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

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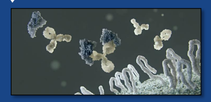


BACKGROUND

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 immunotherapies 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 both Merkel cell and urothelial carcinomas. Avelumab inhibits PD-L1-PD-1 interactions and also has the potential to induce ADCC.

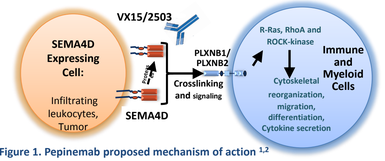


Figure 1. Pepinemab proposed mechanism of action [1,2]

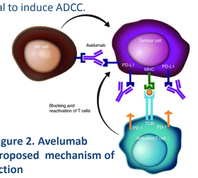


Figure 2. Avelumab proposed mechanism of action

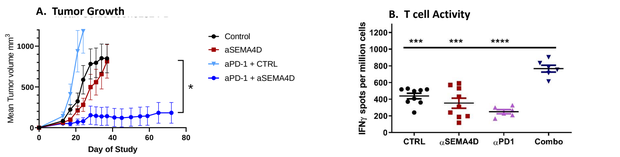


Figure 3. Preclinical data supporting combination therapy to enhance frequency of tumor regression and T cell activity. **A)** Colon26 (500,000 cells) were subcutaneously implanted into Balb/c mice, that were then treated with αSEMA4D / MAb67 (10 mg/kg, weekly IP X2), αPD-1 / MAb RMP1-14 (10 mg/kg, twice/week, 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 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 with advanced (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 patients who are immunotherapy naïve and have either progressed or declined standard first or second-line systemic anticancer therapy.
- Patients 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 a similar patient cohort as well as a second cohort of patients whose tumors progressed during or following immunotherapy.

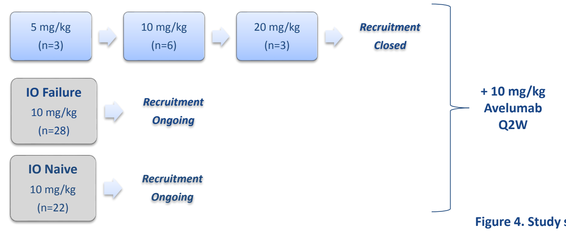


Figure 4. Study schema

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

Demographic Characteristics

- All subjects presented at baseline with stage IV carcinoma
- There was an even distribution of adenocarcinoma and squamous cell carcinoma subjects
- Sixty-seven percent of subjects received prior systemic treatment

Table 1. Phase 1 Baseline Characteristics

Subjects n=12		
Age (years)		61 (30-79)
	18 to <65	7 (58%)
	65 and over	5 (42%)
Sex		
	Men	7 (58%)
	Women	5 (42%)
Race		
	Native Hawaiian or Other Pacific Islander	1 (8%)
	White	11 (92%)
Ethnicity		
	Non-Hispanic or Latino	12 (100%)
ECOG performance status		
	0	4 (33%)
	1	8 (67%)
Disease Stage at Diagnosis		
	IIA	1 (8%)
	IIIA	2 (17%)
	IV	9 (75%)
Disease Stage at Screening		
	IV	12 (100%)
Histology		
	Adenocarcinoma	6 (50%)
	Squamous Cell	6 (50%)
Previous Systemic Treatment		
	Yes	8 (67%)
	No	4 (33%)
PD-L1 Status		
	PD-L1 Postive >=1% cutoff	7 (58%)
	PD-L1 Negative	2 (17%)
	Not Assessable	3 (25%)

PHASE 1b RESULTS

Pepinemab was well tolerated in Dose Escalation Cohort

- No concerning safety signals were identified to date (N = 12)
- The most frequent related AEs were grades 1 or 2 fatigue, pyrexia, or chills; no grade 3 AEs occurred in more than one subject
- No Immune Related Adverse Events identified in Escalation Cohorts
- No Grade 4 or 5 Treatment Related Adverse Events
- One DLT, a grade 3 pulmonary embolism, occurred in the 10mg/kg pepinemab + 10mg/kg avelumab cohort, resolved and did not recur in that same subject or additional subjects in any cohort

Table 2. Treatment-related AEs occurring in subjects >1 time

Arm	Adverse Event Detail	Grade 1	Grade 2	Grade 3	Total Subjects
5 mg/kg (n=3)	Fatigue	1 [1]	1 [1]	0	2
	Total Events	**[1]**	**[1]**	**0**	**2 [2]**
10 mg/kg (n=6)	Fatigue	1 [1]	2 [2]	0	3
	Pyrexia	1 [1]	1 [1]	0	2
	Diarrhea	1 [2]	0	0	1
	Lipase increased	0	0	1 [1]	1
	Systemic inflammatory response syndrome	0	0	1 [1]	1
	Total Events	**[4]**	**[3]**	**[2]**	**5 [9]**
20 mg/kg (n=3)	Anaemia	0	2 [2]	0	2
	Chills	2 [2]	0	0	2
	Amylase increased	1 [1]	1 [2]	1 [3]	1
	Gamma-glutamyltransferase increased	1 [1]	1 [2]	0	1
	Lipase increased	0	1 [1]	1 [2]	1
	Platelet Count Decrease	1 [1]	0	0	1
	Total Events	**[5]**	**[7]**	**[5]**	**2 [17]**

* n denotes the number of subjects, [x] denotes the number of events, (i.e. 2 [2] : 2 Subjects Experienced 2 AEs)

Pepinemab Receptor Occupancy

- Cellular SEMA4D was shown to be saturated at all dose levels

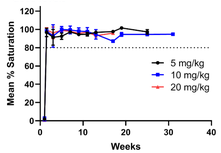


Figure 5. Peripheral whole blood was analyzed pre and post dose using a validated flow cytometry based saturation assay[3].

Pharmacokinetics

- Initial PK results show comparability to previous single agent trials

Figure 6. Pepinemab drug levels (ug/ml)

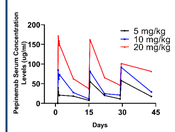
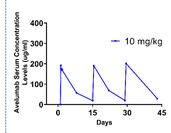


Figure 7. Avelumab drug levels (ug/ml)



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

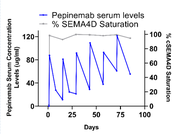


Figure 9. Cellular SEMA4D / PK

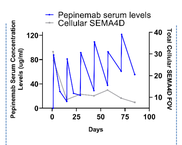
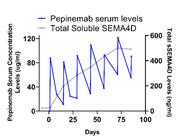


Figure 10. t-Soluble SEMA4D / PK



Immunogenicity

- Overall immunogenicity does not appear to be a concern with this combination
- ADA screened positive in three subjects dosed with pepinemab
- ADA screened positive in two subjects dosed with avelumab
- SEMA4D receptor occupancy was not affected and only one subject developed a response that continued to increase in titer in later cycles

Table 3. Subjects Experiencing ADA

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

Exploratory Biomarkers: Multiplex Tumor Immunohistochemistry

- Pre-treatment tissue shows infiltrating malignant cells (green), stained with pan-cytokeratin.
- Post-treatment biopsy demonstrates reactive alveolar parenchyma and inflammation. According to pathology report, "No evidence of tumor."
- CD8+ to FoxP3 T cell ratio increases in the tumor microenvironment post treatment

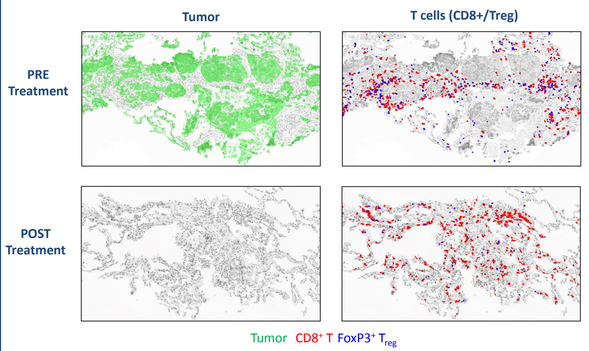


Figure 11. CD8+ and FoxP3 + T-cell Counts

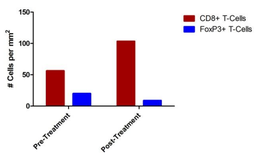
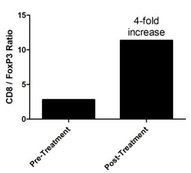


Figure 12. CD8 / FoxP3 T cell Ratio



Tumor IHC samples are from one subject and represent core biopsies that were isolated from the same lung lesion both at 2 days pre-treatment and 33 days post-treatment with pepinemab + avelumab. This patient was a PR according to RECIST, with a -46% lesion decrease at first scan (day 50) and overall lesion shrinkage at every scan after that. 5 micron FFPE sections were stained sequentially with Hematoxylin, pan-cytokeratin, CD8 and FoxP3. Images were taken at 10x magnification with CD8 (red) and FoxP3 (blue) overlays of pre and post treatment biopsies. Scans were co-registered for each stain; total number of CD8+ and FoxP3+ cells were quantified from entire section and normalized by sample area using Visiopharm software.

Correlations of Baseline Levels of Immune Cells with Time on Study

- Initial exploratory analysis of peripheral immune cell subsets[4] at baseline versus weeks on study suggests that higher levels of T cells and lower levels of MDSCs correlate with length of time on study.

Figure 13. Absolute CD8 + T Cells

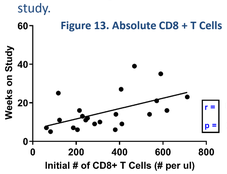


Figure 15. CD8+ vs MDSCs

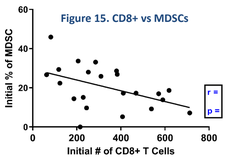
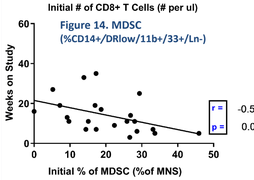


Figure 14. MDSC (%CD14+/DRlow/11b+/33+/Ln-)



Spearman rank-order correlation between cell subsets at baseline and weeks on study. Either absolute or % cell subsets were measured at baseline by flow cytometry at a central lab. The number of weeks on study is plotted versus the absolute (cells/ul) or % (of mononuclear cells) of peripheral subsets at baseline (average of a screening visit and baseline visit). The respective Spearman rank-order correlation coefficients (r) and p values for each analysis are provided. "Weeks on study" is defined as time from first dose to end of treatment. Data cutoff for correlation graphs : 28Jan2019.

Disease Control—Early Assessment

Table 4. DCR	Subjects (n=12)
Overall Disease Control Rate	75% (9/12)
Progressive Disease	2
Non-evaluable	1
Disease Control Rate ≥8 weeks	90% (9/10)
Subjects on study ≥24 weeks	(3/12)
Subjects on study ≥42 weeks	(2/12)

- The overall disease control rate for the Phase 1/b is **75%** (9/12).
- Of the three subjects, 1 died prior to first scan and on had rapidly progressive disease (<8 weeks).
- The disease control rate for subjects on study ≥ 8 weeks is **90%**, which includes 3 subjects on study ≥24 weeks and an additional 2 subjects on study ≥ 42 weeks.

CONCLUSIONS

- The combination therapy was shown to be well tolerated at all dose levels
- Recommended Phase 2 Dose (RP2D) was selected as 10 mg/kg of pepinemab Q2W (w/10 mg/kg avelumab Q2W)
- Initial PK/PD analysis demonstrate patterns similar to previous single agent trials.
- Immunogenicity does not appear to be a concern.
- Disease Control Rate (DCR) for all dose escalation patients is 75% and for subjects treated for at least two months is 90%.
- Time on study correlated with baseline circulating T cells and inversely with baseline MDSC.
- Exploratory: Assays are in place 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. http://cancerimmunolres.aacrjournals.org/content/early/2015/01/22/2326-6066.CIR-14-0171.full.pdf
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