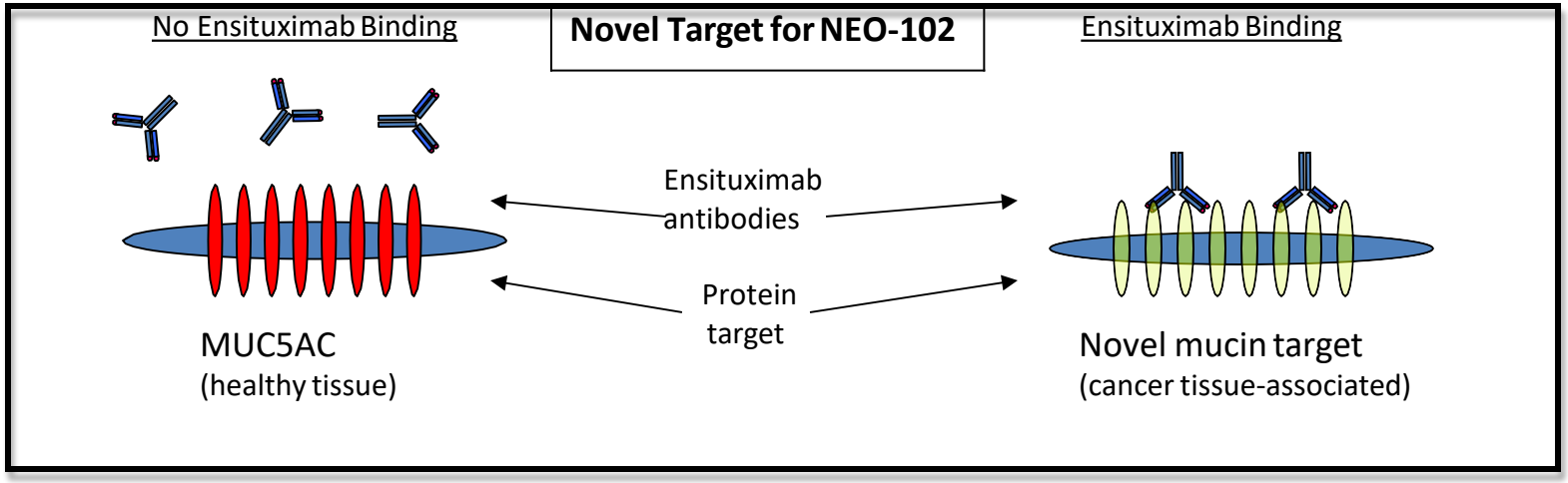
Pipeline

- NEO-102: Phase 2a colorectal and pancreatic (NEO-102 monotherapy)- ***COMPLETE***
- NEO-102: Phase 2b: pancreatic (randomized Gemzar/Abraxane ± NEO-102) ***CLOSED TO ACCRUAL***
- NEO-201: IND-enabling studies, manufacturing completed and Phase 1 commenced in Q1 2019



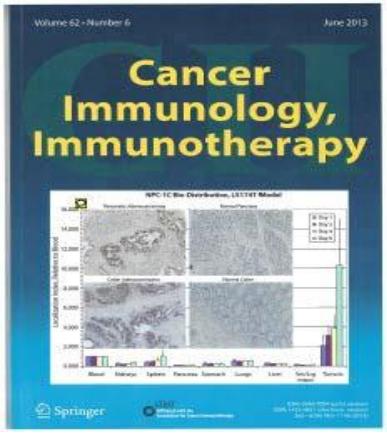
Ensituximab (NEO-102) Binds to *Novel Cancer Target*

- Novel monoclonal antibody that specifically recognizes colorectal and pancreatic cancer.
- Recognizes a novel target which is a member of the mucin family of proteins, similar to BUT distinct from MUC5ac.
- Our novel target is not present in healthy tissues.



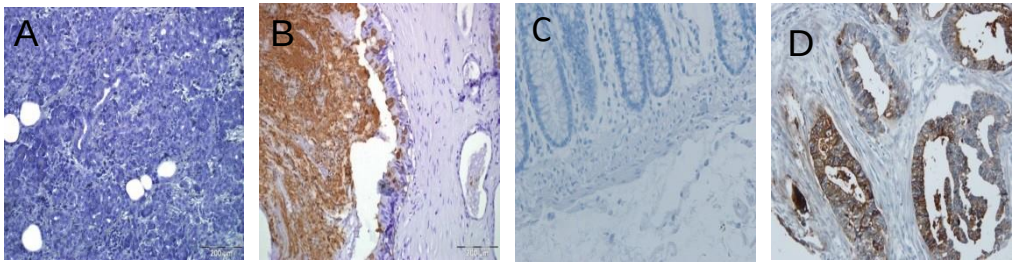
Ensituximab Highlighted on Cover of Cancer Immunology, Immunotherapy

June 2013

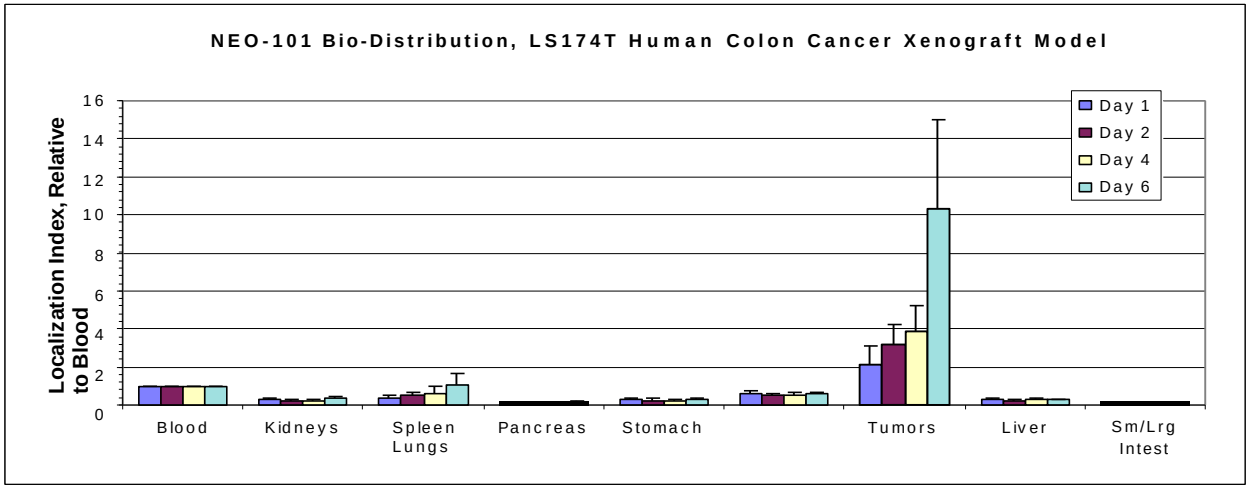


Cancer Immunol Immunother (2013) 62:1011–1019
DOI 10.1007/s00262-013-1420-z

Anti-tumor activity of a novel monoclonal antibody, NEO-102, optimized for recognition of tumor antigen in preclinical models



A) Normal pancreas
B) Pancreas adenocarcinoma
C) Normal Colon
D) Colon Cancer



Mice with pre-established human colorectal tumors (LS174T) were injected iv with I-125 labeled NEO-101; mice were sacrificed on the indicated days and radioactivity was measured in selected tissues

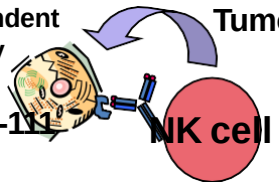
PRECISION BIOLOGICS

Tumor Cell Killing Activity- Antibody Dependent Cellular Cytotoxicity (ADCC) of (NEO-102)

Tumor Cell Line	% Specific Killing (± SEM)		
	Eff/Target Ratio	Control mAb	NEO-101
Colo-205 (Colorectal)	50:1	9.8 ± 1.9	66.7 ± 0.6
	25:1	0.8 ± 1.2	46.4 ± 1.6
	12.5:1	-0.5 ± 0.1	32.8 ± 2.0
SW620 (Colorectal)	50:1	1.6 ± 0.2	63.7 ± 2.9
	25:1	3.5 ± 1.8	61.0 ± 1.8
	12.5:1	0.0 ± 0.3	51.5 ± 0.9
SW1463 (Colorectal)	50:1	0.1 ± 1.1	33.8 ± 1.0
	25:1	-1.3 ± 0.2	25.5 ± 0.6
	12.5:1	-1.2 ± 0.1	17.9 ± 1.7
LS174T (Colorectal)	50:1	-1.2 ± 0.1	26.8 ± 2.9
	25:1	-0.8 ± 0.1	18.5 ± 4.1
	12.5:1	-1.1 ± 0.0	9.5 ± 0.5
AsPC-1 (Pancreatic)	50:1	-0.8 ± 2.9	44.5 ± 6.8
	25:1	-7.0 ± 2.2	36.2 ± 2.6
	12.5:1	-1.2 ± 0.9	26.5 ± 6.7

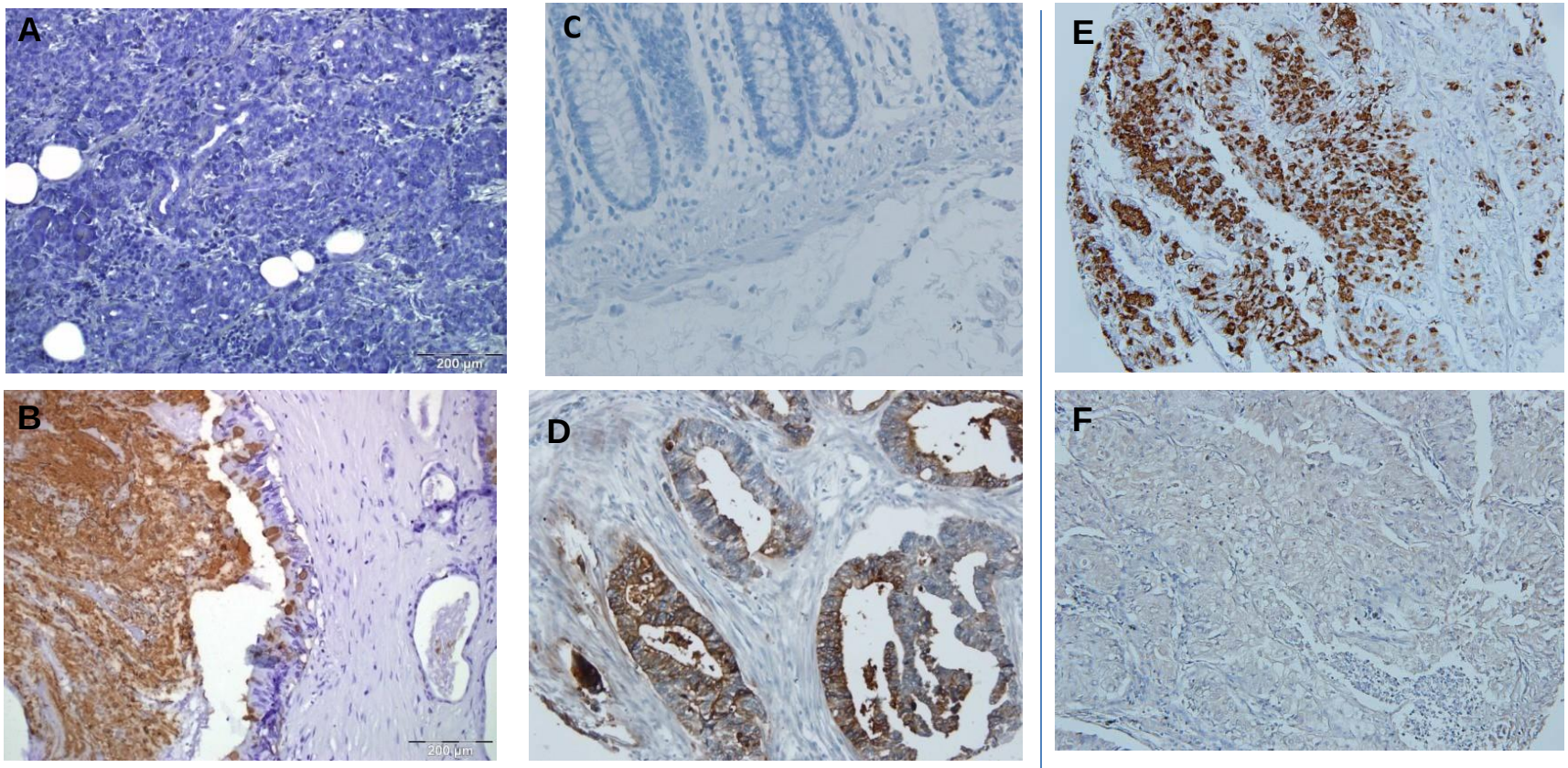
Tumor Cell Line	% Specific Killing (± SEM)		
	Eff/Target Ratio	Control mAb	NEO-101
CFPAC-1 (Pancreatic)	50:1	-1.2 ± 2.3	26.9 ± 1.6
	25:1	-2.4 ± 0.1	23.2 ± 2.2
	12.5:1	-2.0 ± 0.4	11.1 ± 1.6
PANC-1 (Pancreatic)	50:1	-2.2 ± 0.4	46.8 ± 2.1
	25:1	-2.5 ± 0.4	33.2 ± 3.3
	12.5:1	-3.9 ± 0.3	21.2 ± 0.6
SK-MEL (Melanoma)	50:1	2.7 ± 0.7	4.6 ± 1.1
	25:1	1.5 ± 0.3	3.3 ± 1.1
	12.5:1	1.6 ± 0.4	2.3 ± 0.6
DU145 (Prostate)	50:1	-0.3 ± 0.2	-0.5 ± 0.3
	25:1	-0.7 ± 0.1	0.3 ± 0.8
	12.5:1	-0.2 ± 0.2	-0.3 ± 0.1

ADCC:
Antibody-dependent
Cell cytotoxicity



1. NPC-1 Antigen and Epitope

Tissue-Specific Staining with Ensituximab (NEO-102)



A) Normal pancreas

B) Pancreas adenocarcinoma

C) Normal Colon

D) Colon Cancer

E) Lung Cancer (anti-MUC5AC)

F) Lung Cancer (NEO-102)

NEO-102 Monotherapy - Highlights of Clinical Data for Phase 1/2 Study in Colorectal and Pancreatic Cancer

- During the Phase 1 portion of this study: NEO-102 was administered IV every two weeks X 4 doses (D1, D15, D29, D43) and evaluated D57 (1 course)
  - 3 patients with mCRC (metastatic colorectal ca) at **1.5** mg/kg
  - 1 patient with mCRC and 2 patients with pancreatic cancer at **2** mg/kg
  - 3 patients with mCRC at **3** mg/kg
  - 6 patients with mCRC and 1 patient with pancreatic cancer at **4** mg/kg
    - 2 dose limiting toxicities (DLTs) occurred, grade 3 anemia and grade 3 hyperbilirubinemia
  - Dose de-escalated and 3 additional patients treated at **3** mg/kg with one DLT (grade 3 hypoxia)
- Maximum Tolerated Dose (MTD) established at 3 mg/kg

NEO-102 Phase 1/2 Monotherapy in Treatment Refractory Colorectal Cancer Patients- Patient Summary

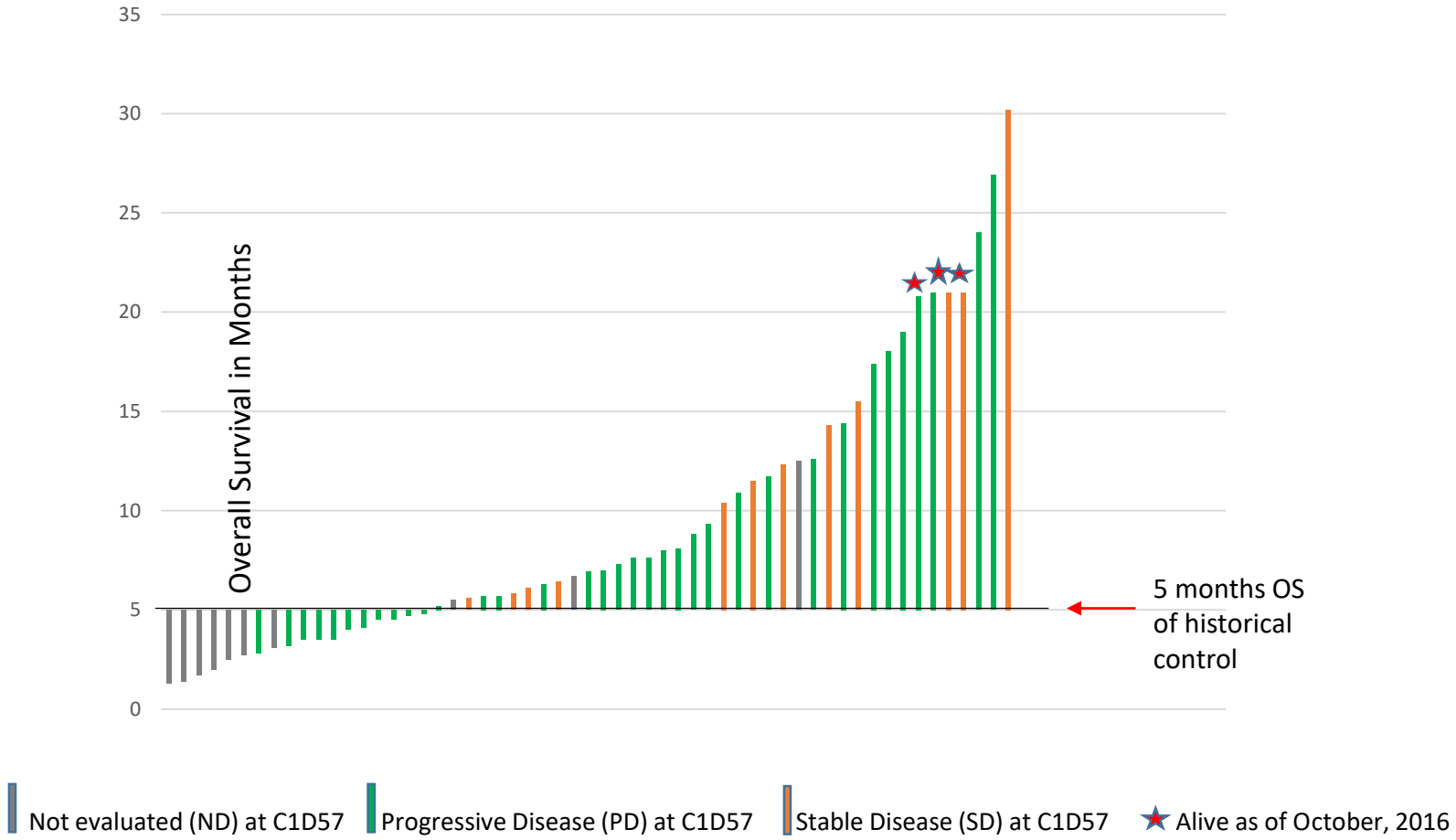
Phase 1 and 2:

- 63 patients with recurrent or metastatic recurrent colorectal cancer received at least 1 dose of NEO-102
- Gender: 35 male (56%), 28 female (44%)
- Age: range 32-83, median 60 years
- Number of Prior Therapies: range 1-9, average 3.7, **median 4.0**
- Number of doses of NEO-102: range 1 – 16, average 4
- Overall survival (OS) of patients with colorectal cancer enrolled in Phase 1/2 who were evaluable for response (57 patients received ≥ 2 doses of NEO-102):
  - ✓ 6.77 months (range 1-30 months after start of therapy)
  - ✓ 15 patients lived greater than 1 year from start of therapy
  - ✓ 3 patients remain alive (20-21 months after start of therapy)

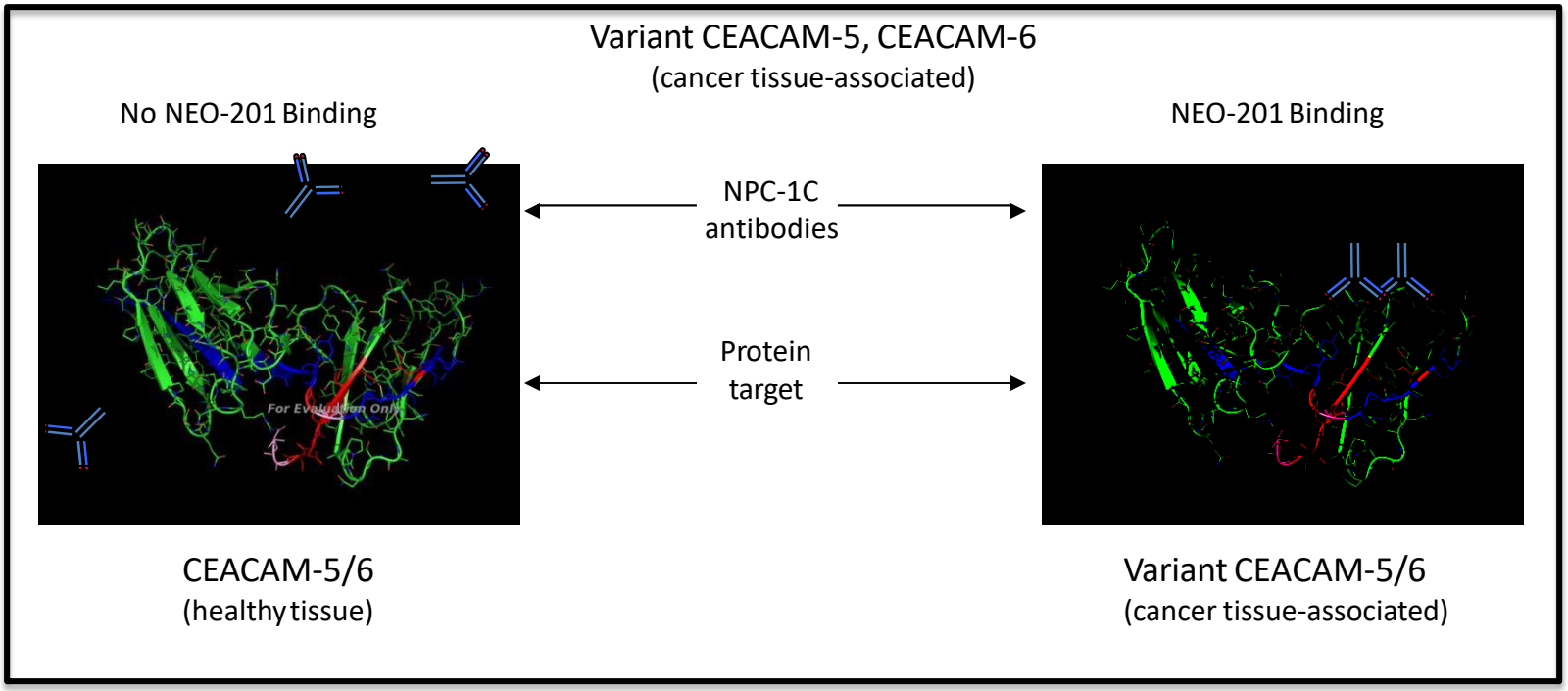
NEO-102 Phase 2 Monotherapy in Treatment Refractory Colorectal Cancer Patients- Patient Summary

- 48 evaluable patients; Gender: 26 male (54%), 22 female (46%)
- Age: range 33-79, median 59 years
- Ethnicity: 32 (67%) Caucasian; 3 (6%) Hispanic; 11 (23%) Black/African Am; 2 (4%) Asian
- Number of Prior Therapies: range 2-9, average 3.7, **median 4**
- 12 of 48 (**25%**) patients in this trial had received prior therapy with Stivarga (regorafenib)
- Number of doses of NEO-102: range 2 – 16, average 3
- Number of subjects removed from therapy for treatment related toxicity: 1 (recovery from anemia delayed >14 days)
- Number of grade 3 / 4 toxicities were limited: anemia (1.3%), hyperbilirubinemia (0.9%), fatigue (0.9%), hemolysis, and nausea, vomiting, headache and hypoxia (0.4 %), respectively.

Overall Survival of Evaluable Colorectal Cancer Patients (≥ 2 doses of NEO-102) in NEO-0901 Compared with 5 months OS in the CORRECT Study (Grothey, et al. 2013)



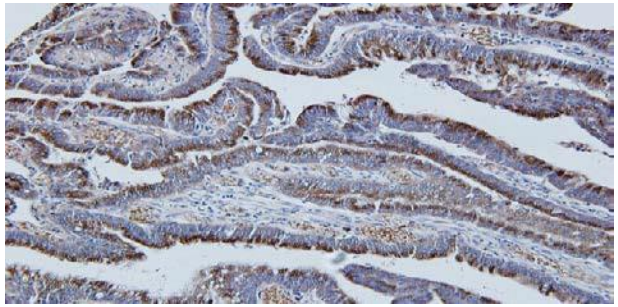
NEO-201 Target



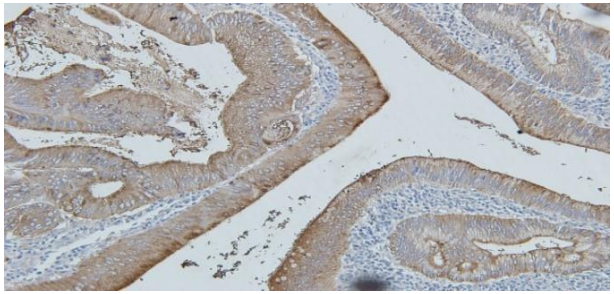
- NEO-201 recognizes tumor-specific variants of CEACAM-5 and CEACAM-6, members of the carcinoembryonic antigen (CEA) family of proteins. These proteins are expressed in normal epithelial tissues, and over-expressed in many solid tumor types (colon, pancreatic, breast, lung, ovarian)
- NEO-201 does not cross-react significantly with healthy tissues that express normal CEACAM-5 or CEACAM-6

Comparison Binding Specificity of NEO-201 with Commercial CEACAM-5/6 Antibodies by IHC

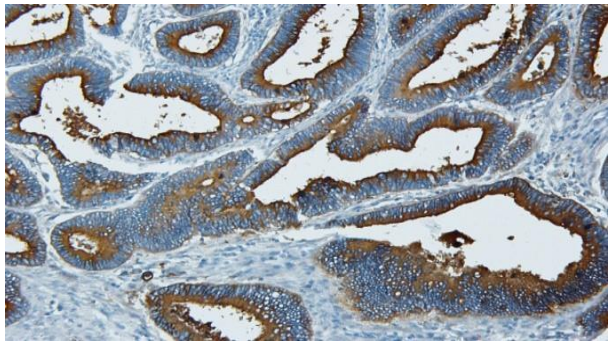
Colon cancer



Anti-CEACAM-6
(9A6 from Cell Signal)

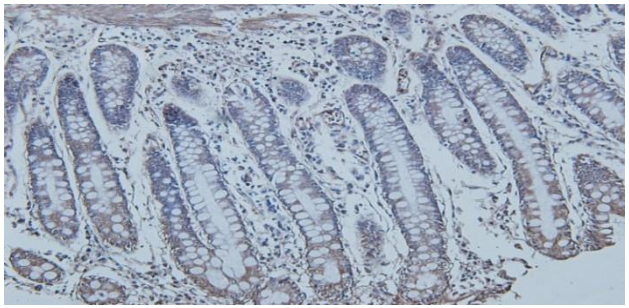


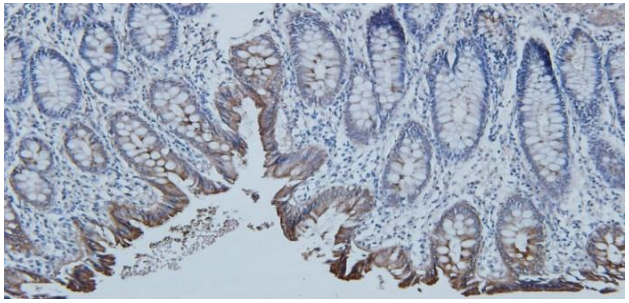
Anti-CEACAM-5
(CB30 from Abcam)

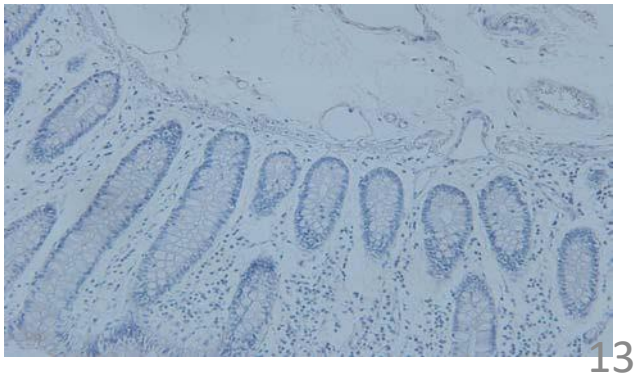


NEO-201

Normal Colon

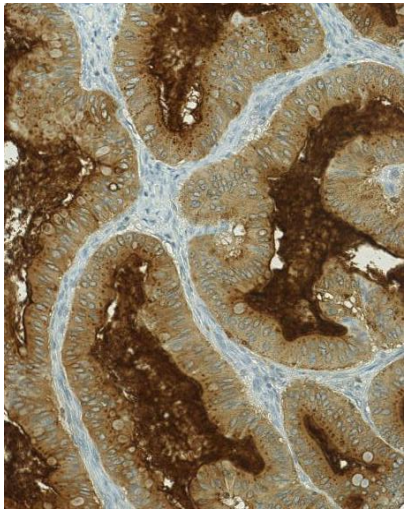




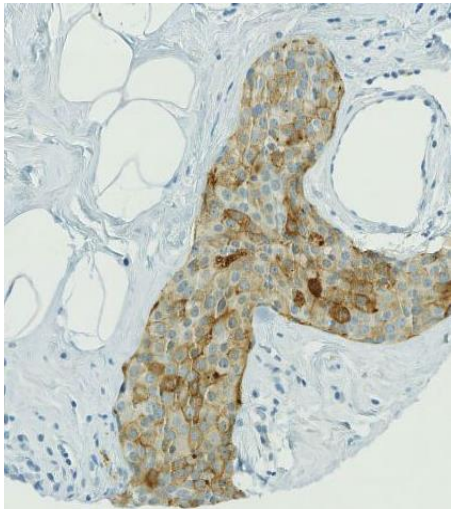


Collaborative Research Project – Precision Biologics and Christina Annunziata, MD, NCI

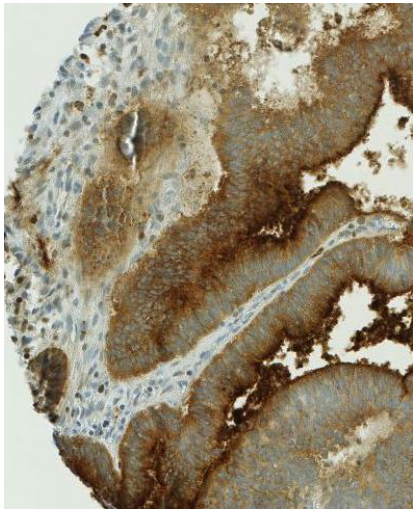
- Binds to tumor-associated antigen
- Minimal binding to healthy tissue



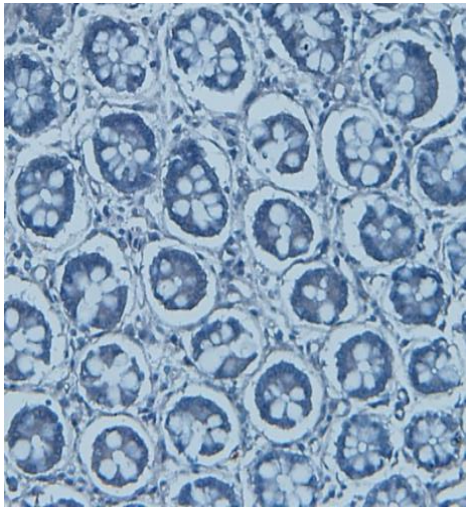
Ovarian Cancer



Breast Cancer

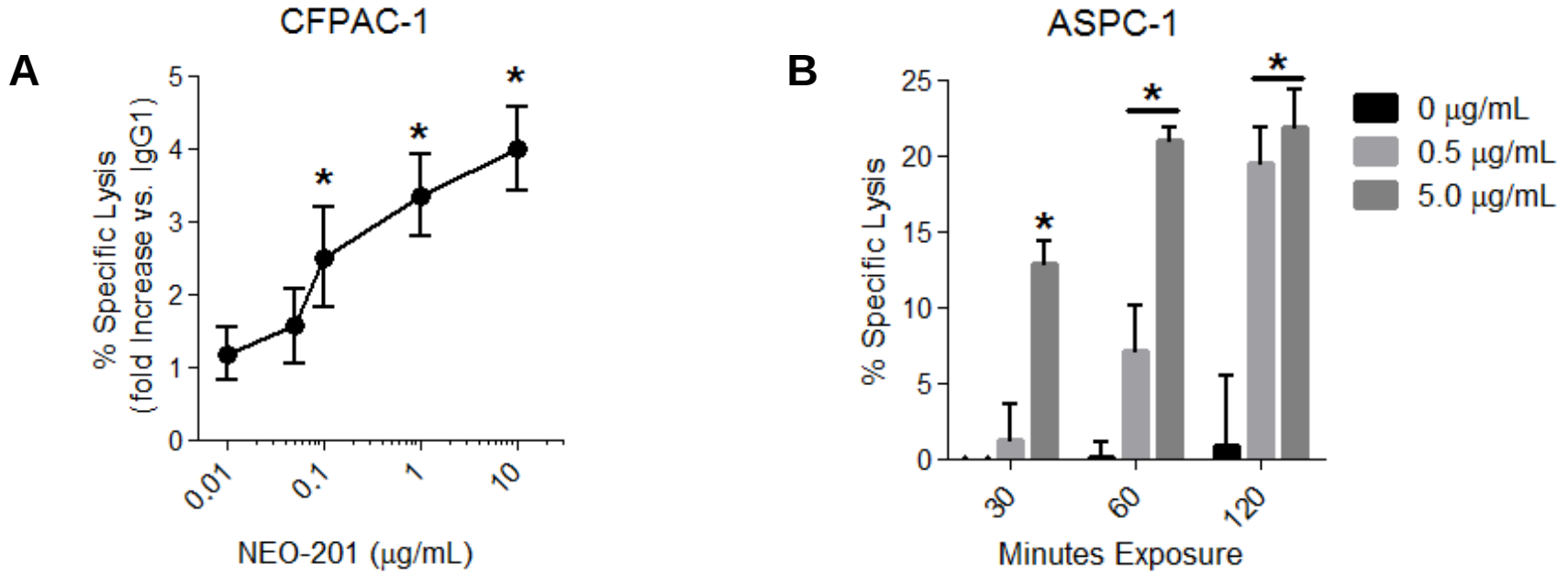


Colon Cancer



Normal colon

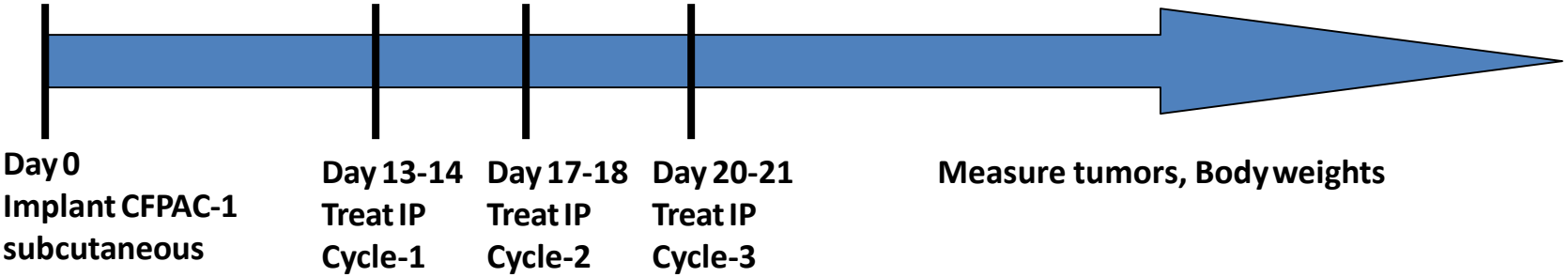
NEO-201 mediates ADCC and CDC against human tumor cells



(A) ADCC assay using CFPAC-1 cells treated with increasing doses of NEO-201. NK cells isolated from a healthy donor were used as effector cells at an E:T ratio of 12.5:1. The graph depicts the fold increase in % specific lysis of NEO-201-treated tumor cells versus that of control cells treated with 10µg/mL human IgG1. (*, statistically significant ($p < 0.05$) by T-test.)

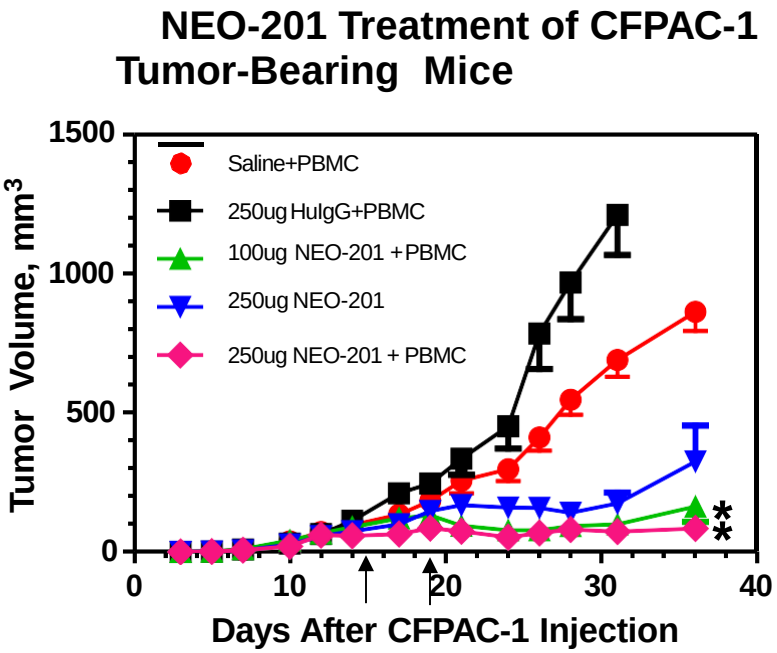
(B) CDC assay using ASPC-1 cells treated with rabbit complement (1:8 dilution) and the indicated doses of NEO-201 for the indicated durations. (*, statistically significant ($p < 0.05$) by T-test.)

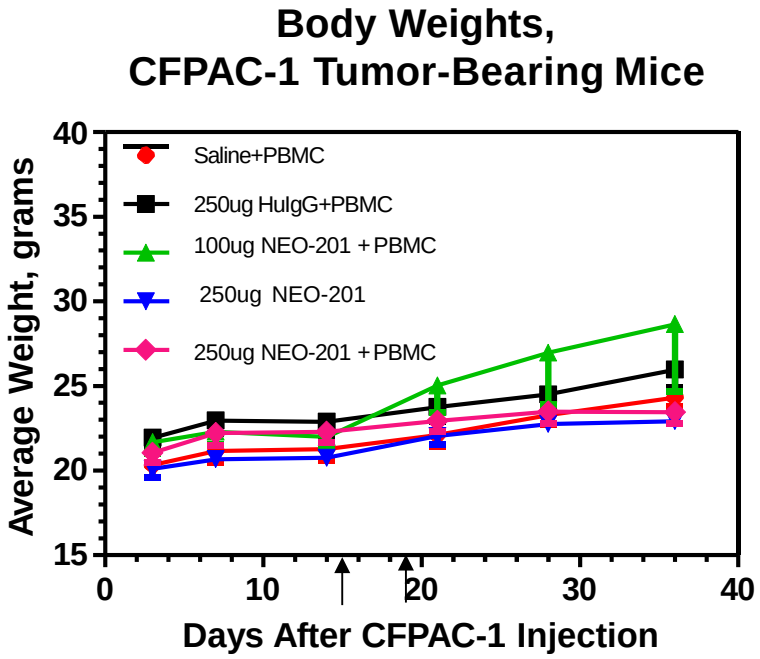
NEO-201(h16C3) Anti-tumor Efficacy in CFPAC-1 Tumor Xenograft Mouse Model



Group (n=10)	Antibody, dose	IL-2 Activated PBMC (NK cells)
1	Saline	~1x10^7
2	Human IgG, 250ug	~1x10^7
3	h16C3, 100ug	~1x10^7
4	h16C3, 250ug	No PBMC
5	h16C3, 250ug	~1x10^7

NEO-201 Anti-tumor Efficacy Results





*, indicates $p<0.05$ vs. saline group

NEO-201 injected intraperitoneally on Days 13, 17, 20
PBMC injected intraperitoneally on Days 14, 18, 21

<u>On Day 36:</u>
100ug NEO-201+PBMC, 1/10 mice tumor-free
250ug NEO-201 +PBMC, 4/10 mice tumor-free

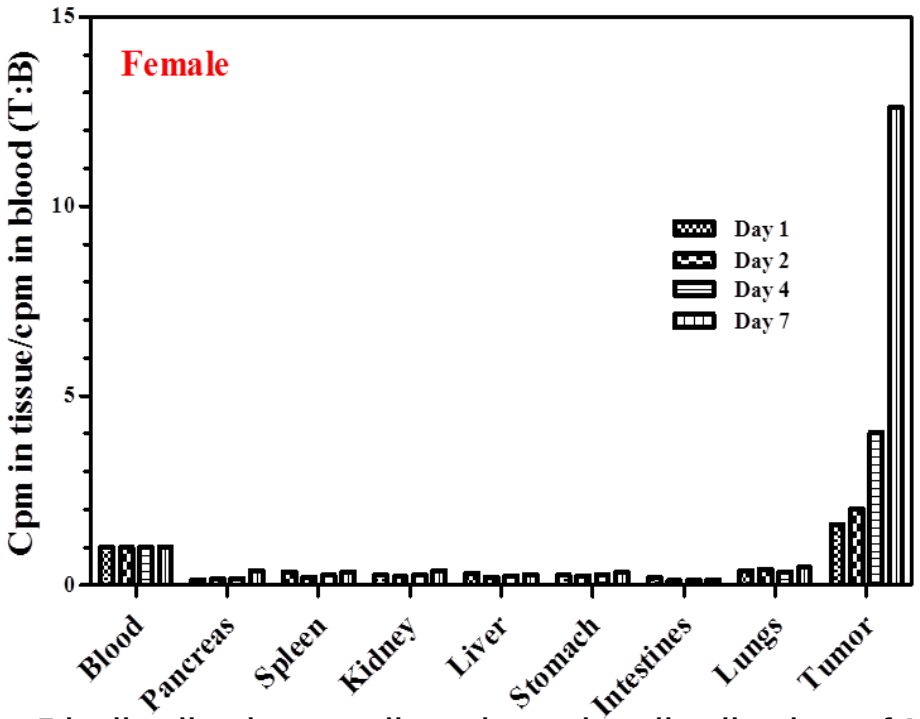
NEO-201 injected intraperitoneally on Days 13, 17, 20
PBMC injected intraperitoneally on Days 14, 18, 21

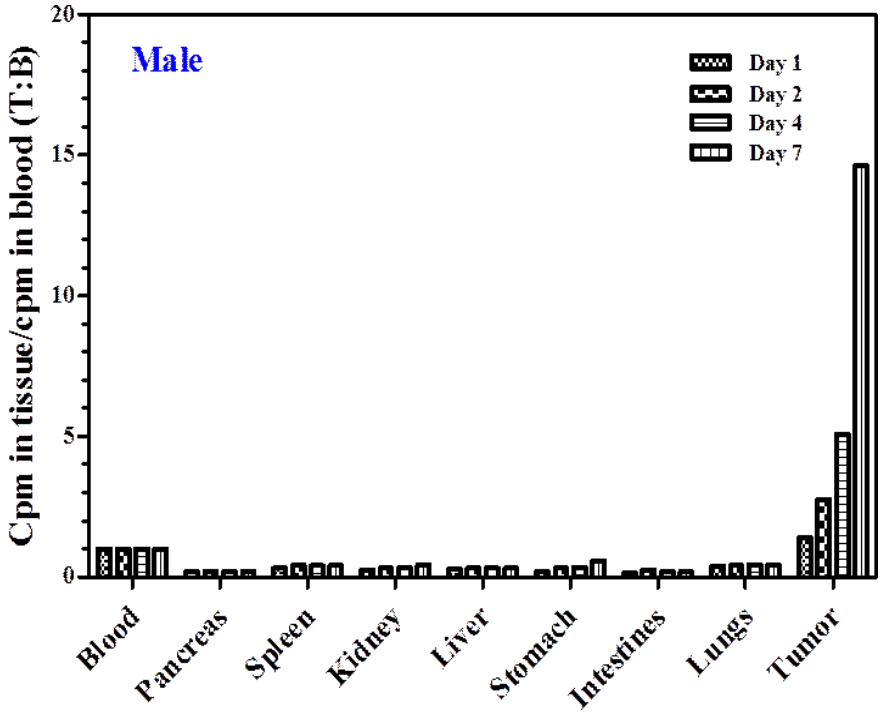
NEO-201 Anti-tumor Efficacy Results

NEO-201 treated mouse

Control/Saline treated mice

NEO-201 Biodistribution Studies





Biodistribution studies show the distribution of NEO-201 in male and female mice with pre-established CFPAC-1 tumors. The mice were injected via tail vein with 20uCi of [^{125}I] labeled NEO-201 monoclonal antibody and necropsied after 1, 2, 4 and 7 days. Blood and tumors were collected. The following organs were removed: lungs, kidneys, liver, spleen, pancreas, intestines, and stomach. All tissues were weighed. Radioactivity in tissues was measured in a gamma counter, and data were calculated as cpm/mg tissue. The data shown above represent the normalization of tissue cpm relative to blood cpm.

NEO-201: FDA interactions and Drug Manufacturing

1. Pre-IND meeting held with FDA in 2017
   a. discussed relevant animal models
   b. pre-clinical studies required prior to IND filing
   c. GMP manufacturing of drug
   d. First in Human Clinical trial
2. GMP- manufacturing completed by Catalent Pharma Solutions
3. Drug Stability Completed and Drug Released for Clinical use
4. IND filed in Q3 2018—FDA proceed letter initiated
5. NCI IRB approved study Q4 2018
6. Clinical Trial – 1st in Human initiated Q1 2019—colon ca, pancreatic ca, breast ca, NSCLC, and mucinous ovarian ca

Nonclinical Testing of NEO-201: Selection of a Relevant Animal Species

1. As shown in the TCR studies, NEO-201 has cross reactivity with human granulocyte populations. Therefore, two studies were used to determine the most relevant animal population.

    a) IHC study using GI tissue from normal mice (both C57BL/6 and BALB/c), cynomolgus monkey, mini pig, cow and rat demonstrated staining of esophagus and colon of cynomolgus monkey and mice, but not the cow, rat or mini pig GI tissues.

    b) Flow cytometry of PBMCs from human, monkey and mouse was conducted to stain granulocytes with NEO-201. Only granulocytes from both monkey and human PBMCs stained similarly positive with NEO-201.

2. Hence the cynomolgus monkey was chosen as the relevant animal for nonclinical testing.

Nonclinical Testing of NEO-201: Single Dose Study

Study #1: Cynomolgus monkeys (8 male and 8 females)

- NEO-201 administered as one (1) intravenous dose
  - ✓ Group 1: 0 mg/kg NEO-201 IV (control group)
  - ✓ Group 2: 5 mg/kg NEO-201 IV (low dose)
  - ✓ Group 3: 20 mg/kg NEO-201 IV (moderate dose)
  - ✓ Group 4: 49 mg/kg NEO-201 IV (high dose)
- Pharmacokinetics (PK) samples were drawn pre-dose, 10 minutes, 1, 2, 4, 6, 24, 48, 72, 96, 168 and 336 hours

Nonclinical Testing of NEO-201: Single Dose Study

- Post NEO-201 infusion observations
  - ✓ No significant changes were observed in body weight, food consumption, urine, or laboratory testing.
  - ✓ Neutrophil count decreases were initially detected on Day 2 in Groups 2, 3, and 4, ranging from mild to moderate; all were transient with improvements by Day 8 and resolution by Day 15, although 2 males in Group 3 and one male and one female in Group 4 had persistently low neutrophil counts through Day 15.

CEACAM-6 is expressed on granulocytes, macrophages and monocytes, and hence this finding appears to reflect an on-target side-effect of NEO-201.

PRECISION BIOLOGICS

Nonclinical Testing of NEO-201: Single Dose Study

- NEO-201 PK Results
  - ✓ Mean TK results

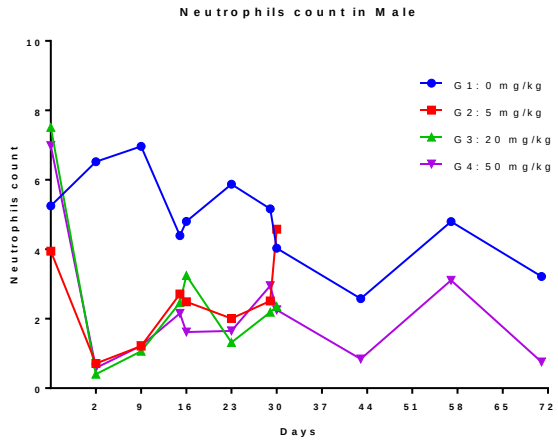
Group	HL (hr)	Tmax (hr)	Cmax (µg/mL)	Cmax/D (µg/mL/mg)	AUCinf (hr*µg/mL)	AUCinf/D (hr*µg/mL/mg)	CL (mL/hr)	Vz (mL)
2 (5 mg/kg)	46.2	0.584	138	11.4	8,220	680	1.54	103
3 (20 mg/kg)	167	0.167	579	11.2	70,100	1,360	0.746	179
4 (49 mg/kg)	170	0.167	1,470	11.8	157,000	1,260	0.830	191

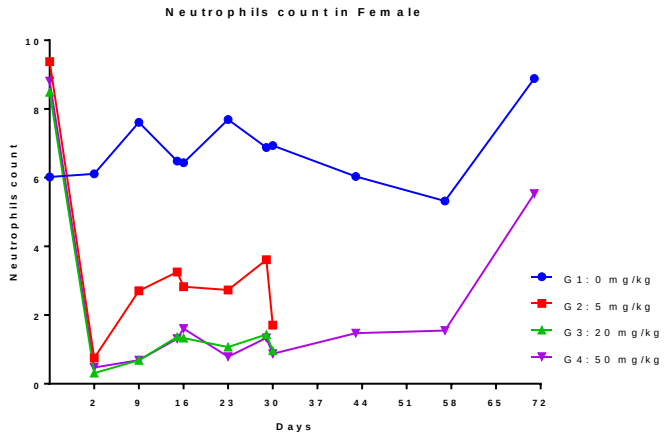
  - ✓ No difference between dose groups in Tmax (0.167 or 0.584 hour)
  - ✓ Peak (Cmax) exposure was dose proportional
  - ✓ Total (AUC) exposure was greater than dose proportional at the lowest doses and approximately proportional from 20 mg/kg to 49 mg/kg

Nonclinical Testing of NEO-201: Multi Dose Study

Study #2: 5-week GLP study with 6-week recovery in cynomolgus monkeys.

- Preliminary report showed similar findings to the observations made during the single dose study, i.e. no changes clinically, no significant changes in body weight, ECG, ophthalmology or urinalysis.
- Hematology laboratory changes were observed as depicted below:

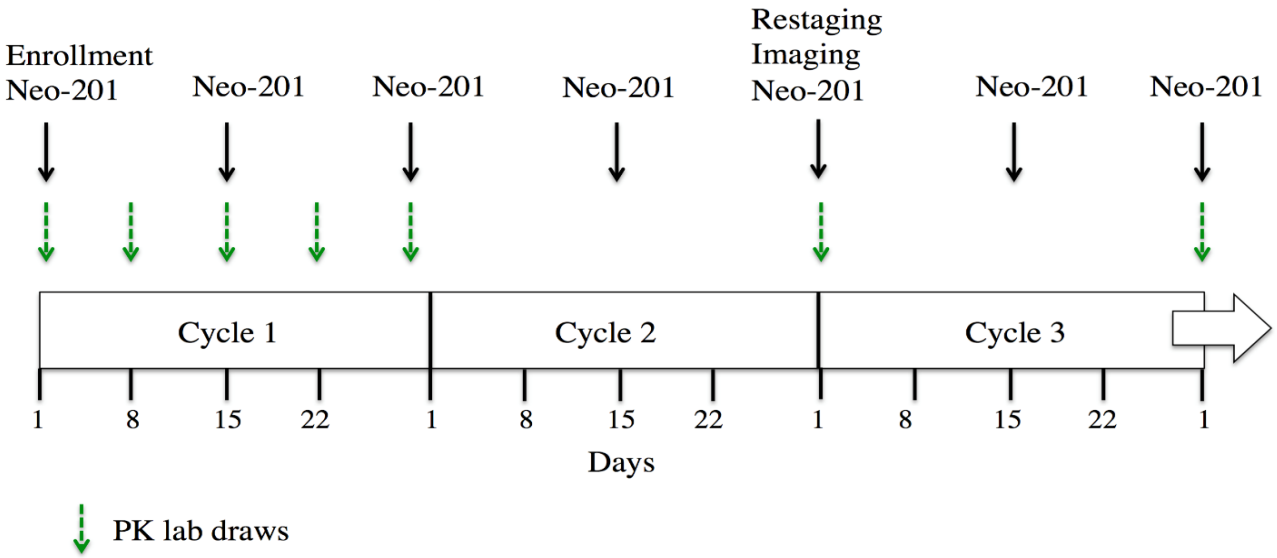




NEO-201 Ongoing Study

- NEO-201- 1st in human studies will treat patients with colon ca, pancreatic ca, breast ca, NSCLC, and mucinous ovarian ca, who are no longer eligible for standard therapy .
- Phase I first in human study at NCI, open label, dose escalation study to determine safety and recommended phase 2 dose (RP2D) in patients with refractory cancers expressing NEO-201 antigen. RP2D will be explored in expansion cohorts in several targeted disease states at multiple centers.

Study Schema



NEO-201 Ongoing Study

- Phase I first in human study at NCI:
  - Planned doses:

Dose Escalation Schedule		
Dose Cohorts	Dose of IND Agent (mg/kg)	Number of Patients planned for enrollment
Level 1	1	3 - 6
Level 2	2	3 - 6
Level 2.5**	3	3-6
Level 3	4	3 - 6
Level 3.5**	5	3-6
Level 4*	6	3 - 6
*additional doses may be investigated if no DLTs or clinical activity is observed. ** dose de-escalation cohorts		

  - Correlative studies to include:
    - Cellular immune monitoring assays (phenotype and functional [killing and suppression] assays with NK, Treg and MDSC; CD16 phenotype of NK/haNK cells);
    - Humoral immune monitoring assays (multi-plex cytokine and chemokine analysis; soluble factors such as MICA, arginase, soluble PD-1 and soluble PD-L1 and IDO, *in vivo* assay- HAHA analysis)

NEO-201 Ongoing Study

- First in human study- Once the Recommended Phase 2 Dose (RP2D) is determined, the study will be expanded to include 4-5 cohorts of up to 35 subjects of different tumor types to gain further information on toxicity, PK, and preliminary clinical response data.
- Future Studies
  - Combinatorial approaches with NEO-201 to be determined based on analysis of the Phase 1 study and *in vitro* laboratory tests.

NEO-201 Summary

- Target is broadly expressed in multiple solid tumors.
- Exhibits both ADCC and CDC killing.
- Promising pre-clinical results with complete regression of tumor in animal models.
- GMP manufacturing completed.
- Pre-clinical testing showed that NEO-201 was well tolerated in cynomolgus monkeys even at high doses.
- Preclinical changes in hematologic laboratory values represents an on-target side effect that appears to be reversible, and supports infusion schedule of every two weeks.
- FDA approved IND July 2018
- 1st in Human Study initiated at NCI Q1 2019