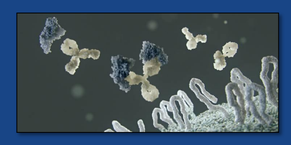
Interim results from CLASSICAL-Lung, a phase 1b/2 study of pepinemab (VX15/2503) in combination with avelumab in advanced NSCLC patients who progressed on prior anti-PDx therapy

Abstract #XXXX



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VACCINEX

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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 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.

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]

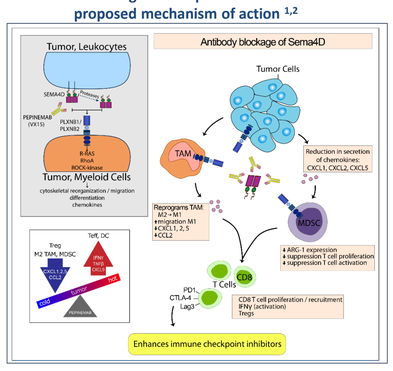


Figure 2. Avelumab proposed mechanism of action

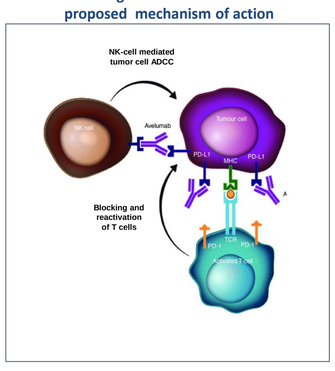


Figure 3. Preclinical data supporting combination therapy

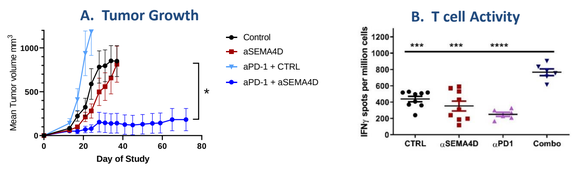


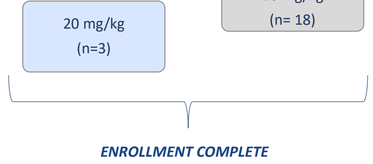
Figure 3: Combination therapy enhances frequency of tumor regression and T cell activity. A) Colon26 (500,000 cells) were subcutaneously implanted into Balb/c mice, that were then treated with αSEMA4D / MAb67 (10 mg/kg, weekly IP X2), αPD-1 / MAb RMP1-14 (10 mg/kg, twice/week, n=20). **B)** T cells from 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, 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 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 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 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

Pepinemab / avelumab combo is well tolerated

- 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).
- A total of (60) grade 1 and (32) grade 2 AEs related to the combination were reported to date.
- No grade 5 AEs related to the combination have been reported. 30 Aug 2019

Adverse Event Detail	Grade 3	Grade 4	Total Subjects
Abdominal Pain	1 [1]		1
Alanine Aminotransferase Increased	1 [1]		1
Aspartate Aminotransferase Increased	1 [1]		1
Elevated Lipase	2 [2]		1
GGT Increased	1 [1]		1
Hyperprogression	1 [1]		1
Immune Mediated Diabetic Ketoacidosis	1 [1]		1
Myositis	1 [1]	1 [1]	1
Pulmonary Embolism	1 [1]		1
Systemic Inflammatory Response Syndrome	1 [1]		1
Wheezing	1 [1]		1
Abdominal Pain	1 [1]		1
Total Events	**[11]**	**[1]**	**13 [13]**

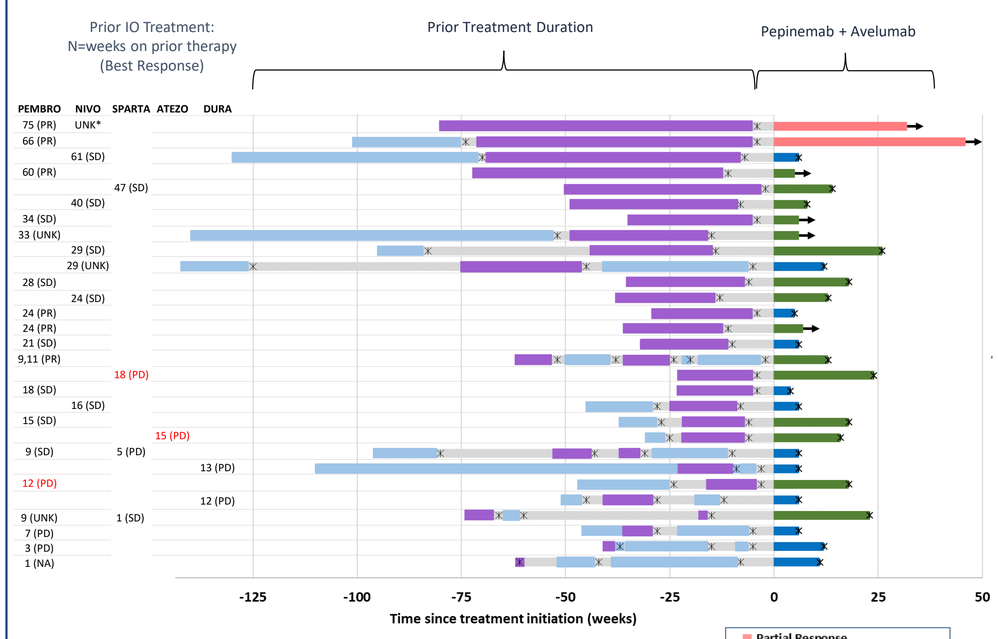
Table 1. Treatment-related Grade 3/4 AEs associated to combination, occurring in all subjects (n denotes the number of subjects, [x] denotes the number of events, (i.e. 2 [2]: 2 Subjects experienced 2 AEs).

Demographic Characteristics

Subjects Enrolled n=	(IO Naïve) 32		(IO Failure) 30		(All) 62	
Age (years)	67 (median)	51-85 (range)	62 (median)	30-83 (range)	66 (median)	30-85 (range)
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 Pacific Islander	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%
Historical PD-L1 (22C3) Status Reported by Investigator Site						
No PD-L1 expression	12	40%	7	22%	19	31%
Low PD-L1 expression	10	33%	7	22%	17	27%
High PD-L1 expression	2	7%	5	16%	7	11%
Unknown	6	20%	13	41%	19	31%

INTERIM RESULTS: CLASSICAL-Lung (NCT03268057)

Duration of Response in IO Failure Subjects



- Duration of response in IO Failure patients following treatment with Pepinemab + Avelumab
  - 4 subjects on study ≥24 weeks (6 months), including one subject with a durable response approaching 1 year
  - 6 additional subjects on study ≥16 weeks (4 months)
  - 3 of these 9 subjects were IO refractory before entering trial (→)
- Partial responses (PR) 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 (SD) was attained in 15 subjects at first scan.
- **59% of evaluable patients (17/29) whose tumors had progressed during or following treatment with an anti-PD-x antibodies benefited from switching to the combination of pepinemab + avelumab which appeared to induce a halt or reversal of tumor progression.**

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

Figure 4: Duration of Response in IO Failure Subjects in Comparison to Previous Treatment(s). Evaluable patients are shown (3 subjects were non-evaluable).

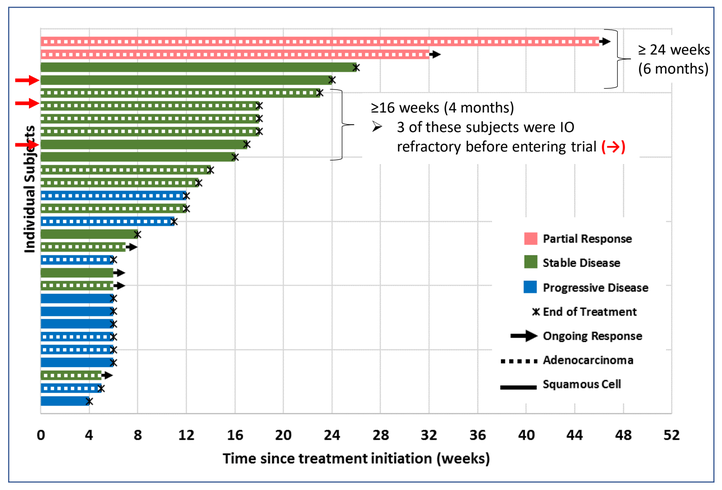


Figure 5: Duration of Response in evaluable IO Failure Subjects. Evaluable patients are shown.

Exploratory Biomarkers: Multiplex Tumor Immunohistochemistry

- CD8+ T cell density increased in most tumors following treatment with pepinemab + avelumab.
- CD8+ T cell levels in tumor appear to correspond with response. Higher T cell densities and highest 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 11/12 biopsies from subjects analyzed with PR or SD, as defined by RECIST criteria.
- No tumor was observed in biopsies from three of five IOF subjects analyzed with stable disease (SD#3, #4, and #5), as defined by RECIST criteria. Instead, biopsies contained fibrotic scar tissue with evidence of inflammation (see below).
- Interestingly, PD-L1 expression was negative in two of these three SD subjects from IO failure cohort. All samples among IO naïve subjects were low or negative for PD-L1.

Figure 6A: CD8 Density

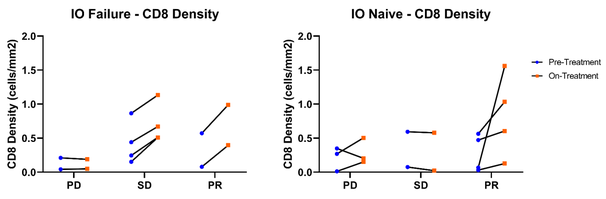


Figure 6B: IO Failure

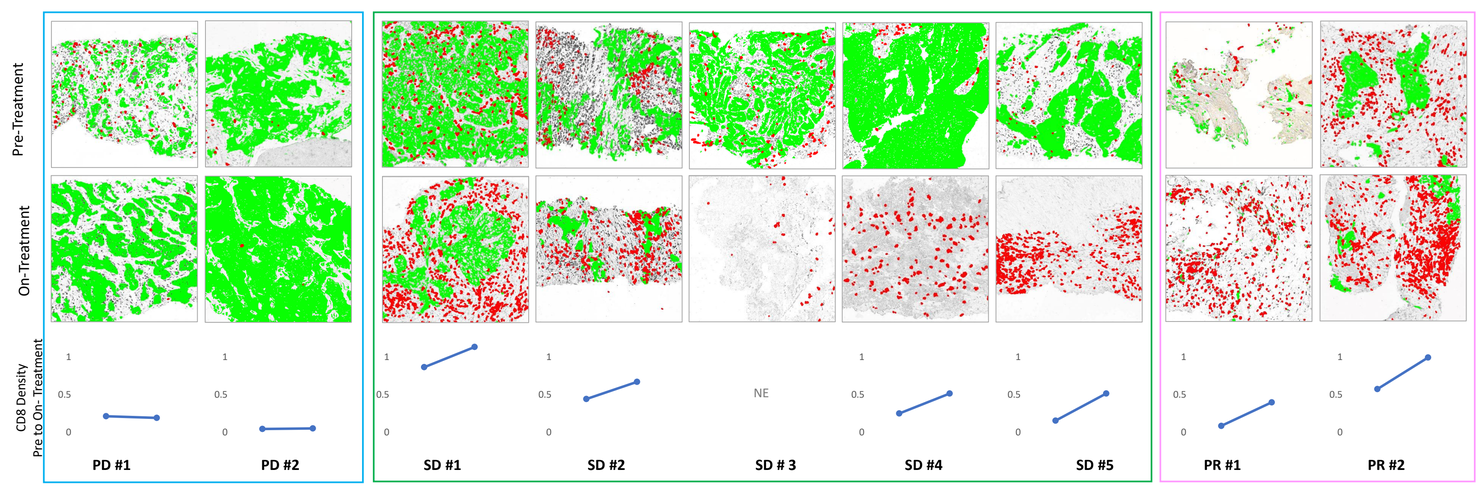


Figure 6C: IO Naïve

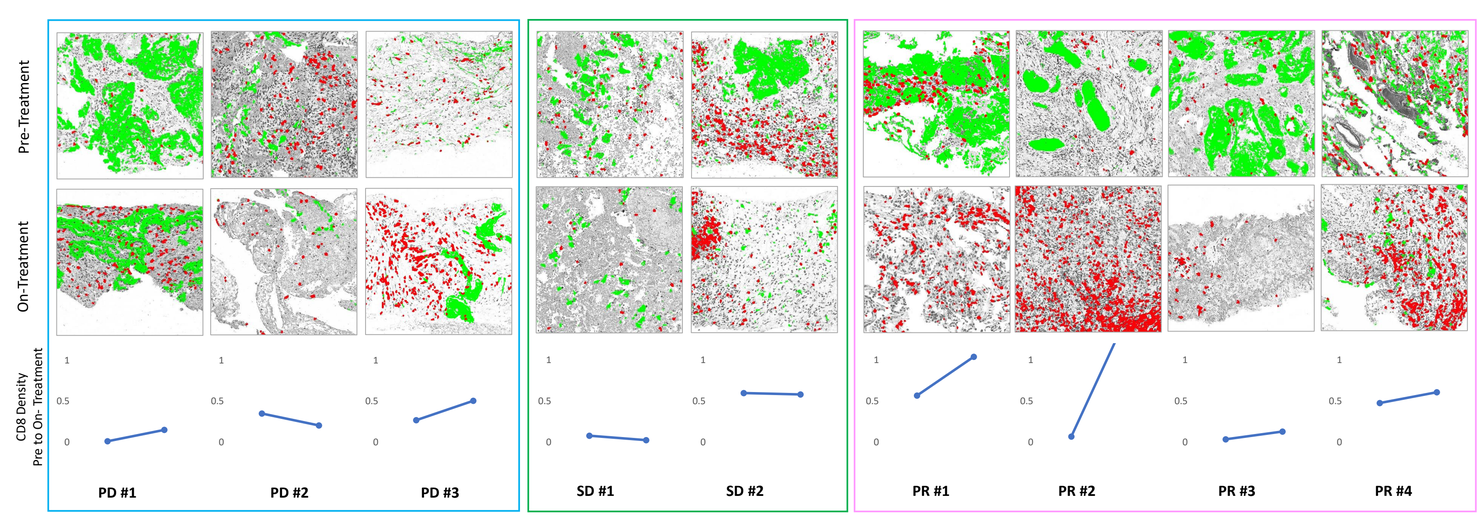
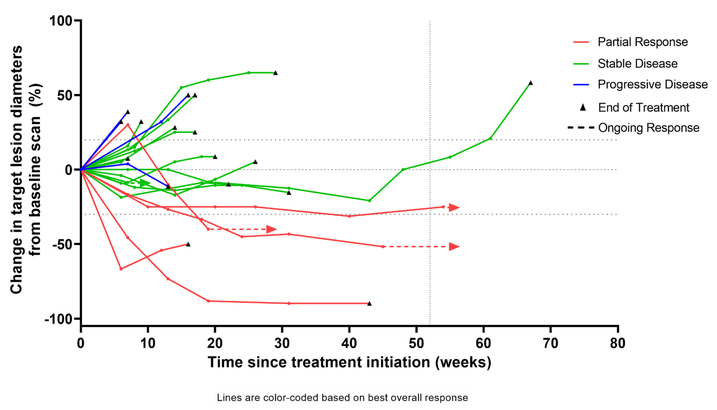


Figure 6: Multiplex IHC demonstrating tumor content and shift in balance of T cells in TME. Core or fine needle biopsies from nine IO-failure subjects (B) and nine IO-naïve subject (C) were analyzed, including pre and on-treatment samples isolated from the same lesion; on-treatment biopsies were collected 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 to determine CD8 density. BC) 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: Not evaluable, excluded from CD8 density analysis due to entire tumor bed consisting of necrotic tissue

Percent Change in Target Lesion Diameter (IO Naïve)



Lines are color-coded based on best overall response

Figure 7: Percent Change in Target Lesion Diameter (IO Naïve), evaluable patients shown

- Changes in the clinical management of IO naïve patients following initiation of this study made it increasingly difficult to enroll immunotherapy naïve subjects, and many of those enrolled were unevaluable and appeared to have lower PD-L1 expression than historic controls.
  - Historical PD-L1 (22C3) status reported by the investigator sites revealed that only 7% (2/28) showed high PD-L1 expression.
  - 30% were found to be unevaluable due to non evaluable scan (n=1), withdrawal of consent (n=4), or death (n=4; all unrelated: not other specified, sudden cardiac death, death due to disease progression and hemorrhage)
- Because of the above considerations, the IO naïve expansion arm of the study was closed after enrolling only 18 patients. **Nevertheless, among evaluable IO naïve subjects enrolled in either dose escalation or dose expansion, the Disease Control Rate (PR+SD) was 81%.**

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=20) enrolled in either dose escalation or dose expansion, 5 immunotherapy naïve patients experienced a PR, 3 patients have durable responses 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 an 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).
- Exploratory:
  - Initial histopathological analysis demonstrates increased CD8+ T cell density 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 11/12 biopsies from subjects analyzed with PR or SD, as defined by RECIST criteria. Interestingly, no tumor was detected in biopsies analyzed from 3/6 subjects with PR and 3/7 subjects with SD. PD-L1 expression was negative in two of these three SD subjects, and all samples among IO naïve subjects were low or negative for PD-L1.
  - ➢ 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.**

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

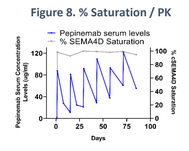


Figure 9. Cellular SEMA4D / PK

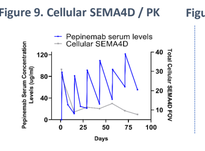
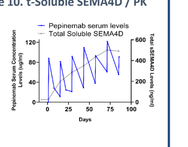


Figure 10. t-Soluble SEMA4D / PK



Pharmacokinetics

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

Figure 11. Avelumab drug levels (ug/ml)

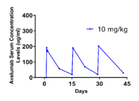
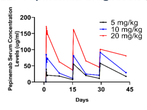


Figure 12. Pepinemab drug levels (ug/ml)



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.

Table 2: Escalation subjects Experiencing ADA

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

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)

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