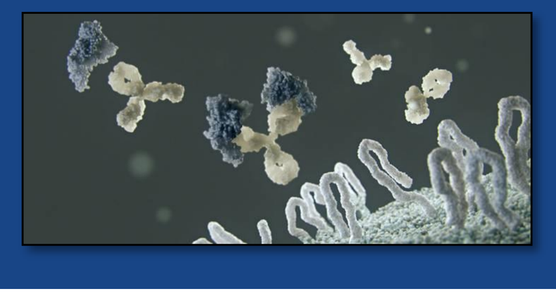
Interim results from CLASSICAL-Lung, a phase 1b/2 study of pepinemab (VX15/2503) in combination with avelumab in advanced NSCLC

Michael Rahman Shafique[1], Terrence Lee Fisher[2], Elizabeth E. Evans[2], John E. Leonard[2], Desa Rae Electa Pastore[2], Crystal L. Mallow[2], Ernest Smith[2], Maurice Zauderer[2], Andreas Schröder[3], Kevin M. Chin[4], J. Thaddeus Beck[5], Megan Ann Baumgart[6], Ramaswamy Govindan[7], Rachel E. Sanborn[8], Jonathan Wade Goldman[9]; Department of Thoracic Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL[1]; Vaccinex, Inc., Rochester, NY[2]; Merck KGaA, Darmstadt, Germany[3]; EMD Serono, Inc., Billerica, MA[4]; Highlands Oncology Group, Fayetteville, AR[5]; University of Rochester, Rochester, NY[6]; Washington University School of Medicine, St. Louis, MO[7]; Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR[8]; UCLA Medical Center, Los Angeles, CA[9]

tfisher@vaccinex.com

Abstract #2601

NCT03268057



BACKGROUND

Blockade of the PD/PD-L1 pathway is an effective immunotherapy for NSCLC, however rational combination therapies are needed to overcome resistance mechanisms. The CLASSICAL-Lung clinical trial tests the combination of pepinemab with avelumab to couple immune activation via checkpoint inhibition with beneficial modifications of the tumor immune microenvironment via pepinemab.

Pepinemab

- Is an IgG4 humanized monoclonal antibody targeting semaphorin 4D (SEMA4D, CD100). *In vivo* preclinical models demonstrated antibody blockade of SEMA4D promoted infiltration of CD8+ T cells and dendritic cells, and reduced function and recruitment of immunosuppressive myeloid and regulatory T cells (Treg) within the tumor. Importantly, preclinical combinations of anti-SEMA4D with various immunotherapeutic agents enhanced T cell activity and tumor regression.

Avelumab

- Is a fully human anti-PD-L1 IgG1 antibody that has been approved for the treatment of patients with metastatic Merkel cell carcinoma, advanced or metastatic urothelial carcinoma and in combination with axitinib for patients with advanced renal cell carcinoma. Avelumab inhibits PD-L1-PD-1 interactions and also has the potential to induce ADCC.

Figure 1. Pepinemab proposed mechanism of action [1,2]

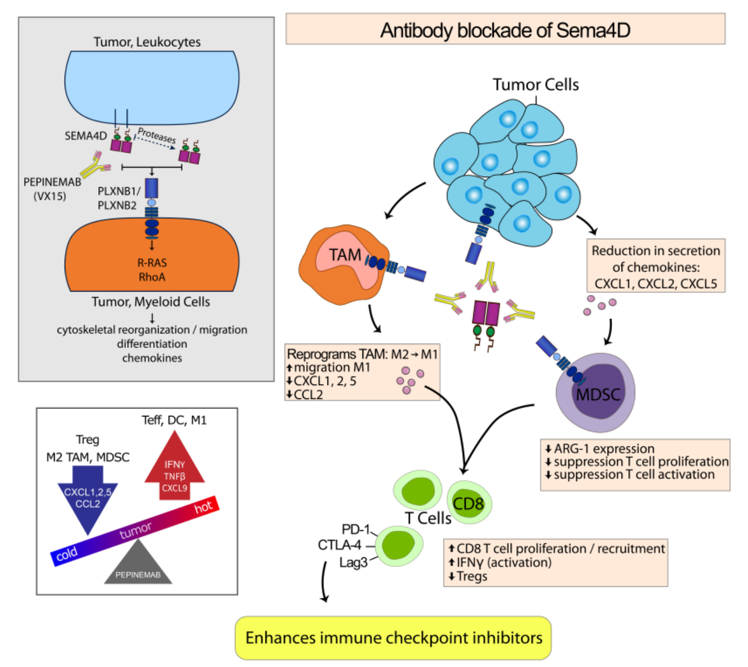


Figure 2. Preclinical data supporting combination therapy

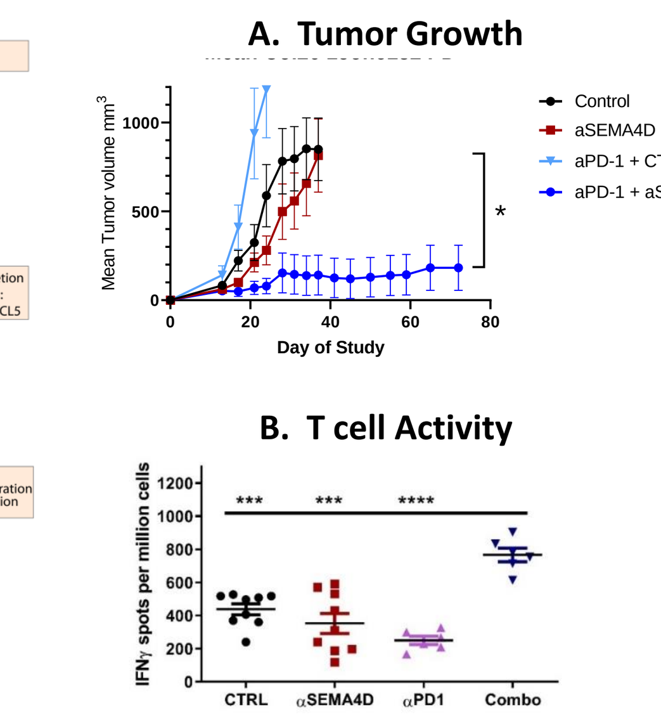


Figure 3. Avelumab proposed mechanism of action

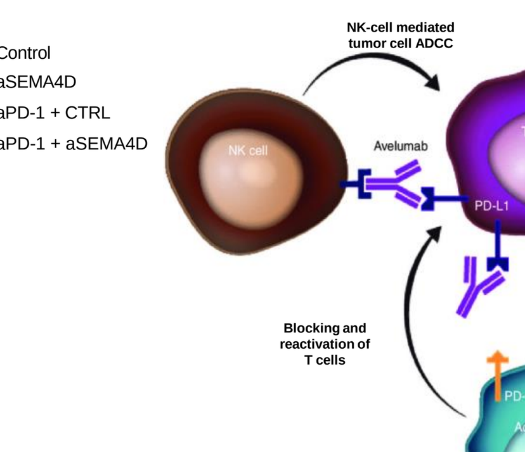


Figure 2: Combination therapy enhances frequency of tumor regression and T cell activity. A) Colon26 (500,000 cells) were subcutaneously implanted into Balb/c mice, that were then treated with αSEMA4D / MAb67 (10 mg/kg, weekly IP X2), αPD-1 / MAb RMP1-14 (10 mg/kg, twice/week, n=20). **B)** T cells from tumor draining lymph node were isolated and stimulated with MHC-I restricted immunodominant peptide AH-I of gp70; frequency of IFNg-secreting spots was enumerated by ELISPOT. (*, p<0.05; ***, p<0.001; ****, p<0.0001)

METHODS

This ongoing phase 1b/2, open label, single arm, first-in-human combination study is designed to evaluate the safety, tolerability and efficacy of pepinemab in combination with avelumab in 62 subjects (pts) with advanced (stage IIIB/IV) NSCLC.

Study Design

- The trial is split into dose escalation (n=12) and dose expansion (n=50) phases.
- The dose escalation portion includes subjects who are immunotherapy naïve and have either progressed or declined standard first or second-line systemic anticancer therapy.
- Subjects in the dose escalation cohorts received ascending doses of pepinemab (5, 10, 20 mg/kg, Q2W) in combination with avelumab (10mg/kg, Q2W).
- The expansion phase includes an IO naïve (ION) cohort as well as a second cohort of subjects whose tumors progressed during or following immunotherapy (IO failure, IOF).

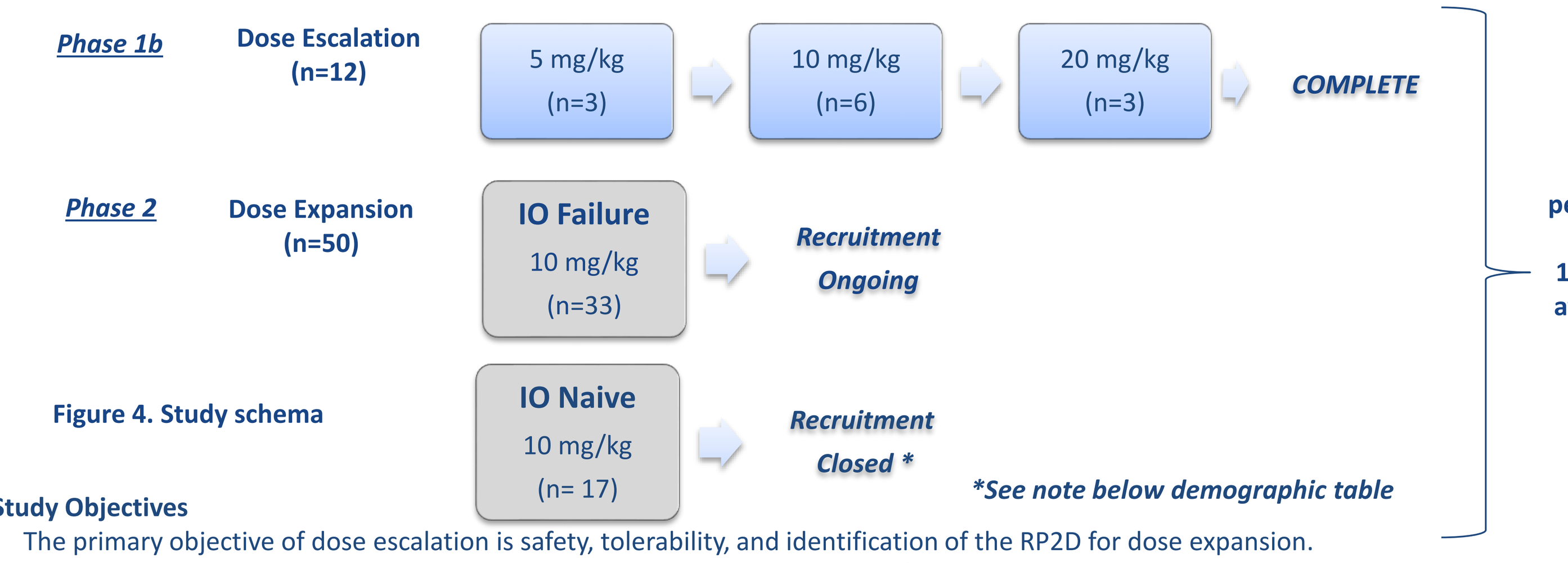


Figure 4. Study schema

Study Objectives

- The primary objective of dose escalation is safety, tolerability, and identification of the RP2D for dose expansion.
- Secondary objectives include evaluation of efficacy, immunogenicity, and PK/PD, and an exploratory objective is to identify candidate biomarkers of activity

INTERIM RESULTS

Demographic Characteristics (10 May 2019)

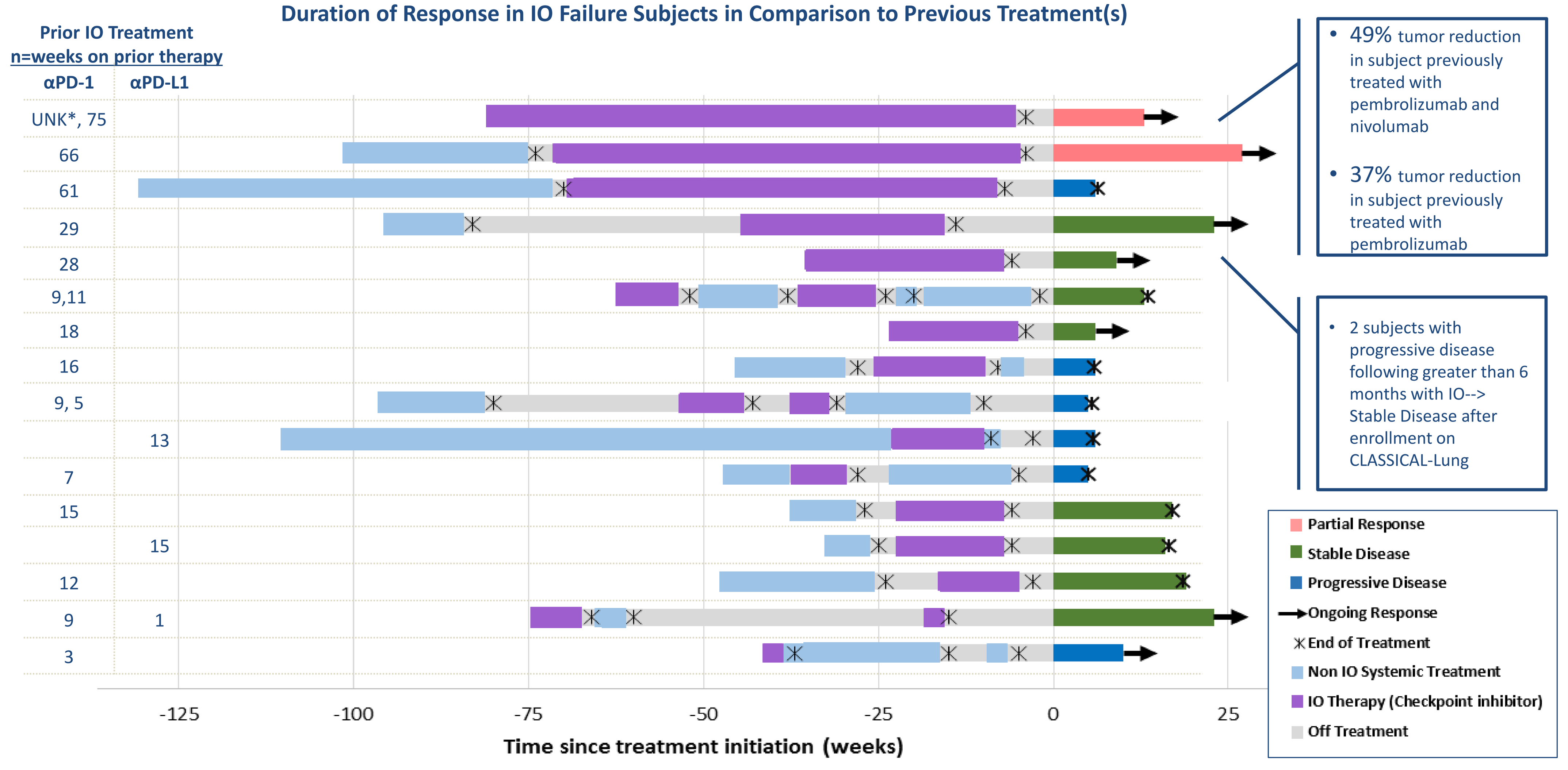
Table 1. Demographics

Baseline Characteristics	ION (1b & Phase 2)	IOF	ALL
Subjects Enrolled n=	28	21	49
Age (years)			
Median (Min-Max)	62 (30-83)	66 (51-79)	66 (30-83)
18 to <65	15 (54%)	7 (33%)	22 (45%)
65 and over	13 (46%)	14 (67%)	27 (55%)
Sex			
Men	14 (50%)	16 (76%)	30 (61%)
Women	14 (50%)	5 (24%)	19 (39%)
Race			
Asian	0 (0%)	1 (5%)	1 (2%)
Black or African American	0 (0%)	2 (10%)	2 (4%)
Native Hawaiian or Other Pacific Islander	1 (4%)	1 (5%)	2 (4%)
White	27 (96%)	17 (81%)	44 (90%)
Ethnicity			
Non-Hispanic or Latino	28 (100%)	19 (90%)	47 (96%)
Hispanic or Latino	0 (0%)	2 (10%)	2 (4%)
ECOG performance status			
0	10 (36%)	3 (14%)	13 (27%)
1	18 (64%)	18 (86%)	36 (73%)
Disease Stage at Screening			
IIIA	0 (0%)	1 (5%)	1 (2%)
IV	28 (100%)	20 (95%)	48 (98%)
Histology			
Adenocarcinoma	17 (61%)	13 (62%)	30 (61%)
Squamous Cell	11 (39%)	8 (38%)	19 (39%)
Historical PD-L1 (22C3) Status Reported by Investigator Site			
No PD-L1 expression	11 (39%)	3 (14%)	14 (29%)
Low PD-L1 expression	9 (32%)	1 (5%)	10 (20%)
High PD-L1 expression	2 (7%)	3 (14%)	5 (10%)
Unknown at data cut	6 (21%)	14 (67%)	20 (41%)
Evaluability (Subjects who achieved first restaging)			
Unevaluable subjects	8 (29%)	0 (0%)	8 (16%)

ION Population

- Historical PD-L1 (22C3) status reported by the investigator sites revealed that only 7% (2/28) showed high PD-L1 expression.
- 29% were found to be unevaluable due to withdrawal of consent (n=4) or death (n=4; all unrelated, not other specified, sudden cardiac death, death due to disease progression and hemorrhage).
- Changes in clinical management of IO naïve subjects following initiation of this study made it increasingly difficult to enroll immunotherapy naïve subjects and many of those enrolled were; 1) unevaluable, or 2) appeared to have low PD-L1 expression.
- Among 20 evaluable IO naïve subjects enrolled, the Disease Control Rate (PR+SD) was 75%.

Duration of Response in IO Failure Subjects in Comparison to Previous Treatment(s)



*Additional treatments of carboplatin/paclitaxel, nivolumab and carboplatin/alimta were reported by the investigator site at unknown intervals

Figure 5. Swimmer plot showing the duration and best overall response of IO Failure subjects in comparison to previous treatment(s)

- **Partial responses were observed for 2 IO Failure subjects at first scan and PR status has been maintained at most recent restaging. These subjects had previously progressed following treatment with pembrolizumab.**
- **Stable disease was attained in 8 subjects at first scan and has been maintained for three subjects at most recent restaging.**
- **Based on current understanding of mechanism of action, pepinemab may overcome immune exclusion and myeloid suppression, intrinsic or acquired mechanisms of resistance in IO failure patients.**

Response Rate in IO Failure Subjects

- The overall disease control rate for the IO Failure subjects is 62.5% (10/16), as of 10 MAY 2019.
- The disease control rate for subjects on study ≥ 8 weeks is **90%**, including 6 subjects with durable responses ≥16 weeks.

Subjects (n=16)	
Overall Disease Control Rate	62.5% (10/16)
Progressive Disease	6
Non-evaluable	0
Disease Control Rate ≥8 weeks	90% (9/10)
Responses	
Partial Response	13% (2/16)
Stable Disease	50% (8/16)

Table 3. Disease control and response rate in IO Failure Subjects

Duration of Response in all IO Failure Subjects

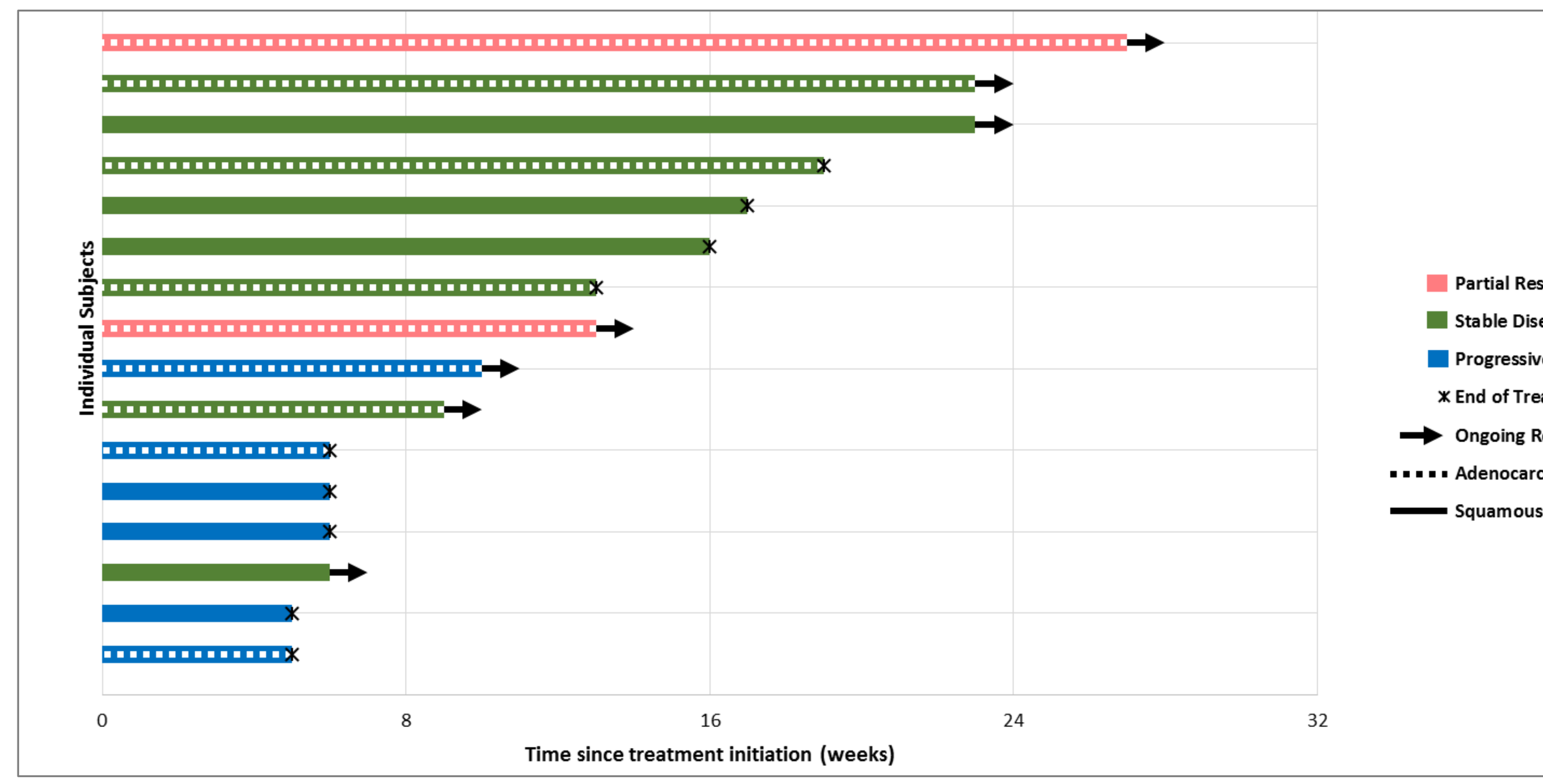


Figure 6. Swimmer plot showing the duration and best overall response of IO failure subjects

Pharmacodynamics of SEMA4D

- SEMA4D saturation, cellular SEMA4D levels, and total soluble SEMA4D (circulating complex) levels change as expected, based on historical experience with single agent pepinemab treatment.

Figure 8. % Saturation / PK

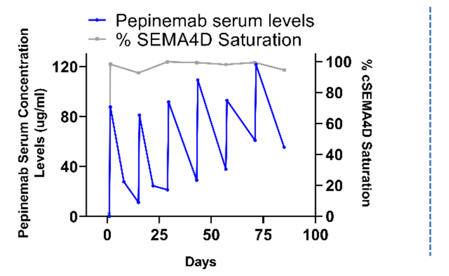


Figure 9. Cellular SEMA4D / PK

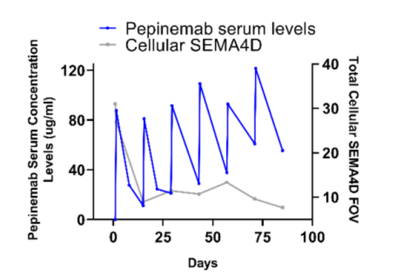
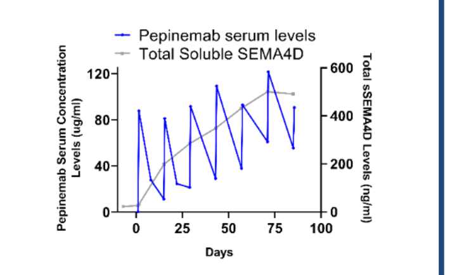


Figure 10. t-Soluble SEMA4D / PK



Pharmacokinetics

- Initial PK results show comparability to PK data from previous single agent trials.

Figure 11. Avelumab drug levels (ug/ml)

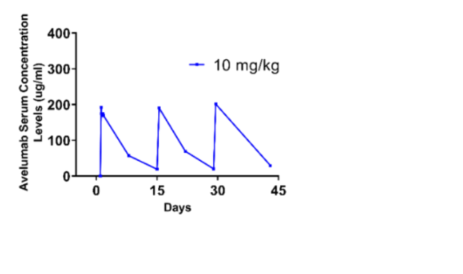
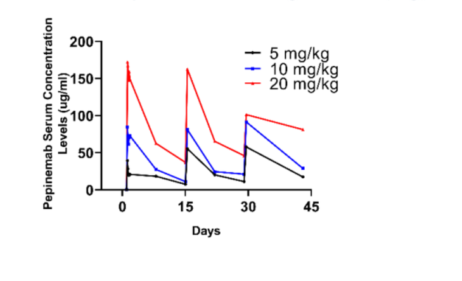


Figure 12. Pepinemab drug levels (ug/ml)



Immunogenicity

- Overall immunogenicity does not appear to be a concern with this combination.
- SEMA4D receptor occupancy was not affected and only one subject developed a response that continued to increase in titer in later cycles.

Subjects n=12	Pepinemab 105 Samples	Avelumab 153 Samples
Positive ADA	3	2
Positive ADA in >1 Cycle	2	2

Table 2. Escalation subjects Experiencing ADA

Exploratory Biomarkers: Multiplex Tumor Immunohistochemistry

- CD8+ T cell density and CD8:FoxP3 ratio increased in tumor following treatment with pepinemab + avelumab.
- CD8+ T cell levels in TIL appear to correspond with response. Low T cell density was observed in tumor tissue from two subjects with rapidly progressing disease (PD).
- Tumor was absent or reduced in biopsies from two subjects analyzed with partial response (PR) as defined by RECIST criteria.
- No tumor was observed in biopsies from three of four subjects analyzed with stable disease (SD#1, #2, #3), as defined by RECIST criteria. Instead, biopsies contained fibrotic tissue with evidence of inflammation (see below). Interestingly, tumors from two of these three SD subjects were PD-L1 negative.

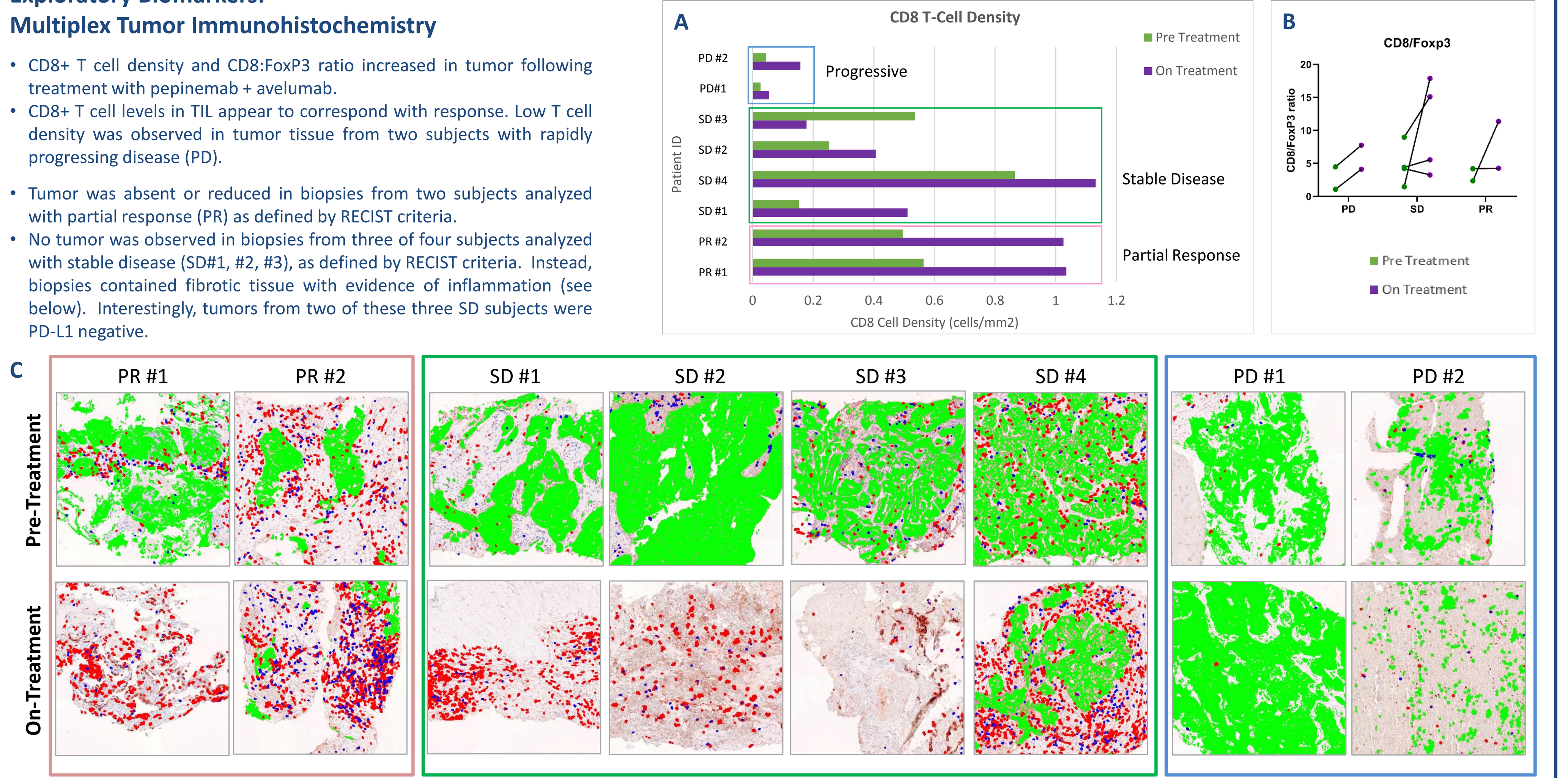


Figure 7. Multiplex IHC demonstrating tumor content and shift in balance of T cells in TME. Biopsies from seven IO-failure subjects and one IO-naïve subject (PR #1) were analyzed, including pre and on-treatment samples isolated from the same lesion; on-treatment biopsies were collected at cycle 3, week 5 visit, ~30 days post first treatment with pepinemab + avelumab. 5 micron FFPE sections were stained sequentially with Hematoxylin, pan-cytokeratin, CD8 and FoxP3; scans were co-registered for each stain. A) # of CD8+ T cells/sample area (mm2) was determined: total number of CD8+ cells were quantified from entire section, excluding necrotic areas, and normalized by sample area using Visiopharm software. B) # of FoxP3+ cells/sample area (mm2) was determined as in A and ratio was calculated for each patient biopsy. C) Images were taken at 10x magnification with CD8 (red) and FoxP3 (blue) overlays on cytokeratin stain; cytokeratin-positive tumor is colored green. Tumor content was verified by pathologist* review.

Pepinemab / avelumab combo is well tolerated to date (10 May 2019)

- The combination therapy of pepinemab plus avelumab is well tolerated at all dose levels; no concerning safety signals identified to date.
- One DLT, a grade 3 pulmonary embolism, occurred in the 10mg/kg pepinemab + 10mg/kg avelumab escalation cohort, resolved and did not recur in that same subject or additional subjects in any cohort.
- Two immune-related Adverse Events (irAE): Myositis and Diabetic ketoacidosis (related to avelumab only).

Table 4[c]. Treatment-related Grade 1/2 AEs associated to combination, occurring in subjects >1x or Grade 3

Arm	Adverse Event Detail	Grade 1	Grade 2	Grade 3	Total Subjects[d]
IO Naïve[a]	Alanine aminotransferase increased	3 [3]	1 [1]	1 [1]	4
	Amylase increased	1 [2]	1 [1]		1
	Anaemia	2 [2]			2
	Aspartate aminotransferase increased	2 [2]	1 [1]	1 [1]	2
	Blood creatine phosphokinase increased	1 [1]			1
	Chills	2 [2]	1 [1]		3
	Decreased appetite	1 [1]	1 [1]		2
	Diarrhoea	1 [2]			1
	Fatigue	4 [4]	3 [3]		7
	Gamma-glutamyltransferase increased	2 [2]	2 [3]		2
	Iron deficiency		1 [2]		1
	Lipase increased	1 [1]		2 [2]	2
	Myalgia	3 [3]			3
	Myositis			1 [1]	1
	Pulmonary embolism			1 [1]	1
	Pyrexia	3 [3]	1 [1]		3
	Rash	1 [3]	1 [2]		1
	Systemic inflammatory response syndrome			1 [1]	1
	Total Events	[31]	[16]	[7]	16 [54]
IO Failure[b]	Abdominal pain		1 [1]	1 [1]	1
	Chills		1 [1]		1
	Decreased appetite		1 [1]		1
	Fatigue	2 [2]	1 [1]		3
	Pyrexia	1 [1]			1
	Rash	1 [1]			1
	Total Events	[4]	[4]	[1]	4 [9]

[a] Denotes subjects dosed w/5, 10 or 20 mg/kg of pepinemab + 10 mg/kg of avelumab
[b] Denotes subjects dosed w/10 of pepinemab + 10 mg/kg of avelumab
[c] n denotes the number of subjects, [x] denotes the number of events, (i.e. 2 [2] : 2 Subjects Experienced 2 AEs)
[d] totals may not add up since the same subject could have experienced multiple AEs

CONCLUSIONS

- The combination therapy of pepinemab plus avelumab is well tolerated at all dose levels; no concerning safety signals identified to date.
- Recommended Phase 2 Dose (RP2D) was selected as 10 mg/kg of pepinemab Q2W (w/10 mg/kg avelumab Q2W).
- Interim analysis of efficacy in IOF subjects is promising with 13% PR, 50% SD, and several subjects on trial for approximately 6 months.
- Initial PK/PD data are similar to those seen in previous single agent trials.
- Immunogenicity does not appear to be a concern.
- Exploratory:
  - ➢ Initial IHC work demonstrates increased intratumoral CD8 density and CD8:FoxP3 ratios following combination treatment.
  - ➢ Interestingly, no evidence of tumor was detected in 3 of 4 on-treatment biopsies from patients with stable disease; two of these tumors were PD-L1-negative.
  - ➢ Additional studies are planned to interrogate the tumor microenvironment and peripheral immune compartment for lymphocyte and suppressor cell subset analysis. Additional exploratory work may include SEMA4D and PLEXIN IHC, T-cell inflamed gene expression profile, tumor mutation burden, PD-L1 IHC, and RNAseq.

1. Evans, EE et al 2015. *Cancer Immunol Res*. 3(6):689-701.
2. Fisher et al, 2016. *MAbs.* 8(1): 150-162.
3. Fisher et al, 2016. *Cytometry B Clin Cytometry.* 90B: 199-208.
4. Patnaik et al, 2016. *Clin. Can. Res*. 22(4): 827-36.
5. Clavijo et al, 2019. *Cancer Immunol Res.* 7(2): 282-291.

*We would like to acknowledge Jerome Jean-Gilles Jr., MD, Department of Pathology & Lab Medicine, University of Rochester Medical Center for pathology assessment.

Funding: This study receives funding from Merck KGaA as part of the alliance between Merck KGaA, Darmstadt, Germany and Pfizer, Inc, New York, NY, USA.

Link to poster on Vaccinex.com (Events & Presentations)