Interim subgroup analysis for response by PD-L1 status of CLASSICAL-Lung, a phase 1b/2 study of pepinemab (VX15/2503) in combination with avelumab in advanced NSCLC

#3011

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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 a novel first-in-class anti-SEMA4D antibody pepinemab with PD-L1 antibody avelumab to couple beneficial modifications of the immune microenvironment via pepinemab with immune activation via checkpoint inhibition.

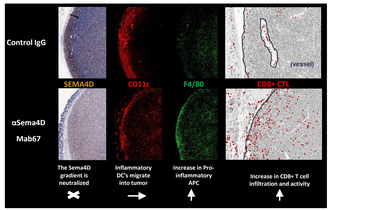
Pepinemab

- Is an IgG4 humanized monoclonal antibody targeting semaphorin 4D (SEMA4D, CD100). *In vivo* preclinical studies demonstrated antibody blockade of SEMA4D neutralizes the SEMA4D barrier and "open the gates" of the tumor to the immune system, and 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. Preclinical Model - Colon26



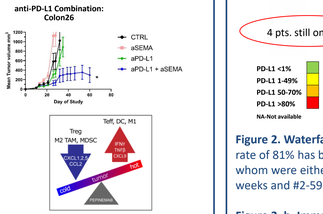


Figure 1. SEMA4D regulates organization of PLXNB1 and APC in the tumor microenvironment of preclinical models. Dendritic cells express high affinity receptor PLXNB1 and CD11c+ and by this binding to SEMA4D at the tumor edge, it restricts penetration of PLXNB1 and dendritic cells into the tumor. Antibody neutralization of SEMA4D, enhances penetration and differentiation of pro-inflammatory CD11c and F4/80 double-positive APC into tumor interior. This shift in balance of immune cells and factors, facilitates CD8+ T cell infiltration, thus enhancing immune checkpoint therapies.

METHODS

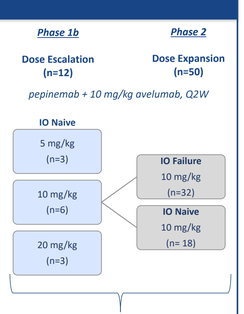
This ongoing completely enrolled phase 1b/2, open label, single arm, first-in-human combination study is designed to evaluate the combination of pepinemab with avelumab in 62 subjects (pts) with advanced (stage IIIB/IV) NSCLC.

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



INTERIM RESULTS: CLASSICAL-Lung (NCT03268057)

Figure 2. Durable clinical benefit observed, including patients who had previously progressed on anti-PDx therapy and in difficult to treat PD-L1 low/negative disease

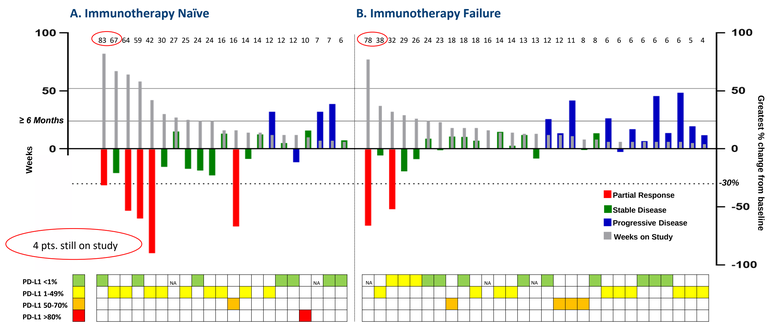


Figure 2. Waterfall Plot of Best Systemic Response in Immunotherapy Naïve and Failure Patients a. Immunotherapy Naïve. A disease control rate of 81% has been achieved (17/21 patients with either a PR and SD). Partial responses have been observed for (5) IO Naïve subjects, all of whom were either PD-L1 negative or Low (1-49%). Durable responses of ≥1 year have been achieved in 4 patients, with 2 still on study (#1-82 weeks and #2-59 weeks) at data cutoff*.

Figure 2. b. Immunotherapy Failure. 59% (17/29) of IO Failure patients benefited when switching to the combination therapy, which appears to induce a halt or reversal of tumor progression. Partial responses have been observed for (2) IO Failure subjects, one whose PD-L1 status was unknown and the other whom is PD-L1 Low (1-49%). A durable response of ≥1 year has been achieved in 1 patient, with 2 still on study (#1-78 weeks and #2-38 weeks) at data cutoff*.

- Data cutoff (27 Apr 2020)
- PD-L1 analysis was performed via Dako 73-10 pharmDx. PD-L1 status was available for 51/62 subjects. A total of 29 SD and PR subjects were analyzed and 28 were reported to be PD-L1 negative or low (0-80%); 10 of these were PD-L1 negative (<1%).

IO naïve, negative and low PD-L1 patients achieved higher response rates with pepinemab combination, than historical patient treated with single agent avelumab*

- Tumor biopsies showed increased T cell infiltration & less tumor in both PR & SD pts.
- Durable clinical responses have been achieved in both IO Naïve & Failure pt. populations
- Combination is safe and tolerable in all doses tested

Figure 3. Multiplex IHC demonstrating tumor content and shift in balance of T cells in tumor microenvironment

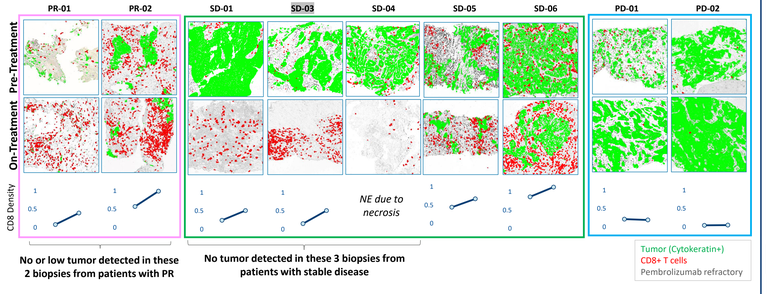


Figure 3: Exploratory Biomarkers: Multiplex Tumor Immunohistochemistry in Patients that Failed on Immunotherapy. Core biopsies from nine IO-failure subjects were analyzed, including pre and on-treatment samples isolated from the same lesion; on-treatment biopsies were collected ~30 days post first treatment 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

Figure 4. Overall Response Rate by PD-L1 Comparison of Javelin Solid Tumor to CLASSICAL-Lung.

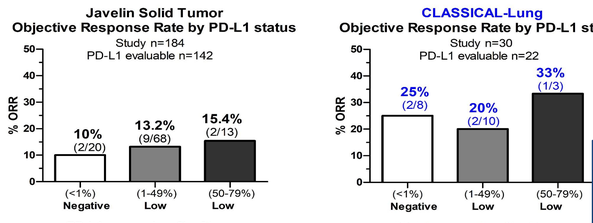


Figure 4. PD-L1 low (1-79%) and negative (<1%) patients responded better to the combination therapy, resulting in a higher response rate that previously observed in historical data of Avelumab

1. Calculated from previously published data (5,6)
2. 27% (8/30) subjects did not have PD-L1 status reported and 9.5% (2/21) subjects were non-evaluable for post dose scans (included in ORR calculation) due to withdrawal prior to first scan.

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 grade 1 or 2 AEs are fatigue, pyrexia, Gamma-Glutamyl Transferase (GGT) increase and 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) (20 April 2020)
- Overall immunogenicity does not appear to be a concern with this combination.

DEMOGRAPHICS

Table 1. Baseline Demographics and Clinical Characteristics

	Phase Ib						Phase II	
	5 mg/kg (n = 3)		10 mg/kg (n = 6)		20 mg/kg (n = 3)		ION (n = 18)		IOF (n = 32)	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%
Age, median (range)	37 (30-79)		65 (59-75)		61 (60-69)		64 (54-83)		67 (51-85)	
18 to <65	2	67%	3	50%	2	67%	9	50%	12	38%
65 and over	1	33%	3	50%	1	33%	9	50%	20	63%
Sex										
Men	1	33%	4	67%	2	67%	7	39%	23	72%
Women	2	67%	2	33%	1	33%	11	61%	9	28%
Race										
White	3	100%	5	83%	3	100%	18	100%	28	88%
Black or African American	2	67%	0	0%	0	0%	0	0%	3	9%
Other	0	0%	1	17%	0	0%	0	0%	1	3%
ECOG performance status										
0	1	33%	3	50%	0	0%	6	33%	5	16%
1	2	67%	3	50%	3	100%	12	67%	27	84%
Disease Stage at Screening										
IIIA	0	0%	0	0%	0	0%	0	0%	1	3%
IV	3	100%	6	100 %	3	100%	18	100%	31	97%
Histology										
Adenocarcinoma	1	33%	4	67%	1	33%	13	72%	20	63%
Squamous Cell	2	67%	2	33%	2	67%	5	28%	12	38%
Previous Therapy										
Chemotherapy only	3	100%	3	50%	3	100%	8	44%	0	0%
None	0	0%	3	50%	0	0%	10	56%	0	0%
PD-L1 Status (Dako 73-10 pharmDx)										
No PD-L1 expression	0	0%	2	33%	1	33%	5	45%	11	38%
1-49% PDL-1 expression	1	50%	3	50%	1	33%	5	45%	12	41%
50-79% PDL-1 expression	1	50%	1	17%	0	0%	1	9%	6	21%
≥80% PDL-1 expression	0	0%	0	0%	1	33%	0	0%	0	0%
Cancelled*	1		0		0		7		3	

*Testing was cancelled due to: Sample past stability (1) sample not received (4), no tumor present (4), incorrect sample type (2) and was not included in % calculation

CONCLUSIONS

- Anti-SEMA4D shifts the immune balance in the TME to overcome immune exclusion and myeloid suppression, with increased T cell penetration and T cell activity
- The combination of pepinemab + avelumab is well tolerated in CLASSICAL-Lung trial.
- **ION**: 5 immunotherapy naïve patients experienced a PR, 4 patients have durable benefit over 1 year, and the Disease Control Rate (PR+SD) was 81%. (n=21 evaluable subjects enrolled in either dose escalation or dose expansion)
- **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).
- Notably, clinical response or disease stabilization was observed in majority of patients despite low PD-L1 expression.
  - 97% (28/29) 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)
- 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.

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Patients and their families