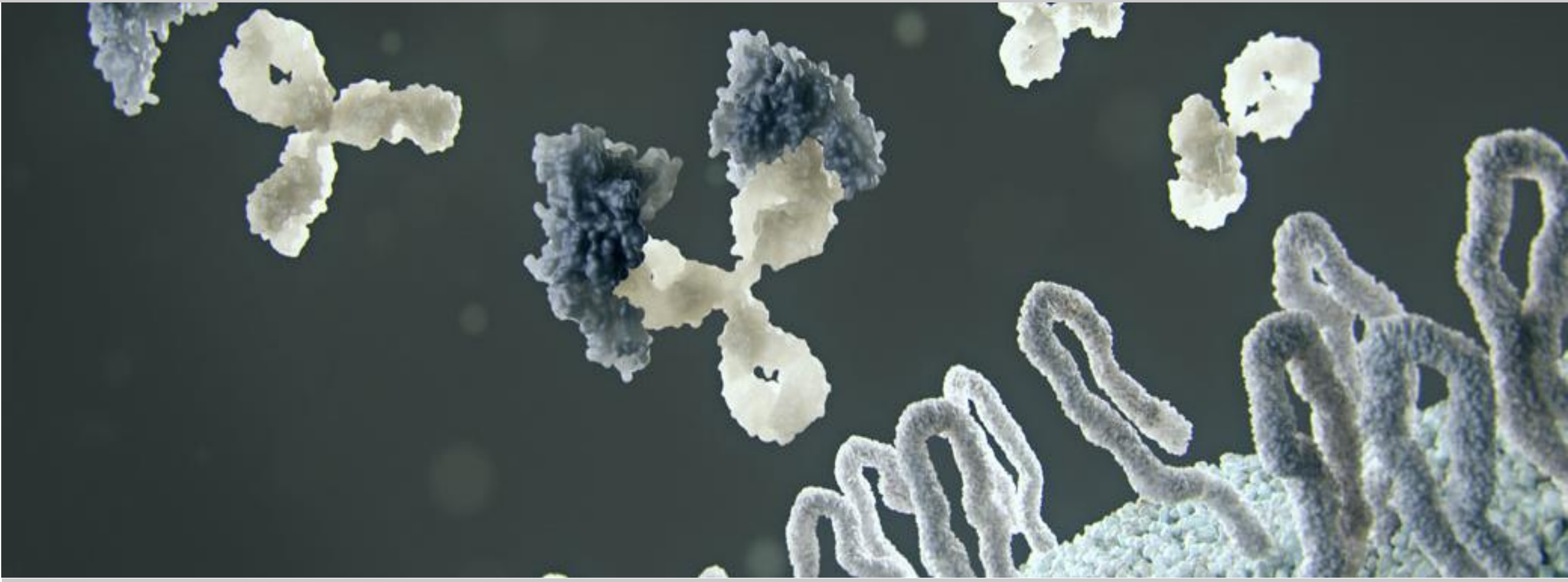


CLASSICAL-Lung Combination trial of Pepinemab with Avelumab

Michael R. Shafique, MD – H. Lee Moffitt Cancer Center, Tampa, FL

Disclosures

Institutional Research Funding

COMPANY	RECIPIENT	COMMENTS
Merck Serono	H. Lee Moffitt Cancer Center	Site Principal Investigator
Vaccinex	H. Lee Moffitt Cancer Center	Site Principal Investigator
Nektar	H. Lee Moffitt Cancer Center	Site Principal Investigator
PsiOxus Therapeutics	H. Lee Moffitt Cancer Center	Site Principal Investigator
Amphivena	H. Lee Moffitt Cancer Center	Site Principal Investigator

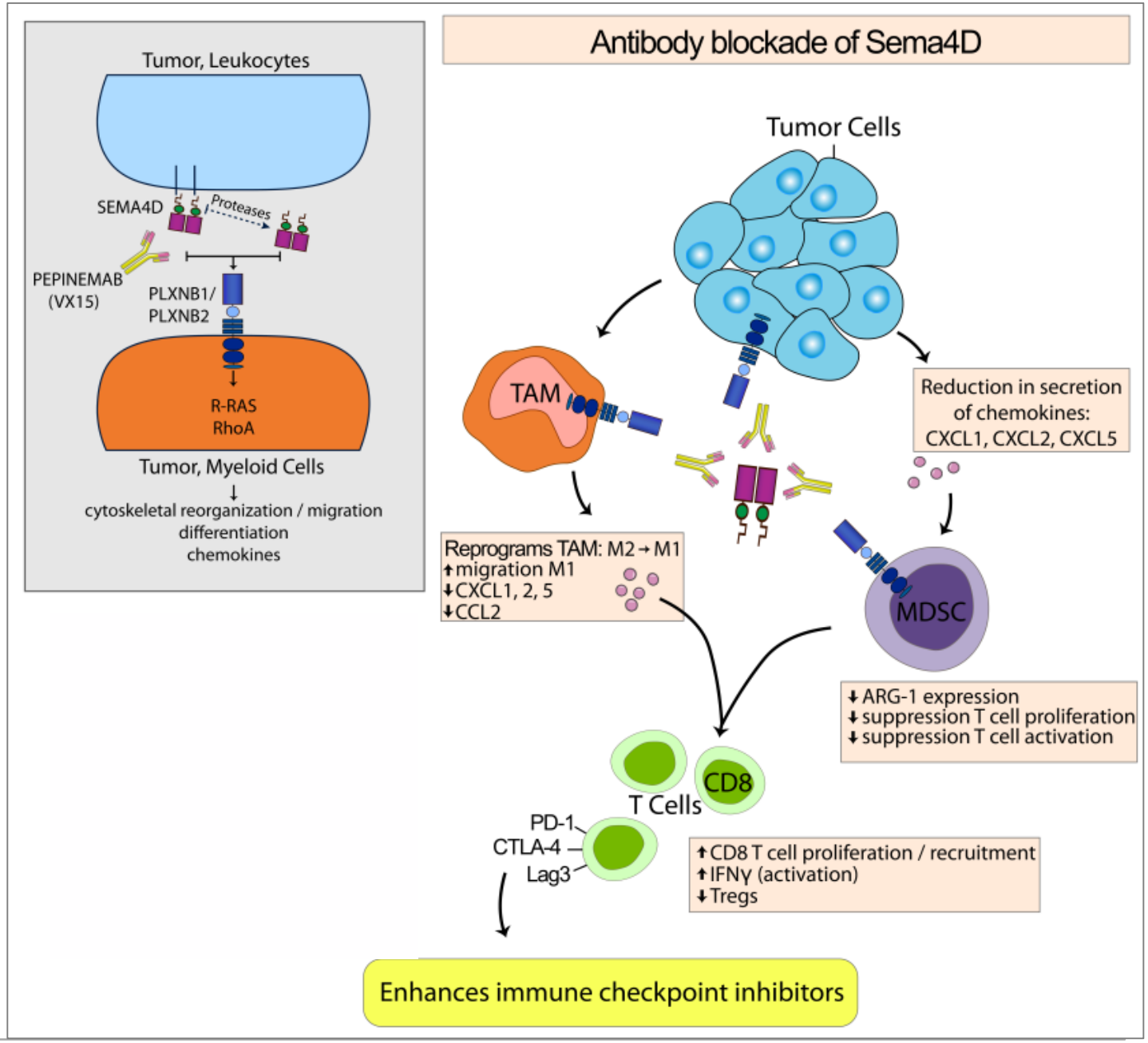
Travel

Janssen	Michael R. Shafique	

Pepinemab

Proposed Mechanism of Action

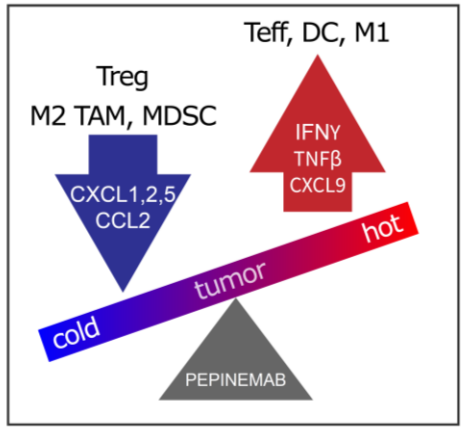
- Semaphorin 4D signals through Plexin B1 and Plexin B2 receptors to regulate cellular cytoskeleton and its function in cell migration and differentiation
- **Anti-SEMA4D shifts the balance of immune infiltration and myeloid suppression to promote anti-tumor T cell activity[1,2]**
  - Promotes infiltration of potent APC
  - Reverses recruitment and function of MDSC, M2 TAM and Treg
  - → Facilitates infiltration and activity of CD8+ T cells
- Pepinemab (VX15/2503), a humanized IgG4 with hinge modification, binds to SEMA4D and blocks its signaling activity

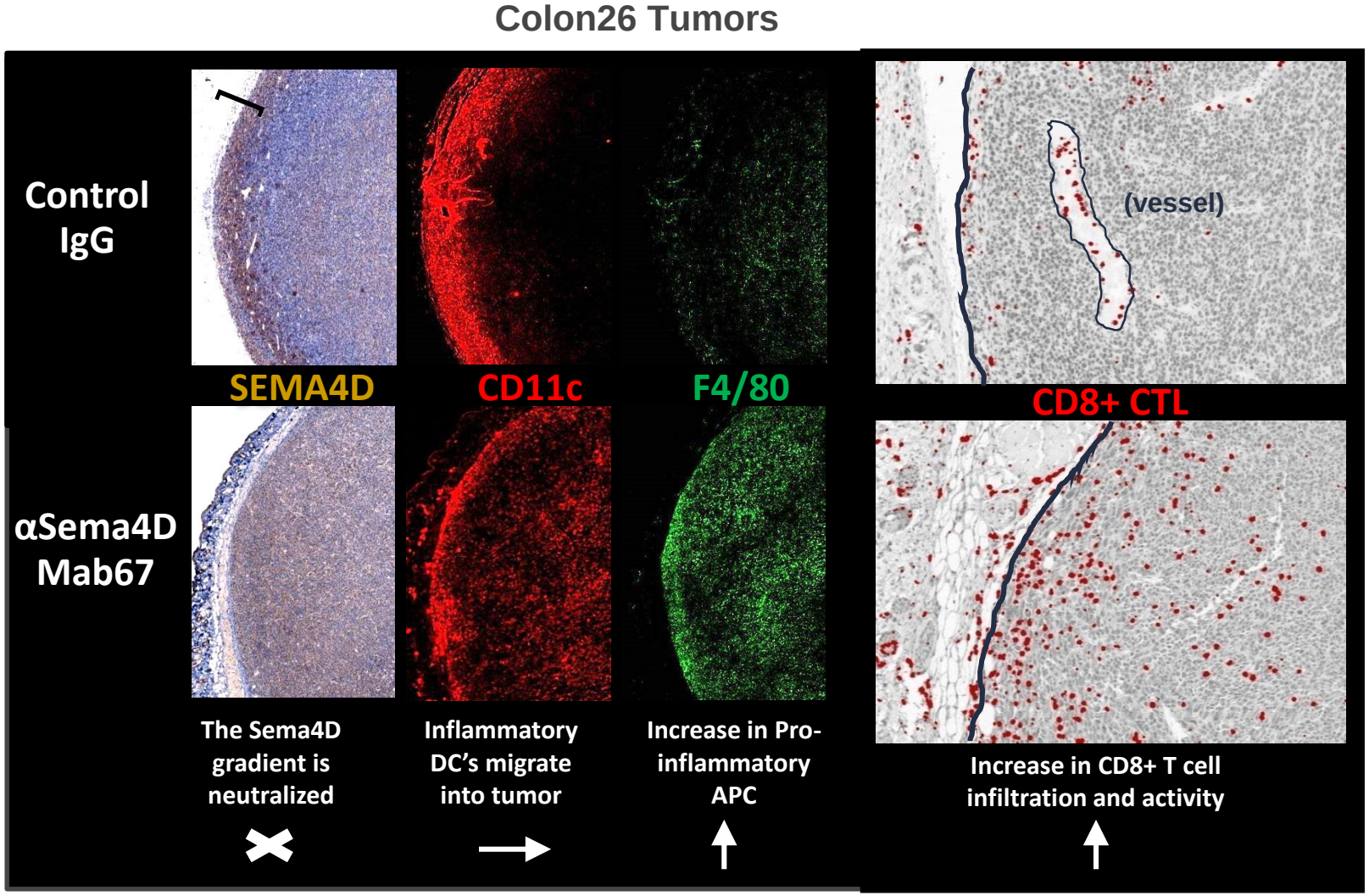


1. Evans EE et al. Cancer Immunol Research 2015
2. Clavijo et al. Cancer Immunol Research 2019

Anti-SEMA4D shifts balance of chemokines and suppressor cells to enhance infiltration and activity of tumoral T cells

1. Dendritic cells (DC) express high affinity receptor PLXNB1 and CD11c+ (red stain).
2. Binding to SEMA4D at tumor edge restricts penetration of PLXNB1+ DC into Colon26 tumor.
3. Shift in balance of immune cells and factors within TME

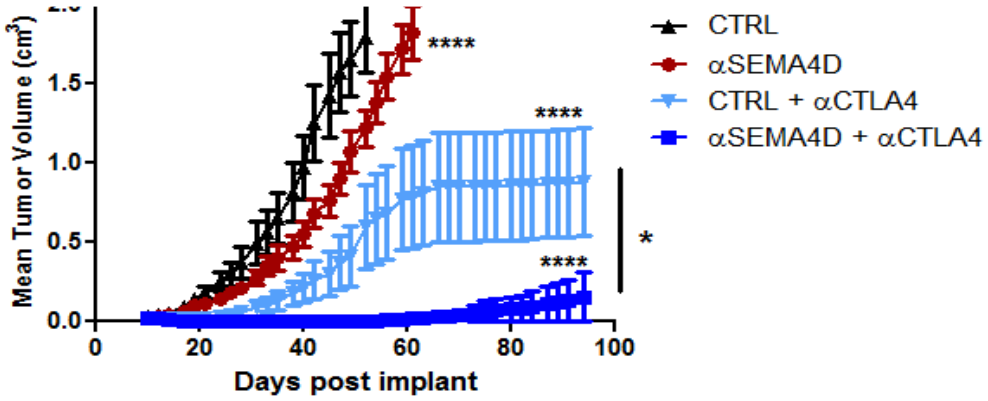




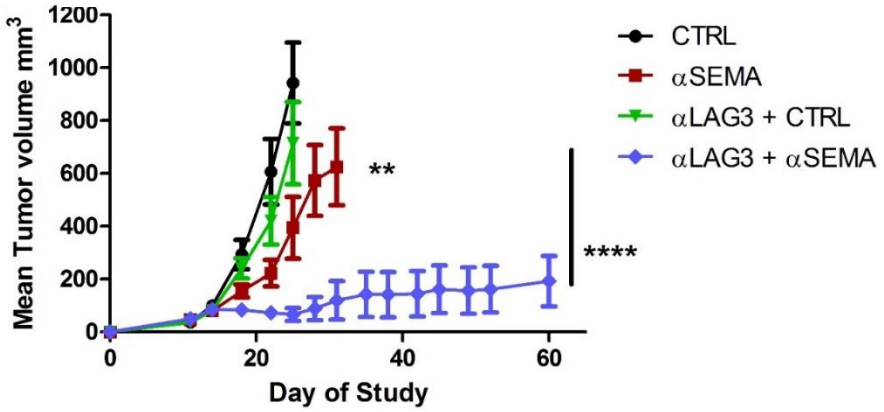
Evans EE et al. Cancer Immunol Research 2015;3(6): 689-701
http://www.ncbi.nlm.nih.gov/pubmed/25614511

Anti-SEMA4D Antibody Enhances Activity of Immune Checkpoint Antibodies in Preclinical Syngeneic Models

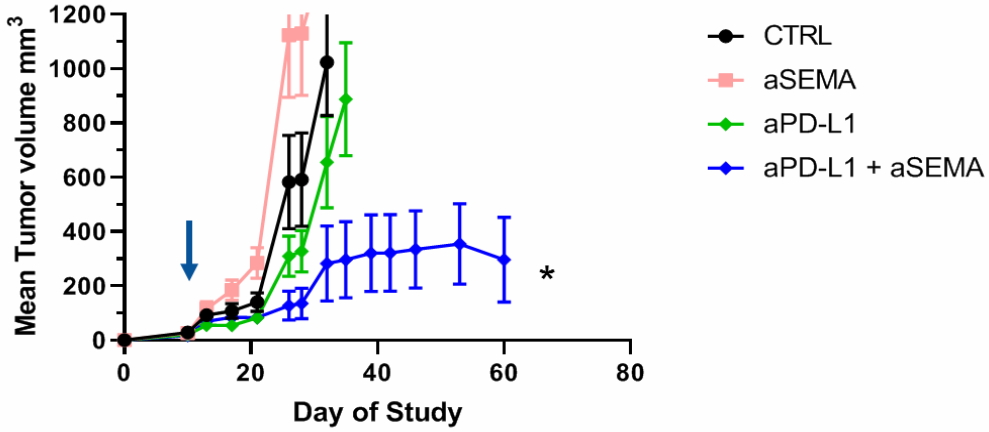
anti-CTLA-4 Combination: MOC1 HNSCC



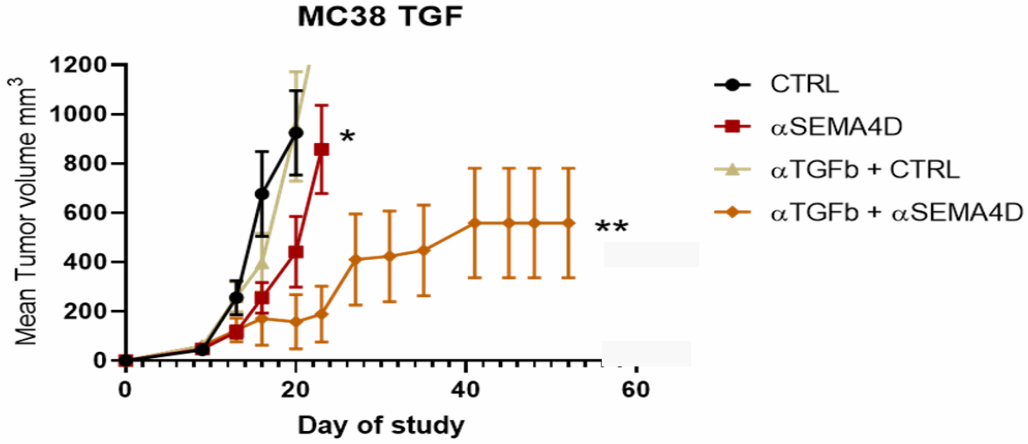
anti-LAG3 Combination: Colon26



anti-PD-L1 Combination: Colon26



Anti-TGFβ: MC38



Phase 1b/2 CLASSICAL- Lung Study Design

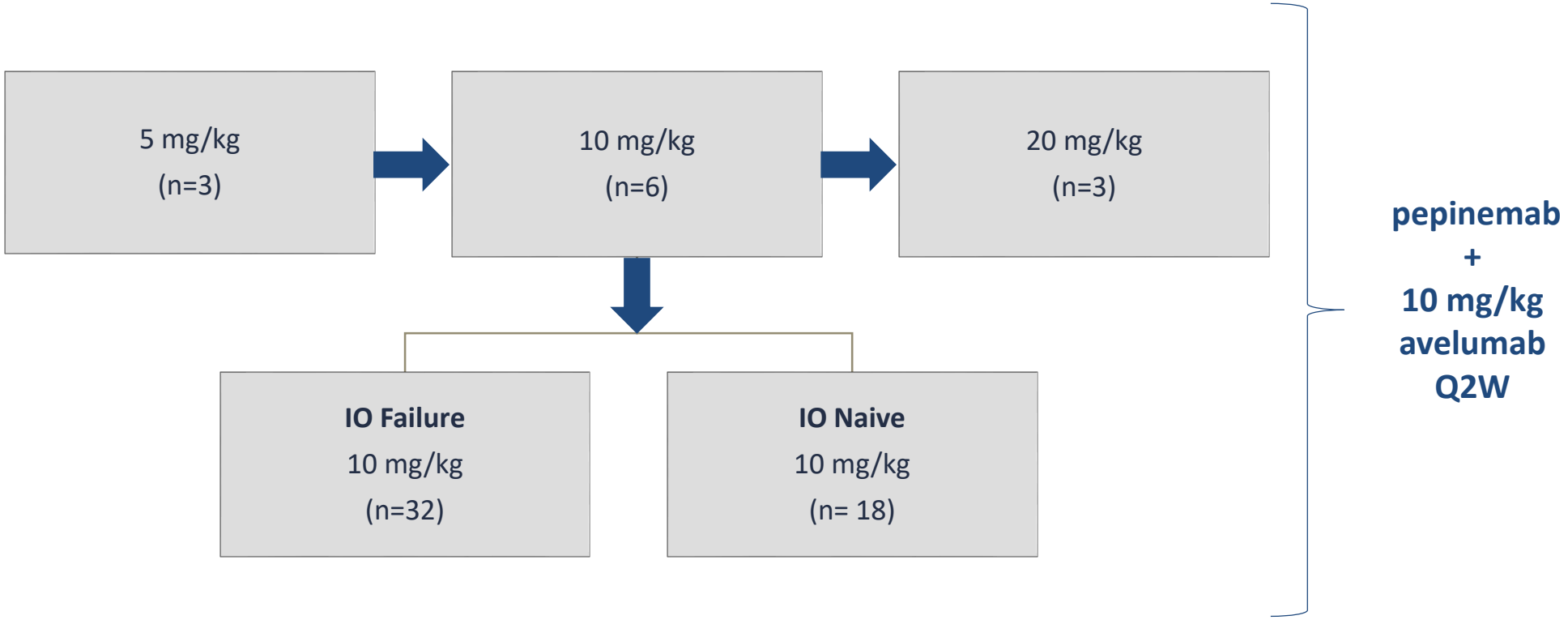
Combination Trial of Pepinemab with Avelumab in NSCLC

Phase 1b

Dose Escalation
IO Naïve
(n=12)

Phase 2

Dose Expansion
(n=50)



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

Demographics

Subjects Enrolled n=	(IO Failure) 32		(IO Naïve) 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	11	38%	8	36%	19	37%
1-49% PDL-1 expression	12	41%	10	45%	22	43%
50-79% PDL-1 expression	6	21%	3	14%	9	18%
≥80% PDL-1 expression	0	0%	1	5%	1	2%
Cancelled*	3		8		11	

*Not included in % calculation

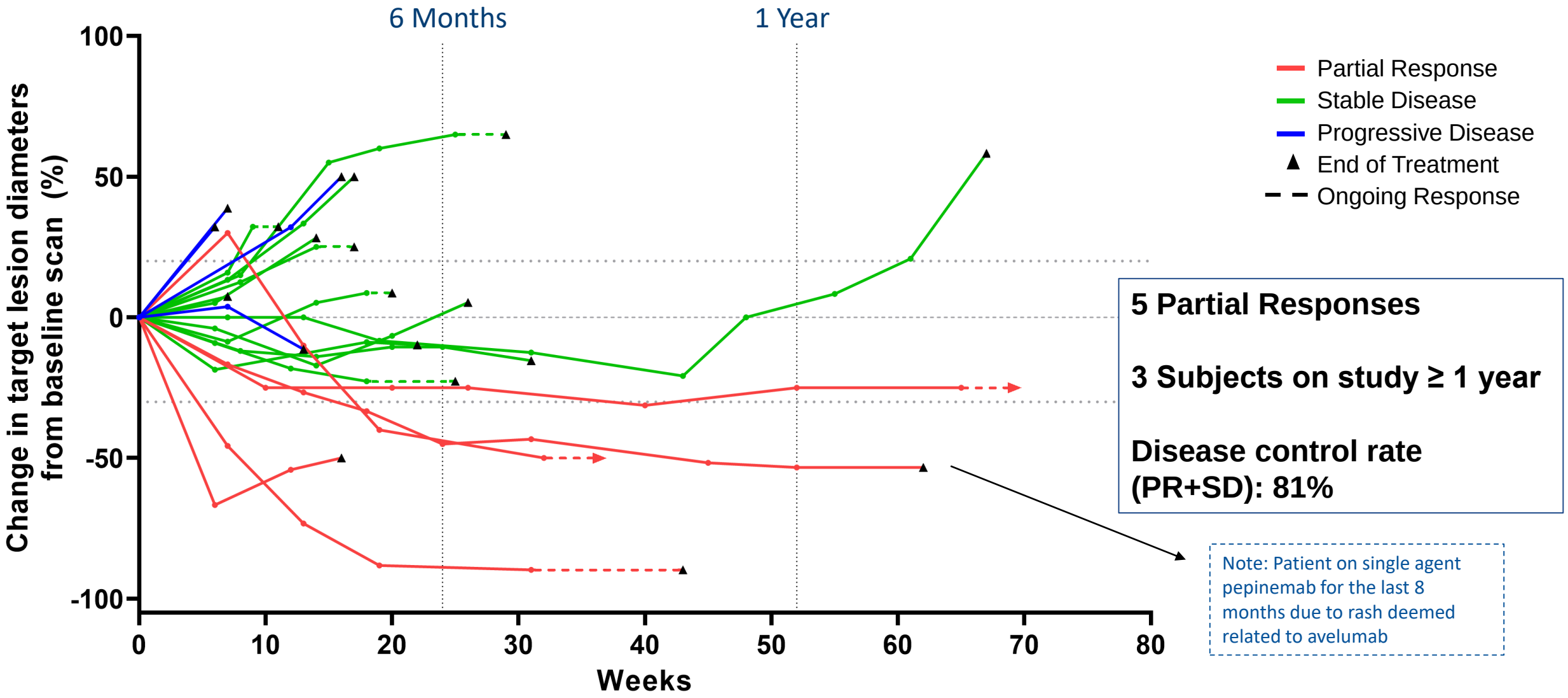
5 subjects still on study:
2 ION / 3 IOF

Safety Summary

CLASSICAL-Lung

- 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 deaths (grade 5) have been reported that were related to study treatment (pepinemab and avelumab) (14 Jan 2020)
- Overall immunogenicity does not appear to be a concern with this combination.

Percent Change in Target Lesion Diameter by Weeks (IO Naïve)



5 Partial Responses

3 Subjects on study ≥ 1 year

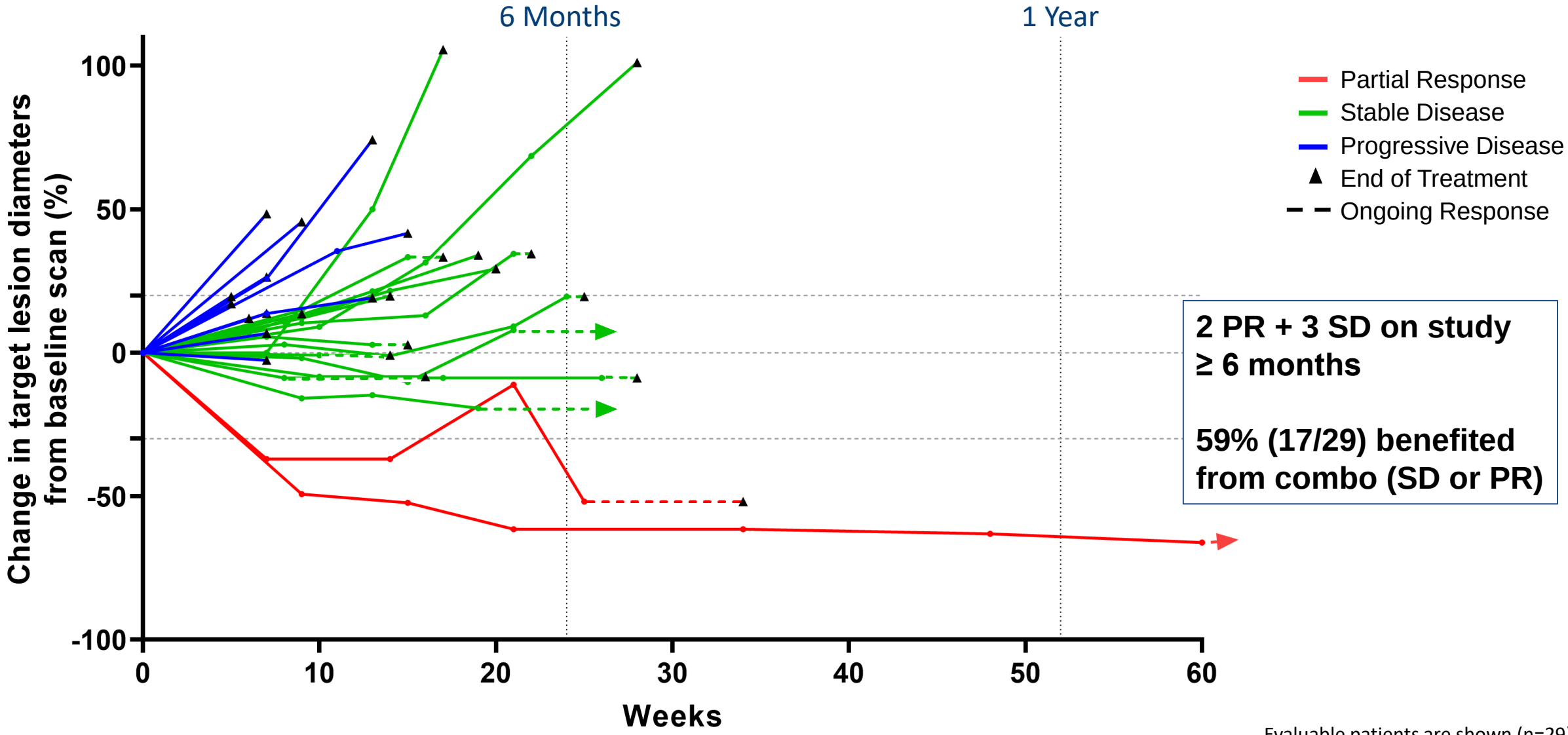
Disease control rate (PR+SD): 81%

Note: Patient on single agent pepinemab for the last 8 months due to rash deemed related to avelumab

Lines are color coded base on best overall response

Evaluable patients are shown (n=21)

Percent Change in Target Lesion Diameter by Weeks (IO Failure)



2 PR + 3 SD on study ≥ 6 months

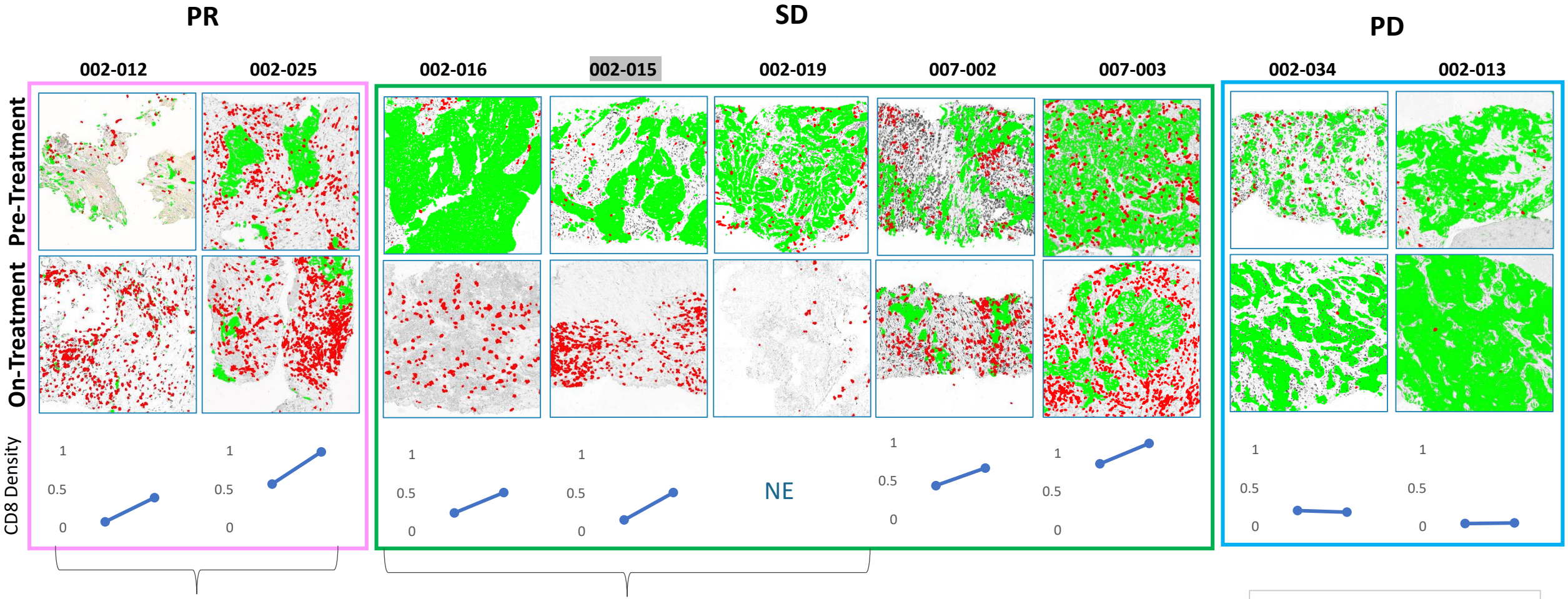
59% (17/29) benefited from combo (SD or PR)

Lines are color coded base on best overall response

Evaluable patients are shown (n=29)

CLASSICAL- Lung: IO Failure

Increase in CD8+ T cell infiltration

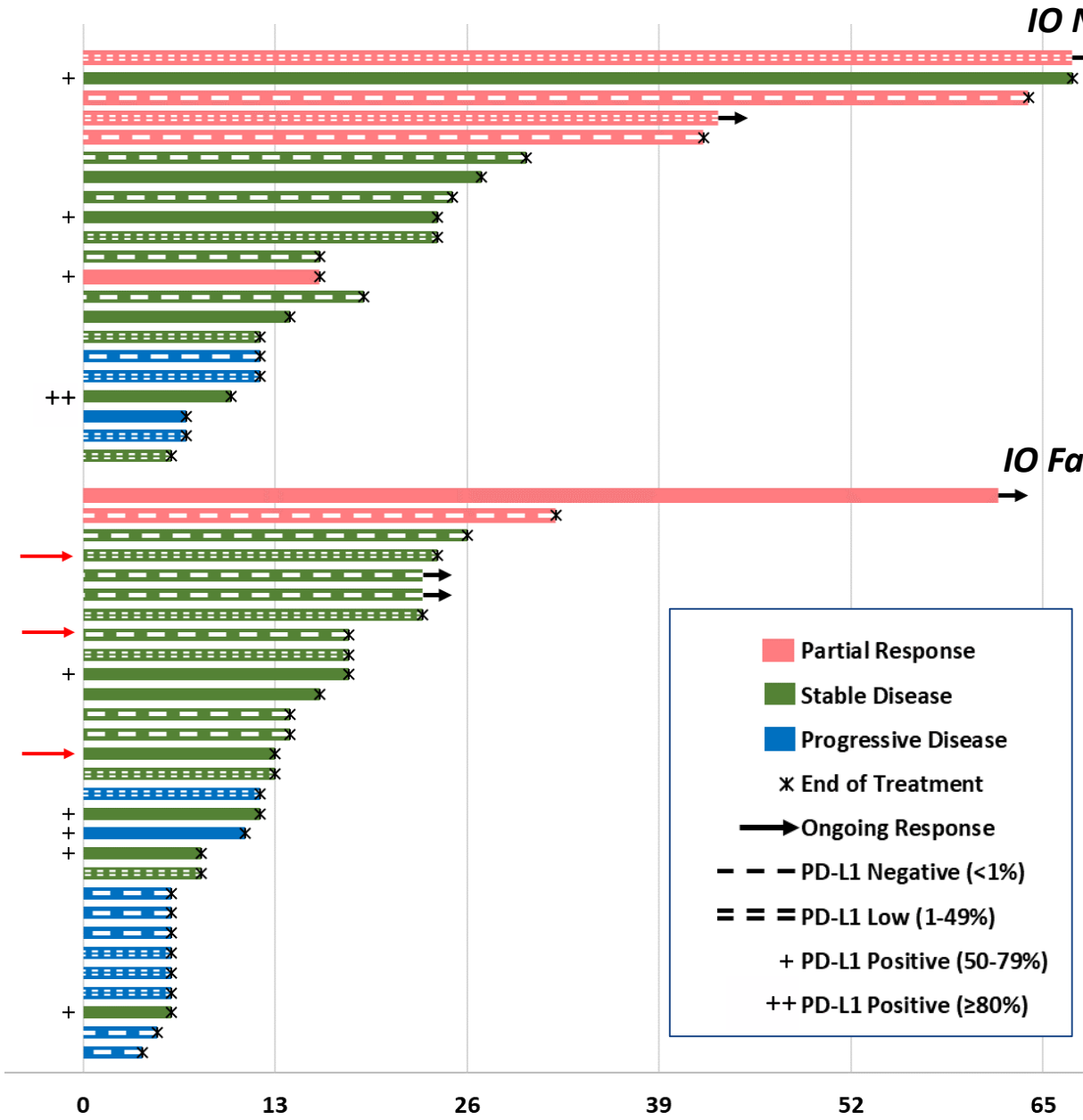


No or low tumor detected in these 2 biopsies from patients with PR

No tumor detected in these 3 biopsies from patients with stable disease

Tumor (Cytokeratin+)
CD8+ T cells
Pembrolizumab refractory

Time on Study in Evaluable Subjects



- 81% of evaluable patients (17/21) have experienced disease control (PR+SD) while receiving the combination.
- Durable clinical benefit of ≥1 year has been achieved in 3 subjects and ≥6 months in 7 subjects

79% of PR & ***SD*** subjects were reported to have Negative or Low PD-L1 expression*

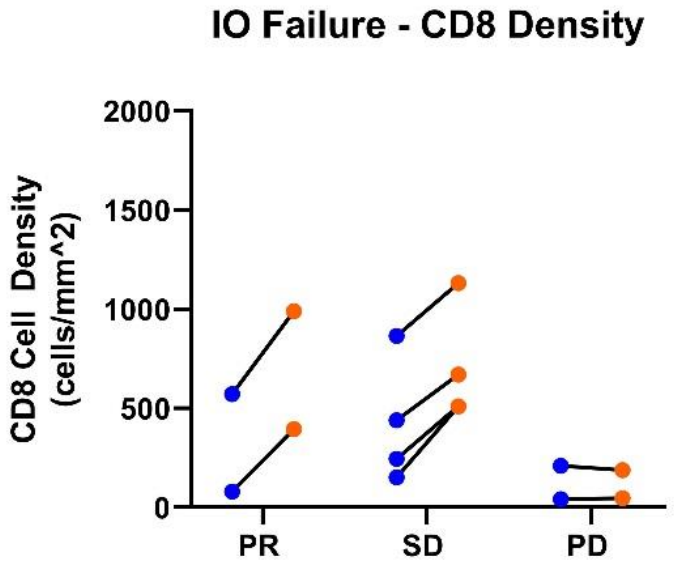
*PD-L1 analysis was performed via Dako 73-10 pharmDx. PD-L1 status reported (44/50 subjects) is from data available at cut off (10 Jan 2020). A total of 29 SD and PR subjects were analyzed and 23 were reported to be PD-L1 negative or low (0-49%); 10 of these were PD-L1 negative (<1%).

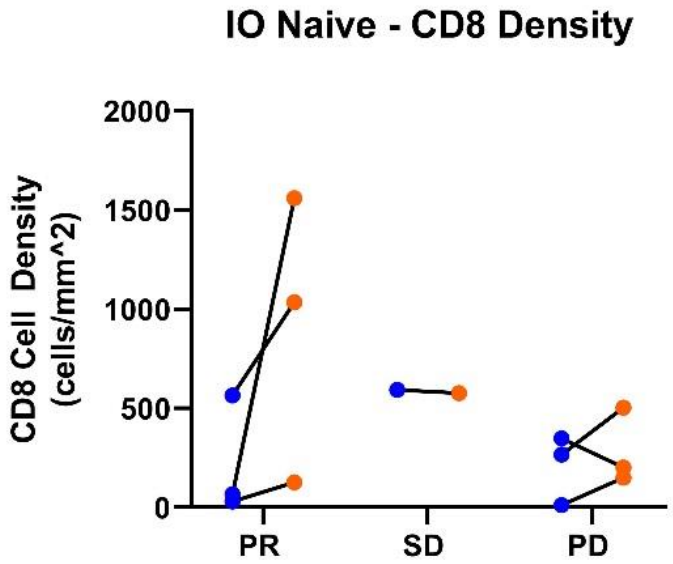
- 59% of evaluable patients (17/29) whose tumors had progressed during or following treatment with anti-PD-x antibodies benefited from switching to the combination therapy, which appears to induce a halt or reversal of tumor progression.
- Three (3) subjects were IO refractory before entering trial (→)
- Two (2) subjects who failed pembro have attained PRs with 66% and 52% tumor reduction at most recent scan.
- Durable response of ≥1 year has been achieved in 1 subject and ≥6 months in 6 subjects

CD8 Density generally increased following treatment

CLASSICAL-Lung

- 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).





- Matched pre and on-treatment from the same lesion
- On-treatment biopsies collected after ~ 5 weeks of treatment
- Core or needle biopsies
- Quantification of tumor bed across the entire biopsy section, excluding necrotic regions. Tumor bed was verified by pathologist review

Summary

- Anti-SEMA4D shifts the immune balance in the TME to overcome immune exclusion and myeloid suppression
  - Increased T cell penetration and T cell activity
  - Reduced myeloid cells and reduced immune suppression
- The combination of pepinemab + avelumab is well tolerated in CLASSICAL-Lung trial.
- Extent and duration of treatment benefit.
  - ION: 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%.
    - Quality of enrollment in this cohort suffered from 30% non-evaluable and low PD-L1 expression.
  - IOF: 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 of pepinemab + avelumab, which appeared to induce a halt or reversal of tumor progression (PR or SD).
  - Clinical response or disease stabilization was observed in majority of patients despite low PD-L1 expression. 82% (18/22) of all subjects with either PR or SD subjects were reported to have negative or low positive PD-L1 expression (Dako 73-10 pharmDx assay)
- Exploratory:
  - Increased CD8+ T cell density was observed in most tumors following treatment with pepinemab + avelumab. CD8+ T cell levels in tumor appear to correspond with response.
  - Tumor was absent or greatly reduced in 10/11 biopsies from subjects analyzed with PR or SD. Interestingly, no tumor was detected in biopsies analyzed from 4/5 subjects with PR and 3/6 subjects with SD.

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