Preclinical/Clinical Development of a Neo-epitope targeted Monoclonal Antibody for Cancer therapy

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Forward Looking Statements

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Precision Biologics is a Biopharmaceutical Company with an Enrichment Strategy, Developing *Tumor-Specific Monoclonal Antibodies*

to Treat a Broad Variety of Cancers





Precision Biologics Wholly-Owned Oncology Pipeline Lead Clinical Programs: NEO-201

Product	Indication	Preclinical	Phase 1	Phase 2	Phase 3	
NEO-201	Phase I Solid Tumors					
	2nd line metastatic Non Small Cell Lung Cancer (NSCLC)					
	2nd line metastatic Head and Neck (H&N) cancers					
NEO-201 + Pembrolizumab	2nd line metastatic endometrial cancer					
	2nd line metastatic cervical cancer					
NEO-201 + IL-15	Refractory colorectal, pancreatic & mucinous ovarian cancer					
NEO-201	Blood tumors and Other malignancies (TBD)					
				Completed	Active	Projected



NEO-201 Monoclonal Antibody

Tumor specificity with Multiple Mechanisms of Action



NEO-201: Direct Tumor Killing & Killing Through Immune Enhancement

- Kills target through <u>Antibody dependent cell-mediated cytotoxicity (ADCC)</u> and <u>Complement dependent</u> <u>cytotoxicity (CDC)</u> unlike other CEA antibodies
- Recognizes tumor-specific variants of CEACAM-5 and CEACAM-6,
- Does not cross-react significantly with healthy epithelial tissues that express normal CEACAM-5 or CEACAM-6
- Enhanced NK tumor killing through CEACAM5/CEACAM1 blockade
- Binding and killing of human regulatory T cells (Tregs) supporting combination therapy with checkpoint therapy



NEO-201 Binds to Various Human Carcinoma Cell Lines

Flow cytometry analysis of NEO-201 binding to tumor cell lines derived from various types of solid tumors

CELL LINE	TUMOR TYPE	% POSITIVE	MFI
COLO 205	Colon	10.33	245
HT-29	Colon	38.40	352
LS174T	Colon	46.46	345
SW1116	Colon	2.36	194
SW1463	Colon	1.23	278
SW480	Colon	1.70	575
ASPC-1	Pancreatic	79.26	8927
BxPC-3	Pancreatic	97.25	2584
CAPAN-2	Pancreatic	29.69	327
CFPAC-1	Pancreatic	97.79	9281
PANC-1	Pancreatic	3.29	289
H441	NSCLC (adenocarcinoma)	69.16	675
H522	NSCLC (adenocarcinoma)	1.38	238
HCC4006	NSCLC (adenocarcinoma)	99.27	9899
HCC827	NSCLC (adenocarcinoma)	77.46	692
SK-LU-1	NSCLC (adenocarcinoma)	1.77	685
CALU-1	NSCLC (squamous)	4.22	571
H1703	NSCLC (squamous)	4.16	111
H226	NSCLC (squamous)	4.83	209
H520	NSCLC (squamous)	61.78	443
AU-565	Breast (HER2+)	50.04	227
BT-474	Breast (PR+/HER2+)	68.79	591
HCC1500	Breast (ER+/PR+)	1.53	597
SK-BR-3	Breast (HER2+)	1.61	329
T-47D	Breast (ER+/PR+)	8.00	161
ZR-75-1	Breast (ER+/PR+/HER2+)	68.80	550
BT-549	Breast (ER-/PR-/HER2-)	1.47	477
HCC1937	Breast (ER-/PR-/HER2-)	19.14	510
HCC38	Breast (ER-/PR-/HER2-)	2.15	226
MDA-MB-468	Breast (ER-/PR-/HER2-)	6.33	344

NEO-201 positive cell lines appear in bold text.

NEO-201 positivity was defined as % positive >10%

Fantini et al. Frontiers in Immunology, 2018



NEO-201

Positivity was determined using fluorescence minus one (FMO) controls. Positive cell lines were ranked according to their quantified expression level (% positive × MFI), and then sorted into groups of low (<200), medium (200-1000), and high (<1000) expression



NEO-201 Binds to a Tumor Associated Form of CEACAM-5 and -6



CELL LINE (CANCER TYPE)	MARKER	% POSITIVE	MFI
ASDC 1	NEO-201	75.86	9,078
ASPC-1	CEACAM5	20.04	869
(pancreas)	CEACAM6	77.87	52,138
BxPC-3 (pancreas)	NEO-201	97.41	5,259
	CEACAM5	79.54	711
	CEACAM6	98.45	18,690
CEDAC 1	NEO-201	85.21	1,728
CFPAC-I	CEACAM5	25.83	1,108
(pancreas)	CEACAM6	96.50	27,792
101747	NEO-201	29.15	858
(colon)	CEACAM5	36.34	1,030
	CEACAM6	63.41	1,462

From these screening the Carcinoembryonic Antigen-Related Cell Adhesion Molecule

(CEACAM)5, also known as CEA, and CEACAM 6 were identified as the most likely

targets of NEO-201

Zeligs et al. Frontiers in Oncology, 2020



IHC Confirmed that NEO-201 Reactivity is Specifically Tumor-Associated



- NEO-201 does not react against normal epithelial tissue CEACAM5/6 positive.
 - Majority of normal tissues stained CEACAM5⁺ and/or CEACAM6⁺
 - Colon (29/31, 94%), pancreatic (26/28, 93%), lung (30/32, 94%)
- NEO-201 reacts against tumor tissue CEACAM5/6 positive.
 - Majority of sampled tumors stained "triple positive" NEO-201⁺ CEACAM5⁺ CEACAM6⁺
 - Colon (28/32, 88%), pancreatic (23/30, 77%), lung (16/32, 50%)



MECHANISMS OF ACTION OF NEO-201



Mechanisms of Action

1) NEO-201 mediates Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) against human tumor cell lines



https://www.genscript.com/ADCC-and-CDC-assay-services.html



NEO-201 Mediates ADCC Against Human Pancreatic Tumor Cell Lines



- (A) ADCC activity using CFPAC-1 or ASPC-1 cells as target cells. Cells were treated with 10µg/mL of NEO-201 or human IgG1 (negative control). Purified NK cells from two healthy donors were used as effector cells at the indicated E:T ratios. (B) ADCC assay using CFPAC-1 cells treated with increasing doses of NEO-201. NK cells were used at an E:T ratio of 12.5:1.
- * statistically significant (*p* < 0.05) by T-test.

Fantini et al. Frontiers in Immunology, 2018



Mechanisms of Action

2) NEO-201 Mediates Complement-Dependent Cytotoxicity (CDC) Against Human Tumor Cell Lines



https://www.genscript.com/ADCC-and-CDC-assay-services.html



NEO-201 Mediates CDC Against Human Tumor Cell Lines





Rabbit complement

- 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.

Fantini et al. Frontiers in Immunology, 2018



Mechanisms of Action

3) NEO-201 Enhances Natural Killer Cell Cytotoxicity Against Tumor Cells Through Blockade of the Inhibitory CEACAM5/CEACAM1 Immune Checkpoint Pathway





NEO-201 Enhances NK-92 Cell Cytotoxicity Against CEACAM5+/NEO-201+ Tumor Cells

Cell line	CEACAM1 ⁺	CEACAM5 ⁺ /NEO-201 ⁺
	% positive (MFI)	
ASPC-1	61.15 (707)	9.26 (869/9,078)
BxPC-3	2.45 (1,471)	58.52 (1,447/6,420)
CFPAC-1	18.67 (1,938)	26.95 (1,108/1,728)
LS174T	2.43 (3,287)	26.84 (1,030/858)



The addition of NEO-201 resulted in a greater enhancement of NK-92 killing at all E:T ratio only against **BxPC-3** cell line (high CEACAM5⁺/NEO-201⁺ /CEACAM1⁻), while in in both CFPAC-1 (low CEACAM1/ low CEACAM5+/NEO-201+) LS174T and (low CEACAM5⁺/NEO-201⁺/CEACAM1⁻) cell lines, the addition of NEO-201 enhanced NK-92 killing only at the highest E:T ratio (12.5:1).

Fantini et al. Cancer Biother Radiopharm, 2020



Mechanisms of Action

4) NEO-201 Targets and Eliminates Human Immunosuppressive Regulatory T cells



Foxp3-expressing Treg cells can suppress the activation of T cells, the function of NK, neutrophils, dendritic cells, monocytes and macrophages in the tumor microenvironment (TME).

 Depletion of Treg cells is an effective strategy to enhance the anti-tumor immunity

Seike M. J Dermatological Research, 2019



NEO-201 targets human immunosuppressive Tregs: comparison between healthy donors and cancer patients

	CD4+/NEO-201+	CD25+/CD127-	Foxp3+/CD15s+	Foxp3+/CD15s-
Healthy donor #	% positive (MFI)	% positive (MFI)	% positive (MFI)	% positive (MFI)
1	3.54 (2,444/889)	97.22 (1,054/82)	5.00 (2,236/1,180)	84.64 (1,895/229)
2	2.75 (3,222/2,691)	99.33 (2,324/109)	5.39 (3,746/1,617)	94.61 (3,600/709)
3	2.71 (248/532)	96.73 (415/109)	4.22 (293/1,323)	88.19 (271/893)
4	2.55 (255/428)	98.61 (765/99)	14.55 (443/2,477)	80.28 (364/1,089)
5	1.85 (193/375)	96.35 (3,705/98)	37.12 (545/3,986)	49.24 (484/1,252)
6	1.73 (3,183/1,437)	88.82 (1,152/79)	72.22 (5,179/2,277)	27.78 (2,786/231)
Average	2.52 (1,591/1,059)	96.18 (1,569/96)	23.08 (2,074/2,143)	70.71 (1,567/553)
Cancer patient #	% positive (MFI)	% positive (MFI)	% positive (MFI)	% positive (MFI)
1	4.80 (355/747)	94.35 (1,359/260)	61.25 (1,993/818)	34.11 (1,851/220)
2	3.74 (404/2,136)	94.19 (1,244/371)	78.63 (907/885)	18.80 (807/316)
3	4.83 (924/266)	94.56 (221/194)	85.38 (4,072/1,726)	11.46 (3,542/446)
4	2.38 (3,699/1,067)	92.72 (839/159)	61.57 (2,716/2,513)	34.71 (2,394/1,151)
5	5.66 (1,589/672)	92,67 (970/158)	84.85 (2,297/1,113)	14.14 (2,308/438)
Average	*4.28 (1,394/978)	93.70 (927/228)	*74.33 (2,397/1,411)	22.64 (2,180/553)

The percentage of **CD4+/NEO-201+ cells** in PBMCs from cancer patients as compared to healthy donors is significantly higher (4.28% vs 2.52%; p<0.01)

The percentage of **CD4+/NEO-201+** /**CD127neg/CD25+Foxp3+CD15s** Treg (highly suppressive) cells were significantly higher in cancer patients as compared to normal donors (74.33% vs 23.08%; (p<0.01)

CD4+/NEO-201+ cells gated from live PBMCs; CD25+/CD127- gated from CD4+/NEO-201+ cells;

Foxp3+/CD15s+ and Foxp3+/CD15s+ cells gated from CD25+/CD127- cells.

* p<0.01, CD4+/NEO-201+ cancer patients vs healthy donors

p < 0.01, Foxp3+/CD15s+ cancer patients vs healthy donors



NEO-201 Eliminates Human Immunosuppressive Regulatory T cells (Tregs) Through CDC



B. Flow cytometry analysis of NEO-201 CDC activity against isolated Treg cells from PBMCs from 3 healthy donors using the EasySepTM Human CD4+CD127lowCD25+ Regulatory T Cell Isolation Kit. Isolated Treg cells were used as target cells in the presence of 10 μ g/mL of NEO-201 plus complement or complement alone in the CDC assay

Data are presented as percentage of viable cells expressing cell-surface Treg cells markers. Asterisks denote statistical significance of complement + NEO-201 vs untreated cells (unpaired t-test). *** p < 0.001. Positivity was determined by using fluorescence-minus-one controls. Positivity was defined as % of positive cells $\geq 10\%$.

Figure panel A: in Treg cells incubated with complement plus NEO-201, there was a reduction of 33.56% (28.59% vs 43.03%), 53.4% (13.34% vs 28.60%) and 41.32% (30.82% vs 52.52%) of CD4+/CD15s+ cells compared to untreated Tregs in healthy donor #1, #2 and #4, respectively.

Figure panel B: When the average of CD4+/CD15s+ cells after incubation with complement plus NEO-201 was analyzed compared to untreated Treg cells from these 3 healthy donors, we observed that the reduction was statistically significant (p<0.001)



Phase 1 Dose Escalation of NEO-201

Gender	Male: 6 (35%)	Female: 11 (65%)			
Age (years)	30-50: 5 (29%)	51-60: 4 (24%)	61-70: 5 (29%)	71-80: 2 (12%)	> 80: 1 (6%)
Cancer Type	Colorectal: 11 (65%)	Pancreatic: 4 (24%)	Breast: 2 (12%)		
Race	White: 15 (88%)	African American: 2 (12%)			
Ethnicity	Non-Hispanic: 17 (100%)				
Performance Status	ECOG 0: 6 (35%)	ECOG 1: 9 (53%)	ECOG 2: 2 (12%)		

17 subjects who failed all standard therapies were enrolled in this 1st in human study with 9 evaluable for clinical response

- 4 received NEO-201 at dose level 1 (1 mg/kg)
- 7 received NEO-201 at dose level 2 (2 mg/kg)
- 6 received NEO-201 at dose level 1.5 (1.5 mg/kg)

4 of the 9 evaluable subjects with durable stable disease (up to 15 doses)



Phase 1 Dose Escalation of NEO-201: PK Analysis



- PK analysis showed no difference between 1.5 mg/kg and 2 mg/kg cohorts
- 1.5 mg/kg and 2 mg/kg cohort: it is very likely at these dose levels, NEO-201 could be cleared from the blood between C1D7 and C1D9.
- NEO-201 was chosen at the recommended Phase 2 dose at 1.5mg/kg IV every 2 weeks



Phase 1 Dose Escalation of NEO-201: Toxicity

Body System, Adverse Event	(Dose Lev n= 4 subje	/el 1 mg/kg cts/12 dose	l s)		Dose Le (n= 7 subje	vel 2 mg/kg ects/34 doses)	Dose Level 1.5 mg/kg (n= 6 subjects/23 doses)				Cumulative Incidence (n =17 subjects/69 doses)
	Gr 1	Gr 2	Gr 3	Gr 4	Gr 1	Gr 2	Gr 3	Gr 4	Gr 1	Gr 2	Gr 3	Gr 4	
Blood and Lymphatic System	m Disorde	rs	_										
Anemia	2 (17%)	4 (33%)			4 (12%)	9 (26%)	2 (6%)		3 (13%)	3 (13%)	-		27 (39%)
Febrile Neutropenia							2 (6%)	1 (3%)			1 (4%)		4 (6%)
General Disorders and Adm	inistration	Site Cond	litions										
Chills/Rigors	2 (17%)	1 (8%)			2 (6%)	1 (3%)							6 (9%)
Fatigue	1 (8%)	1 (8%)				2 (6%)			2 (9%)				6 (9%)
Fever	6 (50%)	1 (8%)			4 (12%)	1 (3%)			4 (17%)				16 (23%)
Injury, Poisoning and proce	dural com	plications	-										
Infusion related reaction		8 (66%)		-		7 (21%)				3 (13%)			18 (26%)
Investigations													
Lymphocyte count decreased	1 (8%)		1 (8%)	-		6 (18%)	4 (12%)	2 (6%)	2 (9%)	1 (4%)	-	1 (4%)	18 (26%)
Neutrophil count decreased			2 (17%)	4 (33%)	1 (3%)		2 (6%)	10 (29%)	2 (9%)		1 (4%)	7 (30%)	29 (42%)
Platelet count decreased	1 (8%)				5 (15%)	1 (3%)			2 (9%)				9 (13%)
Weight loss					2 (6%)								2 (3%)
White blood cell decreased	4 (33%)		2 (17%)		2 (6%)	3 (9%)	7 (21%)	2 (6%)		2 (9%)	1 (4%)	4 (17%)	27 (39%)

Overall, of 17 subjects receiving a total of 69 doses of NEO-201, the most common toxicities included:

neutropenia (42%), anemia (Gr1 and Gr2, 39%), decreased white blood cell count (39%), infusion related reactions (Gr2, 26%), decreased lymphocytes (26%), fever (Gr1 and Gr2, 23%), and thrombocytopenia (Gr1 and Gr2, 13%)



Phase 1 Dose Escalation of NEO-201: DLTs

Body System, Adverse Event	Do (n= 4	se Lev I subjec	el 1 mg cts/12 d	j/kg oses)	De (n=	Dose Level 2 mg/kg (n= 7 subjects/34 doses)					Dose Level 1.5 mg/kg (n= 6 subjects/23 doses)		
	Gr 1	Gr 2	Gr 3	Gr 4	Gr 1	Gr 2	Gr 3	Gr 4	Gr 1	Gr 2	Gr 3	Gr 4	
Blood and Lymphatic System Disorders		'S											
Febrile Neutropenia							2 (6%)	1 (3%)			1 (4%)		4 (6%)
Infections and Infestations													
Sepsis								1 (3%)					1 (1%)

Dose limiting toxicities (DLTs) included fever, neutropenia, febrile neutropenia, and sepsis.

- 1 mg/kg: NO DLTs
- 2 mg/kg: 2 DLTs (1 febrile neutropenia and 1 sepsis). De-escalate to 1.5 mg/kg.
- 1.5 mg/kg (MTD): 1 DLT (febrile neutropenia)

MAIN SIDE EFFECT OBSERVED IN ALL PATIENTS: NEUTROPENIA. Strict infection risk mitigation procedures must be adhered to for ensuring patient safety during the neutropenic phases of NEO-201 dosing.



Phase 1 Dose Escalation of NEO-201: Mitigation of Neutropenia and Correlation With PK

TIME OF TREATMENT TO MITIGATE NEUTROPENIA AFFECT NEO-201 PK

1) TIME OF G-CSF ADMINISTRATION: LESSON FROM 2mg/kg cohort: comparison between patient 7 and patient 9



- Patient 7 got G-CSF at C1D8. Indeed NEO-201 was detected in his serum until C1D8.
- Patient 9 got G-CSF 24h after infusion (C1D2). At C1D4 patient 9 showed a reduction of 51.42% of NEO-201 in the serum compared to a reduction of 36.56% seen in patient 7



Phase 1 Dose Escalation of NEO-201: Mitigation of Neutropenia and Correlation With PK

TIME OF TREATMENT TO MITIGATE NEUTROPENIA AFFECT NEO-201 PK

1) TIME OF G-CSF ADMINISTRATION: LESSON FROM 1.5mg/kg cohort: patients 15, 16, 17.



The best time to administer G-CSF would be C1D6

- Patient 15: received the G-CSF from C1D5 to C1D9. At C1D4 patient cleared already 61.81% of NEO-201 from blood.
- Patient 16: received the G-CSF from C1D6 to C1D8, and a C1D8 he started to recover from neutropenia. This perfectly correlated with the fact that at C1D8 no NEO-201 was detected in the blood.
- Patient 17: received the G-CSF from C1D6 to C1D10. At C1D4 patient cleared already 48.59 % of NEO-201 from blood.



How NEO-201 kills neutrophils: ADCC or CDC?

NEO-201 DOES NOT KILL NEUTROPHILS THROUGH CDC



2h CDC ASSAY:

- Neutrophils from healthy donors isolated from whole blood and used as target cells
- Neutrophils incubated with NEO-201 for 20 minutes and then with human Ab serum for 2h at 1:8 and 1:4 dilution

How NEO-201 kills neutrophils: ADCC or CDC?

NEO-201 KILLS NEUTROPHILS THROUGH ADCC!!!



4h ADCC ASSAY:

- Neutrophils from healthy donors isolated from whole blood and used as target cells
- PBMCs from the same donor were used as effectors cells at the indicated E:T ratios in presence of 10 ug/ml of NEO-201

Phase 1 Dose Escalation of NEO-201: CLINICAL ACTIVITY

EFFECTS OF SOLUBLE FACTORS ON NK CELL STATUS

Soluble MICA: The immunoreceptor NKG2D present on NK cells is a factor involved in the activation of NK cells and costimulates CD8 T cells. MICA molecules are ligands of NKG2D and are expressed on malignant, but not on normal, cells. The release of MICA from cancer cells constitutes an immune escape mechanism that systemically impairs antitumor immunity. Analysis of sMICA in sera of 512 individuals revealed significantly (p < 0.0001) higher levels in patients with various malignancies (n = 296, median 161 pg/ml) than in healthy individuals (n = 62, median <30 pg/ml). In cancer patients, elevated sMICA levels correlated significantly with cancer stage and metastasis

Stieber et al. Int J Cancer 2006

 Soluble CEACAM-5 and -6: Soluble CEACAM-5 and -6 released by tumors are present in the circulation of patients with cancer and are correlated with cancer progression. Soluble CEACAM-5 promote angiogenesis.

Bramswig et al. Cancer Res 2013

CORRELATION BETWEEN HIGH SOLUBLE FACTORS AND ACTIVATED NK STATUS SUMMARY SOLUBLE CEACAM-5 and -6

PROGRESSIVE DISEASE

3 COLON CANCER PATIENTS

SOLUBLE CEACAM-5

(2 treated with 2 mg/kg, 1 with 1.5 mg/kg)

2 PANCREATIC CANCER PATIENTS (1.5 mg/kg)

1 BREAST CANCER PATIENT (1.5 mg/kg)

STABLE DISEASE

4 COLON CANCER PATIENTS

2 treated with 2 mg/kg, 1 with 1.5 mg/kg, 1 with 1mg/kg



SOLUBLE CEACAM-6

SOLUBLE CEACAM-5 and -6 seems to be higher in SD patients than PD

CORRELATION BETWEEN HIGH SOLUBLE FACTORS AND ACTIVATED NK STATUS SUMMARY SOLUBLE MICA

PROGRESSIVE DISEASE

3 COLON CANCER PATIENTS

(2 treated with 2 mg/kg, 1 with 1.5 mg/kg)

2 PANCREATIC CANCER PATIENTS (1.5 mg/kg)

1 BREAST CANCER PATIENT (1.5 mg/kg)

STABLE DISEASE

4 COLON CANCER PATIENTS

2 treated with 2 mg/kg, 1 with 1.5 mg/kg, 1 with 1mg/kg





Analysis of sMICA in sera of 512 individuals revealed significantly (p < 0.0001) higher levels in **patients with various malignancies** (n = 296, median **161 pg/ml**) than in **healthy individuals** (n = 62, median **<30 pg/ml**). In cancer patients, elevated sMICA levels correlated significantly with cancer stage and metastasis

Stieber et al. Int J Cancer 2006

SOLUBLE MICA is higher in PD patients compared to SD patients

CORRELATION BETWEEN SOLUBLE MICA AND ACTIVATED NK STATUS



high percentage of NKG2D⁺/CD107a⁺ and NKp46⁺ NK cells

low percentage of NKG2D⁺/CD107a⁺ NK cells: impairment of NK antitumor activity

SOLUBLE MICA seems to be correlated with NK impairment in PD patients

Conclusions

- NEO-201 has several mechanisms of action. NEO-201 is able to mediate both ADCC and CDC.
- In addition, NEO-201 can block the interaction between tumor cell CEACAM5 and NK cell CEACAM1 to reverse CEACAM1-dependent inhibition of NK cytotoxicity in patients whose tumors express the NEO-201-reactive variant of CEACAM5.
- NEO-201 can also target and eliminate human immunosuppressive regulatory T cells (Tregs)
- Our studies proved the NEO-201 anti-tumor efficacy in animal models
- Phase 1 trial concluded in December 2020: main side effect is Neutropenia, which is manageable with G-CSF administered after 5-6 days from infusion
- NEO-201 CLINICAL EFFECT: stable disease in 4 patients: low sMICA, high expression of activation and cytotoxicity markers in NK cells



Rationale for Combination of NEO-201+ Pembrolizumab

- The response rate of PD-1/PD-L1 blockade against solid cancers is around 15%-30% in front line therapy. It is significantly lower in 2nd line approved indications (10-15%).
- The low response rates and resistance to PD-1/PD-L1 blockade may be due to the action of **Regulatory T (Tregs) cells** in the TME. Tregs cells have been demonstrated to **play a role in increase resistance to PD-1/PD-L1 blockade**
- Our preliminary data showed that NEO-201 can target and eliminate Tregs cells through CDC
- Based on this data we hypothesize that combining NEO201 with PEMBROLIZUMAB may overcome resistance to PD-1/PD-L1 checkpoints inhibitors by depleting negative regulatory T-regs and enhancing immune system mediated anti-tumor activity in subjects for whom pembrolizumab is currently indicated



NEO-201 Targets and Eliminates Human immunosuppressive Regulatory T Cells (Tregs)



- Foxp3-expressing Treg cells can suppress the activation of T cells, the function of NK, neutrophils, dendritic cells, monocytes and macrophages in the tumor microenvironment (TME).
- Data suggests that increased Tregs in the tumor microenvironment diminishes the efficacy of checkpoint blockade therapy
- Depletion of Treg cells is an effective strategy to enhance the anti-tumor immunity
- Eliminating Tregs justifies combining NEO-201 with other immunotherapies (i.e., checkpoint inhibitors)

Seike M. J Dermatological Research, 2019



NEO-201 + Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor

EFFICACY OF PEMBROLIZUMAB:

- **NSCLC**: substantial, clinically meaningful benefits in OS, PFS, and ORR in participants with NSCLC who progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1 and do not have any sensitizing EGFR mutations or ALK rearrangements
- **HNSCC**: On June 2019, the FDA approved pembrolizumab (KEYTRUDA, Merck) for the first-line treatment of patients with metastatic or unresectable recurrent HNSCC
- UTERINE CANCER: On September 17, 2019 the FDA granted accelerated approval to **pembrolizumab plus lenvatinib** for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
- CERVICAL CANCER: On 12 June 2018, the FDA approved pembrolizumab (Keytruda, Merck and Co. Inc.) for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumours express PD-L1 (CPS ≥1)



Significant Unmet Need: Anti PD-1 Therapy Failure

70-80% of Patients Non-responsive to Approved Cancer Immunotherapies – Lower in 2nd line indications



Efficacy of NEO-201

- NEO-201 addresses nonresponsive patient populations
- Mechanism-driven firstin-class combinations
- Anti PD-1 mAb response rates:
 - 2nd Line NSCLC <10% (post prior therapy), endometrial cancer 13%, H&N cancer 16%, and cervical cancer 12%



NEO-201 + Pembrolizumab Phase 2b Clinical Trial

Objectives

- Determine Objective Response Rate (ORR = CR, PR, SD) as determined by RECIST v1.1 guidelines and progression free survival (PFS) in four cohorts of subjects (subjects with NSCLC, HNSSC, uterine and cervical cancers) receiving NEO-201 at the RP2D in combination pembrolizumab at the FDA approved adult dose
- Assess immunogenicity of NEO-201 in adults with relapsed or chemo-resistant solid tumors participating in the dose escalation cohort and in the first 10 subjects receiving combination therapy.





NEO-201 + Pembrolizumab Phase 2b Clinical Trial: Study Design Overview

- Enrollment into Four 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.
- ❑ Including the number of subjects required to determine the RP2D of NEO-201, a minimum of 74 (17 + 57) and maximum of 121 (17 + 104) subjects will participate in this study. Allowing for an additional 5 subjects to replace potentially in-evaluable subjects, the maximum accrual on this study will be 126 subjects.
- □ Using a Simon minimax two-stage design for the accrual to each disease cohort the following accrual targets have been established.

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)

Enrollment to two-stage design per expansion cohort



Summary: NEO-201 Studies

Phase 1/2b Using 2nd Line Checkpoint in Combination with NEO-201

- Targeting 2nd line therapy for NSCLC, H&N cancer, endometrial cancer, and cervical cancer (**Ongoing**)
- Strong scientific data supporting ability of NEO-201 to improve antitumor responses of Pembrolizumab (Keytruda) in 2nd line FDA approved indications where there is a significant unmet need (multibillion dollar annual market)
- Approximately \$25M of trial costs (including Pembrolizumab) are subsidized

Phase 2 Clinical Trials Using NEO-201 + IL-15 in Refractory Solid Tumors

• Targeting refractory solid tumors, including colorectal cancer, pancreatic cancer, and mucinous ovarian cancer, expressing antigen recognized by NEO-201 mAb (Planned)

NEO-201 Phase 2 Hematological Malignancies

- Preclinical data supports binding and killing to hematological malignancies with NEO-201 antibody
- Provisional Patent protection filed in May 2021

