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

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#P414

BACKGROUND

Despite progress of immune checkpoint blockade therapies, many non-small cell lung cancer (NSCLC) patients do not receive durable clinical benefit from these agents, and even in those who do respond initially, acquired resistance and tumor recurrence can develop. Therefore, the development of therapies that can overcome resistance factors remains a critical unmet need. The CLASSICAL-Lung clinical trial evaluates the combination of pepinemab with PD-L1 antibody avelumab to couple beneficial modifications of the immune microenvironment via pepinemab with immune activation via checkpoint inhibition.

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 (also see **Poster P478**).

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 MOA [1,2]

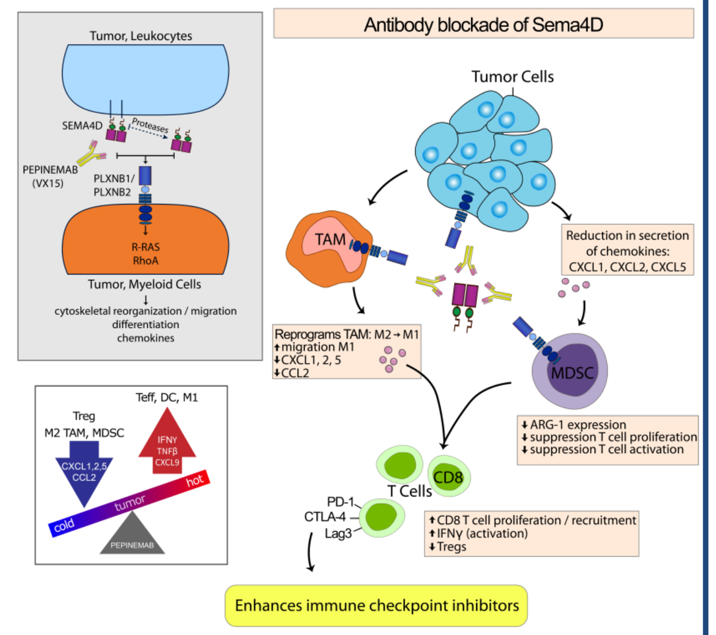

Figure 2. Avelumab proposed MOA

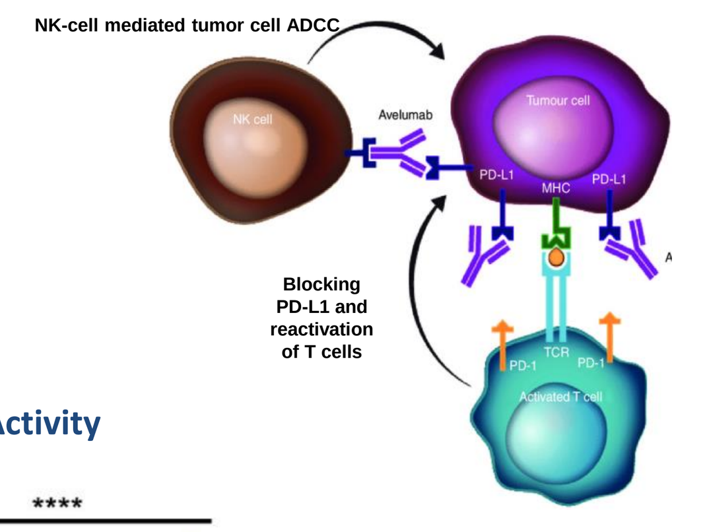

Figure 3. Preclinical data supporting combination therapy

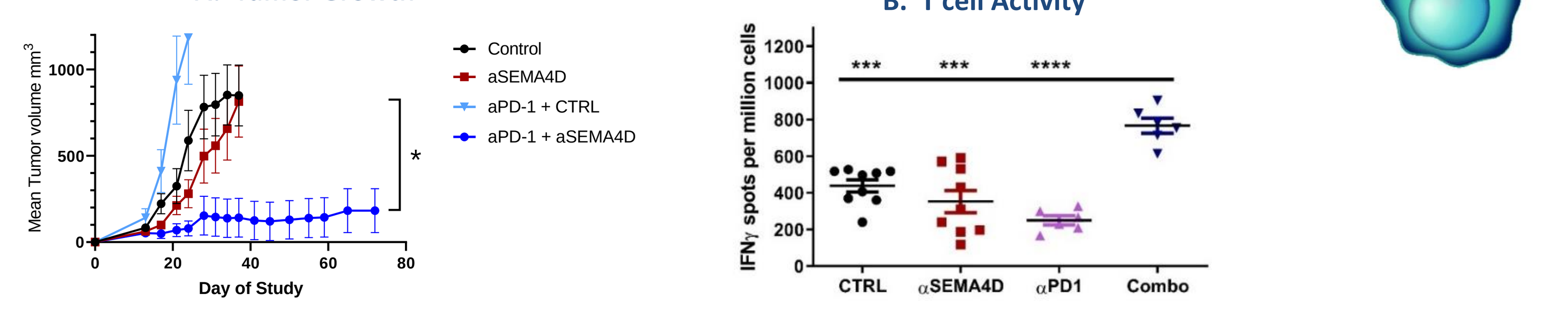

Figure 3: Combination therapy enhances frequency of tumor regression and T cell activity. **A)** Colon26 (500,000 cells) were subcutaneously implanted into Balb/c mice, that were then treated with αSEMA4D / MAb67 (10 mg/kg, weekly IP X2), αPD-1 / MAb RMP1-14 (10 mg/kg, twice/week, n=20). **B)** T cells 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 completely enrolled phase 1b/2, open label, multi-center, first-in-human combination study is designed to evaluate the combination of pepinemab with avelumab in 62 subjects (pts) with advanced (stage IIIB/IV) NSCLC.

Study Design

- The trial is split into dose escalation (n=12) and 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 three 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).

Study Objectives

- The primary objective 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

Phase 1b	*Phase 2*
Dose Escalation (n=12)	Dose Expansion (n=50)

pepinemab + 10 mg/kg avelumab, Q2W

IO Naive

- 5 mg/kg (n=3)
- 10 mg/kg (n=6)
- 20 mg/kg (n=3)

IO Failure 10 mg/kg (n=32)

IO Naive 10 mg/kg (n= 18)

ENROLLMENT COMPLETE

1.Evans, EE et al 2015. *Cancer Immunol Res.* 3(6):689-701. http://cancerimmunolres.aacrjournals.org/content/early/2015/01/22/2326-6066.CIR-14-0171.full.pdf
2.Fisher et al, 2016. *MAbs.* 8(1): 150-162. http://www.tandfonline.com/doi/abs/10.1080/19420862.2015.1102813
3.Fisher et al, 2016. *Cytometry B Clin Cytometry.* 90B: 199-208. https://www.ncbi.nlm.nih.gov/pubmed/26566052
4.Patnaik et al, 2016. Clin. Can. Res. 22(4): 827-36. https://www.ncbi.nlm.nih.gov/pubmed/26446947

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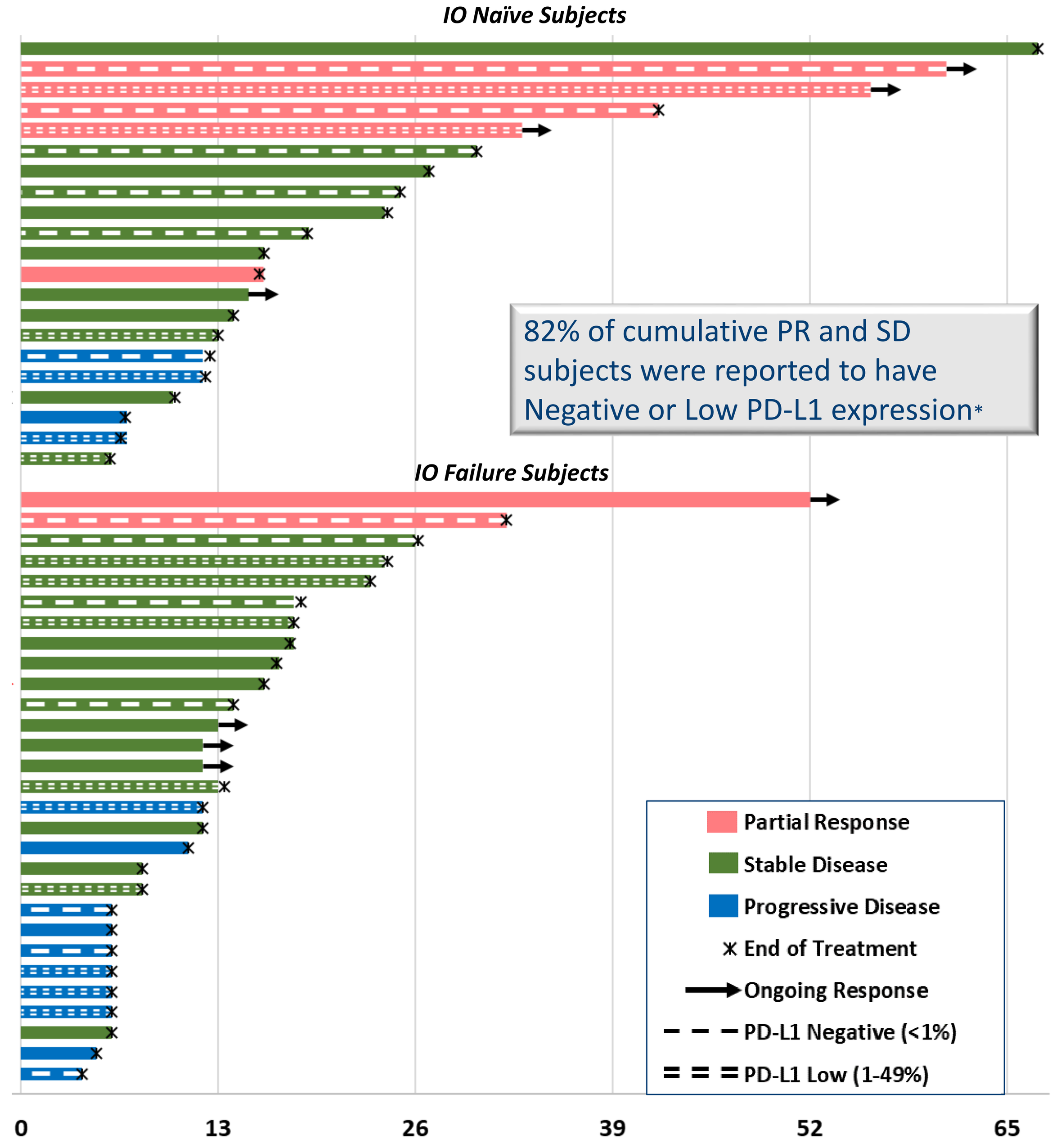
Link to poster on Vaccinex.com (Events & Presentations)

INTERIM RESULTS: CLASSICAL-Lung (NCT03268057)

Figure 4: Duration of Response in Evaluable IO Naive and IO Failure Subjects



*PD-L1 analysis was performed via Dako 73-10 pharmDx. PD-L1 status reported (34/50 subjects) is from data available at cut off (24 Oct 2019). A total of 22 SD and PR subjects were analyzed and 18 were reported to be PD-L1 negative or low (0-49%); 9 of these were PD-L1 negative (<1%).

Figure 5: Percent Change in Target Lesion Diameter in IO Naive and IO Failure Subjects

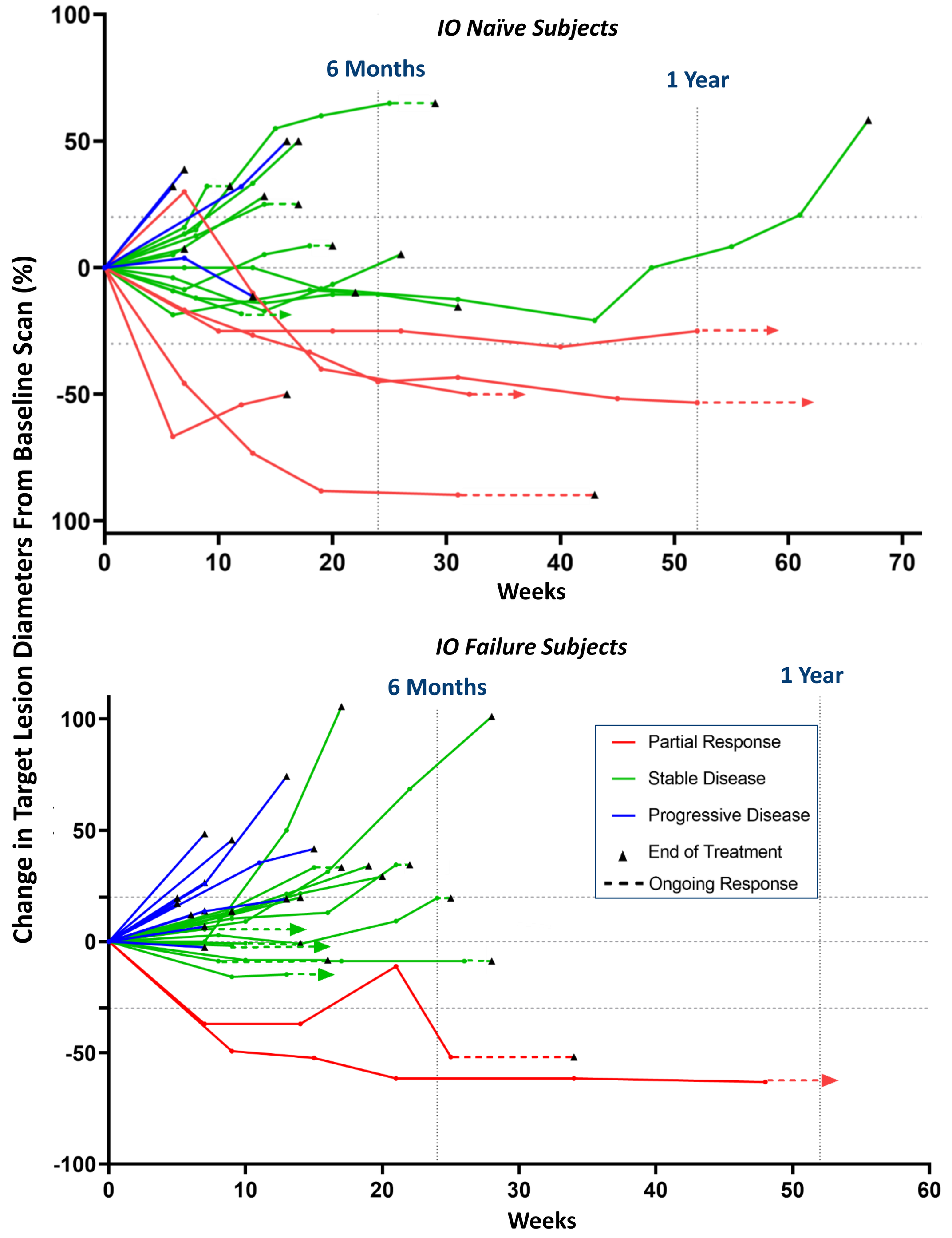
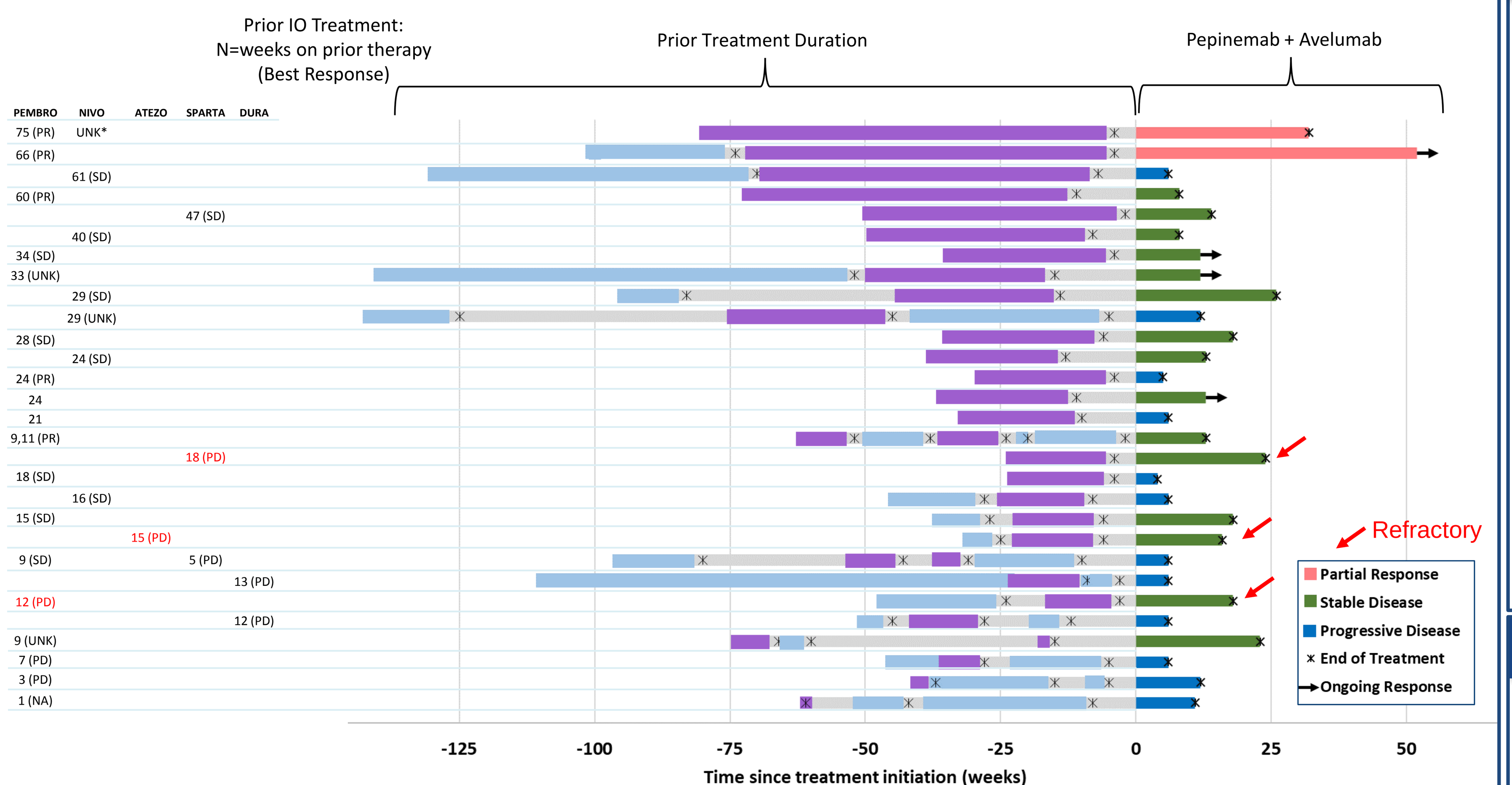


Figure 6: Duration of Response in Evaluable IO Failure Subjects in Comparison to Previous Treatment(s)



* Duration of prior therapy reported was based on subject's initial cancer diagnosis. Additional treatments of carboplatin/paclitaxel, nivolumab and carboplatin/alimta were reported by the investigator site at unknown intervals

- 81% IO Naïve subjects have experienced disease control (PR+SD) while receiving combination therapy of pepinemab + avelumab.
- 59% of evaluable patients (17/29) whose tumors had progressed during or following treatment with anti-PD-x antibodies benefited from switching to the combination therapy, which appeared to induce a halt or reversal of tumor progression. This is inclusive of (3) IO refractory subjects.
- Partial responses (PR) have been observed for (5) IO Naïve and (2) IO Failure subjects, with (3) continuing to respond to treatment for ≥1 year as of data cutoff.
- Durable responses of ≥1 year have been achieved in (3) IO Naïve and (1) IO Failure subject(s)
  - Furthermore, (6) IO Naïve and (3) IO Failure subjects have been on treatment for ≥24 weeks (6 months)

DEMOGRAPHICS

Subjects Enrolled n=	(IO Naïve) 32		(IO Failure) 30		(All) 62	
Age (years)						
Median	67		62		66	
Range	51-85		30-83		30-85	
18 to <65	12	38%	16	53%	28	45%
65 and over	20	63%	14	47%	34	55%
Sex						
Men	23	72%	14	47%	37	60%
Women	9	28%	16	53%	25	40%
Race						
Asian	1	3%	0	0%	1	2%
Black or African American	3	9%	0	0%	3	5%
Native Hawaiian or Other P.I.	0	0%	1	3%	1	2%
White	28	88%	29	97%	57	92%
Ethnicity						
Non-Hispanic or Latino	30	94%	30	100%	60	97%
Hispanic or Latino	2	6%	0	0%	2	3%
ECOG performance status						
0	5	16%	10	33%	15	24%
1	27	84%	20	67%	47	76%
Disease Stage at Screening						
IIIA	1	3%	0	0%	1	2%
IV	31	97%	30	100%	61	98%
Histology						
Adenocarcinoma	20	63%	19	63%	39	63%
Squamous Cell	12	38%	11	37%	23	37%
PD-L1 (Dako 73-10 pharmDx) Status						
No PD-L1 expression	6	35%	10	77%	16	43%
1-49% PDL-1 expression	8	47%	7	54%	15	41%
50-79% PDL-1 expression	2	12%	3	23%	5	14%
≥80% PDL-1 expression	1	6%	0	0%	1	3%
Unknown at Data Cut*	15		10		25	

*Not included in % calculation

SAFETY

- 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.
- The most frequent related AEs still remain at grades 1 or 2 fatigue, pyrexia, or chills.
- Two (2) Immune Related Adverse Event (irAE) occurred during the Expansion Cohort (immune related myositis and immune mediated pneumonitis).
- No (0) subjects were discontinued from the study due to treatment related adverse events. Two (2) subjects discontinued avelumab and received pepinemab monotherapy.
- No deaths (grade 5) have been reported that were related to study treatment (pepinemab and avelumab) (15 Oct 2019)

Exploratory Biomarkers: Multiplex Tumor Immunohistochemistry

Figure 7A: IO Failure / **Figure 7B: IO Naive**

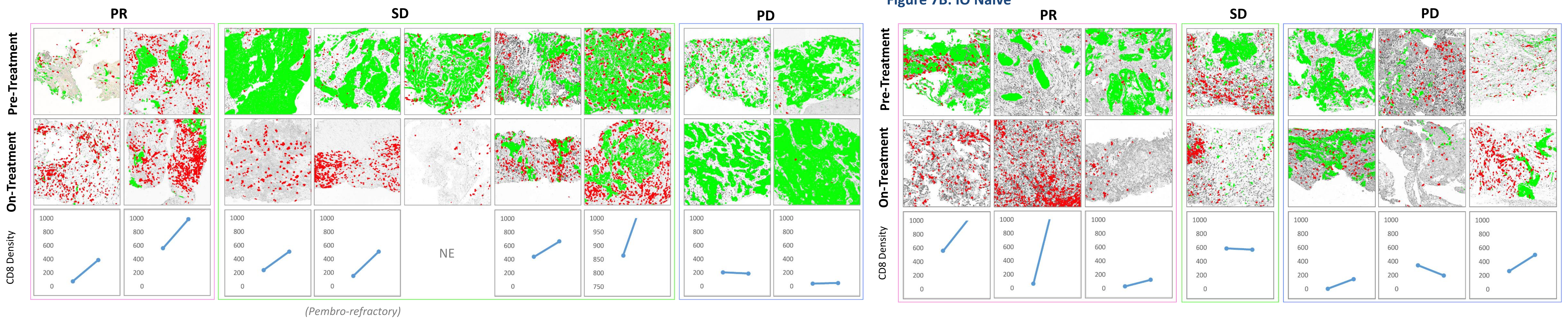


Figure 7C: CD8 Density

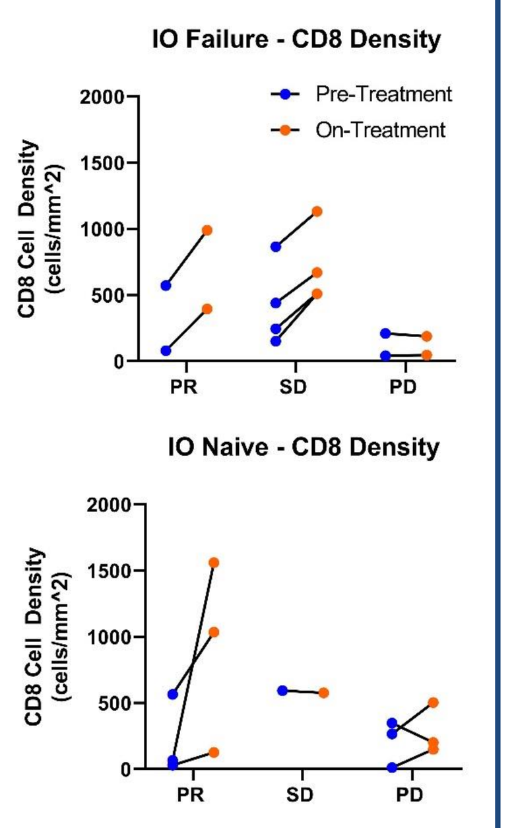


Figure 7: Multiplex IHC demonstrating tumor content and shift in balance of T cells in TME. Core biopsies from eight IO-failure subjects (A) and seven IO-naïve subject (B) were analyzed, including pre and on-treatment samples isolated from the same lesion; on-treatment biopsies were collected ~30 days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

- CD8+ T cell density increased in most tumors following treatment with pepinemab + avelumab in patients experiencing a PR (5/5) or SD (4/5).
- CD8+ T cell levels in tumor appear to correspond with response. Higher T cell densities and largest increases in density were observed in patients with PR or SD, while low T cell density was observed in tumor tissue from subjects with rapidly progressing disease (PD).
- Tumor was absent or greatly reduced in 10/11 biopsies from subjects analyzed with PR or SD, as defined by RECIST criteria.
- Interestingly, no tumor was detected in biopsies analyzed from 4/5 subjects with PR and 3/6 subjects with SD. Instead, biopsies contained fibrotic scar tissue with evidence of inflammation. In one of the IOF patients, no response to prior pembrolizumab treatment was reported (disease progression), but treatment with combination of pepinemab + avelumab resulted in disease stabilization by RECIST criteria and no detectable tumor in biopsy.

CONCLUSIONS

- The combination therapy of pepinemab plus avelumab is well tolerated at all dose levels; no concerning safety signals identified to date.
- Among evaluable IO naïve subjects (n=21) enrolled in either dose escalation or dose expansion, 5 immunotherapy naïve patients experienced a PR, 3 patients have durable benefit over 1 year, and the Disease Control Rate (PR+SD) was 81%.
- 59% of patients (17/29) whose tumors had progressed during or following treatment with anti-PD-x antibodies benefited from switching to the combination of pepinemab + avelumab, which appeared to induce a halt or reverse of tumor progression (SD or PD).
- Clinical response or disease stabilization was observed in majority of patients despite low PD-L1 expression. 82% (18/22) of cumulative PR and SD subjects were reported to have negative or low positive PD-L1 expression (Dako 73-10 pharmDx assay).
- Exploratory:
  - Initial histopathological analysis demonstrates increased CD8+ T cell density in most tumors following treatment with pepinemab + avelumab, indicating a favorable treatment-related change in the tumor micro-environment of patients experiencing SD and PR.
  - Tumor was absent or greatly reduced in 10/11 biopsies from subjects analyzed with PR or SD, as defined by RECIST criteria. Interestingly, no tumor was detected in biopsies analyzed from 4/5 subjects with PR and 3/6 subjects with SD.
  - 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.
- **Based on current understanding of mechanism of action, pepinemab may overcome immune exclusion and myeloid suppression, which may contribute to intrinsic or acquired mechanisms of resistance in IO failure patients.**