Phase II of CD40 Agonistic Antibody Sotigalimab (APX005M) in Combination with Nivolumab in Subjects with Metastatic Melanoma with Confirmed Disease Progression on Anti-PD-1 Therapy

Abstract 389 Apexigen

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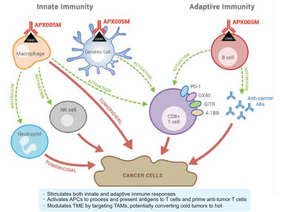
I. Rationale/Background

- CD40 is a member of the TNF receptor superfamily expressed on B cells, dendritic cells (DCs), macrophages, monocytes. Signaling through CD40 induces immune cell activation and is independent of innate stimulators such as toll-like receptors and STING.
  - Binding of CD40 to its cognate ligand, CD40L, or by agonist Mabs can activate DCs and induce maturation, allowing optimal priming and activation of T cells.
  - Agonist CD40 Mabs can substitute for T helper cell interaction and directly "license" DCs to activate/drive CD8 cytolytic responses.
  - CD40 agonists can induce production of IL-12 & IL-15 potentiating NK and T cell activity and can activate macrophages to infiltrate and deplete tumor stroma.
  - In preclinical studies, CD40 agonists can increase the effectiveness of cancer vaccines, chemotherapy, radiation, and increase *in vivo* expansion and efficacy of adoptive T cell therapies as well as CAR-T approaches.
  - Importantly, the combination of CD40 agonist and anti-PD-1/PD-L1 mAbs demonstrated additive or synergistic improvement of T-cell function and animal survival in solid tumor models and could resensitize T cells to overcome tumor resistance to PD-1 blockade.
- Patients (pts) with unresectable or metastatic melanoma who develop resistant, progressive disease (PD) while receiving an anti-PD-1 regimen have limited, less effective salvage treatment options. While a small subset of pts may exhibit delayed tumor shrinkage after continued anti-PD-1 therapy, most will not, and effective treatment for this refractory population represents an unmet need.
- This study was designed to investigate the efficacy of sotigalimab and nivolumab in pts with confirmed, anti-PD1/PD-L1 refractory melanoma.

Sotigalimab (APX005M)

- APXiMAB™ derived, humanized IgG Mab targeting CD40
- Binds with an affinity of 1.2x10^{-10}M to the human CD40L binding domain on CD40 to mimic natural CD40L signaling and effect
- Different from other CD40 agonist Mabs and uniquely engineered to have higher binding to FcγRIIb, thereby increasing crosslinking and potency by Fc bearing cells
- Undetectable binding to FcγRIIIa eliminating ADCC effects on CD40-expressing antigen presenting cells (APCs)
- In a separate ongoing study, sotigalimab demonstrated single-agent activity and safety in immunotherapy naïve pts with advanced melanoma.

(APXiMAB™ is Apexigen's proprietary rabbit-based antibody discovery platform)



II. Study Design

In this study, we investigated the safety and efficacy of sotigalimab in combination with nivolumab in pts with advanced melanoma. Dose Escalation examined sotigalimab at 0.03, 0.1 and 0.3 mg/kg IV in combination with nivolumab 360 mg IV q21d in cohorts of pts using a 3+3 design. Sotigalimab 0.3 mg/kg was determined to be the maximal safe dose examined and confirmed the same RP2D established in a Phase 1 single agent study.

Here we present the Phase 2 Expansion cohort of melanoma pts whose disease had progressed on anti-PD-1/PD-L1 therapy. ClinicalTrials.gov Identifier: NCT03123783, completed 16 Nov 2020.

Eligibility:

- Pts with relapsed/refractory (R/R) melanoma that had confirmed PD on an anti-PD-1 or anti-PD-L1 mAb were eligible.
- Confirmation of PD should have been documented by 2 consecutive tumor measurements ≥4 weeks apart.
- Study treatment should have started ≤8 weeks following the last dose of anti-PD-1/PD-L1.
- Prior anti-CTLA4 was allowed as long as there was no progression while on therapy and the last treatment was >3 months prior to study start.

III. Patient Characteristics

- Safety Population: 38 enrolled pts received at least 1 dose of sotigalimab and were evaluable for safety.
- Efficacy population: 33 pts were evaluable for efficacy.
  - 5 pts were not evaluable due to no post-treatment tumor assessments or to major inclusion criteria violations.

Table 1: Efficacy Population

		(N=33)
Age	Median [Range]	61 [32, 83]
Gender: Female/Male	n (%)	14 (42.4) / 19 (57.6)
ECOG PS at baseline		
0 1	n (%)	25 (75.8) 8 (24.2)
Time (mos) from first Dx biopsy to consent	Median [Range]	26.00 [7, 300]
Number of prior therapies*		
1 2 3	n (%)	26 (78.8) 5 (15.1) 2 (6.1)
Prior Treatment with anti-PD-1 / anti-PD-L1 agent	Anti-PD-1 (%) / Anti-PD-L1 (%)	(100 / 0)
Elevated LDH at baseline (>ULN)	n (%)	14 (42.4)
Histology: Melanoma		
Acral lentiginous Lentigo maligant Nodular malignant Superficial spreading Missing	n (%)	6 (18.2) 2 (6.1) 11 (33.3) 5 (15.1) 9 (27.3)
Metastatic Sites at Study Entry		
Any	n (%)	33 (100)
Lung (58%); Skin or Subcutaneous (42%); Distant lymph nodes (LN, 33%); Local/regional LNs (27%); Liver (18%); Bone (12%); Brain (6%); Breast (3%); Other (27%)		

*Includes 8 pts (24%) who received an anti-CTLA4 regimen

IV. Clinical Results

Safety of Sotigalimab and Nivolumab in Melanoma Patients

- Adverse events (AEs) of any grade ***regardless if considered related to study drugs or not*** were reported in the majority of pts (95%). The majority of these AEs were grade 1/2 and grade ≥3 AEs were reported in 29% of pts.
- AEs considered ***related to sotigalimab or nivolumab or both occurring in >10% of pts*** are shown in Table 2.
  - Majority of AEs were CTCAE (ver 4.03) grade 1/2 and transient.
  - Low incidence of reported infusion reactions and no cytokine release syndrome
- Serious adverse events (SAEs) were reported in 15.8% of pts; none were considered related to either sotigalimab or nivolumab [bacteremia, pain, appendicitis, bone fracture, intestinal obstruction, and (1 pt) influenza, opioid toxicity, confusion].
- There were no treatment withdrawals/discontinuations or deaths reported as due to AEs.
- The incidence of immune related AEs (e.g. colitis 1 pt Gd 1; pneumonitis 2 pts Gd 1 or 2; hyperthyroidism 1 pt Gd 1; etc.) were low and not more than expected with nivolumab alone.

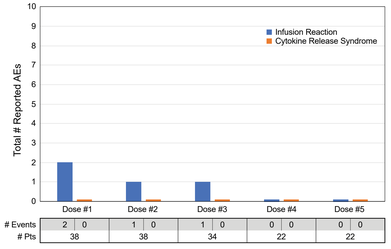
(Note: SAEs related to sotigalimab and/or nivolumab, including SAEs leading to treatment withdrawal, were reported in other treatment arms.)

Table 2: Related Adverse Events Occurring in ≥10%

N= 38	Related to sotigalimab alone, not related to Nivo		Related to Nivo alone, not related to sotigalimab		Related to Both		Overall	
	Grade 1-2	Grade 3+	Grade 1-2	Grade 3+	Grade 1-2	Grade 3+	All Grades	
Related AEs	Subjects n (%)	Subjects n (%)	Subjects n (%)	Subjects n (%)	Subjects n (%)	Subjects n (%)	Events n	Subjects n (%)
Pyrexia	11 (28.94)	1 (2.63)	.	.	13 (34.21)	0 -	55	24 (63.15)
Fatigue	4 (10.52)	0 -	1 (2.63)	0 -	15 (39.47)	0 -	41	20 (52.63)
Chills	8 (21.05)	0 -	2 (5.26)	0 -	13 (34.21)	0 -	48	19 (50.00)
Nausea	7 (18.42)	0 -	1 (2.63)	0 -	9 (23.68)	0 -	17	15 (39.47)
Pruritus	2 (5.26)	0 -	1 (2.63)	0 -	10 (26.31)	0 -	15	13 (34.21)
ALT increased	2 (5.26)	1 (2.63)	0 -	1 (2.63)	6 (15.78)	1 (2.63)	17	10 (26.31)
AST increased	1 (2.63)	1 (2.63)	.	.	6 (15.78)	1 (2.63)	14	8 (21.05)
Headache	2 (5.26)	0 -	.	.	6 (15.78)	0 -	17	8 (21.05)
Rash	2 (5.26)	0 -	1 (2.63)	0 -	4 (10.52)	0 -	10	7 (18.42)
Vomiting	2 (5.26)	0 -	1 (2.63)	0 -	4 (10.52)	0 -	14	7 (18.42)
Arthralgia	.	.	3 (7.89)	0 -	4 (10.52)	0 -	14	6 (15.78)
GGT increased	1 (2.63)	0 -	.	.	4 (10.52)	1 (2.63)	16	6 (15.78)
Myalgia	1 (2.63)	0 -	1 (2.63)	0 -	4 (10.52)	0 -	10	6 (15.78)
Alk Phos increased	1 (2.63)	0 -	.	.	5 (13.15)	0 -	10	5 (13.15)
Diarrhoea	.	.	0 -	1 (2.63)	3 (7.89)	0 -	6	4 (10.52)

Events = Number of events. Subjects = Number of subjects with highest severity.
Percentages on the patients' column are based on the number of subjects (N) in a given study group or overall as the denominator.
For each row category, a subject with two or more adverse events in that category is counted only once for the patients column.
ALT, Alanine aminotransferase ; AST, Aspartate aminotransferase; Alk Phos, alkaline phosphatase: GGT, gamma-glutamyltransferase

Low Incidence of Reported Infusion Reactions and No Reported Cytokine Release Syndrome (CRS)



- Incidence of infusion reactions were highest with the first dose (2 events, 5%) and decreased with subsequent doses.
- # AEs reported as: CRS, 0 events; Infusion Reactions, 4 events in 3 pts, all grade 2
- Other AEs reported as at least possibly related to APX005M ***and considered possibly part of an Infusion Reaction or CRS*** (separate question to investigator in database) but not reported as such (preferred term) include: pyrexia in 37% of pts (19.5% of doses 1-5; all Gd1 except 1 Gd2), hypotension 2.6% of pts (<1% of doses 1-5; Gd1, 1 event), rash/rash maculopapular 7.9% of pts (2.6% of doses 1-5; Gd1/2, all transient <1 day).
- No CRS AEs were reported in this safety cohort of anti-PD-1 refractory melanoma pts but have been reported in other studies/indications.

Table 3: Best Overall Response

Best Overall Response		Evaluable Patients (N=33)
PR	n (%)	5 (15.2)
SD	n (%)	11 (33.3)
PD	n (%)	17 (51.5)
Objective response rate (ORR)	Rate (CI 90%)	15.2 (6.2, 29.3)
Duration of Response (PR)* (First documented PR to end of study)	Range	6 to 25 months

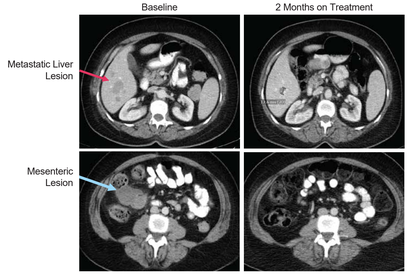
*At completion of therapy and study follow-up as shown in the Swimmer plot, 4 PR pts remained in PR without further systemic treatment (end of treatment to end of study: up to 16 months); 1 pt received stereotactic RT for an isolated brain lesion ~10 months after stopping study therapy and had not required further local or systemic therapy.

Percentages are based on the number of subjects (N) in a given group as the denominator.
CI = Confidence Interval (calculated using exact (Clopper-) method).
PR = Partial response, SD = Stable disease, PD = Progressive disease

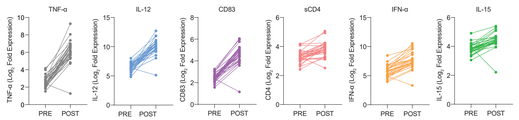
- One additional pt achieved an unconfirmed radiologic PR but developed new lesions on the next evaluation. Of note: pt had an ~64% reduction of target lesions and resolution of nearly all NT lesions. Best overall response: RECIST v1.1: SD. Confirmation of progression was not obtained.
- Duration of SD: up to 14.8 months; SD >3.5 months: 9 pts (82%); SD >6 months: 2 pts (18.2%)

Response in a Mucosal Melanoma Patient with Refactory Disease

- 54 yo initially diagnosed with mucosal melanoma in 2013 and underwent several surgeries and RT for recurrences.
- In 2017, pt started ipilimumab/nivolumab x3 cycles and then nivolumab alone due to tolerability.
- After ~10 months of SD on nivolumab maintenance, developed rapid progression in multiple sites and had an elevated LDH.
- Two months after starting sotigalimab/nivolumab, achieved a PR and later had resolution of all target lesions.
- Pt completed ~11 mos (15 cycles) of combination therapy and maintained a PR for 25+ months without additional therapy.



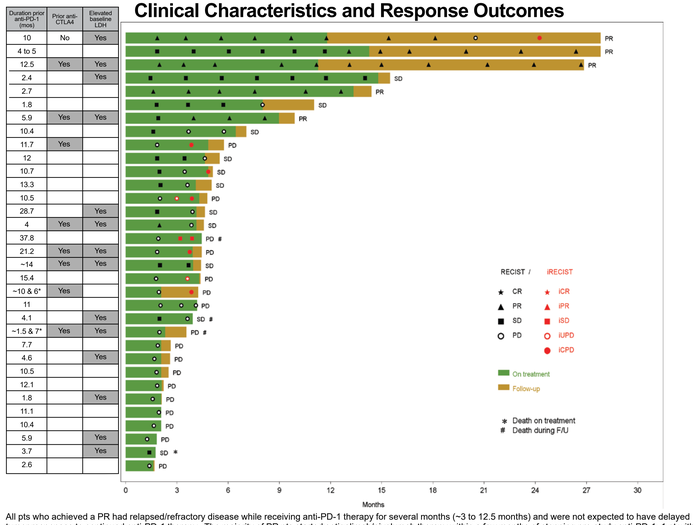
Sotigalimab/Nivolumab Therapy Induces Soluble Analytes Associated with APC and T Cell Activation



- Blood pre- and 4 hours post-start of infusion of the first dose were collected and plasma were analyzed using Proximity Extension Assay (PEA) technology for 92 protein biomarkers (Olink Target 96 Immuno-Oncology panel, Olink Proteomics).
- Data are qualitative changes and represented as Normalized Protein eXpression (NPX) values on a $\log_2$ scale.
- Sotigalimab and nivolumab treatment induced significant increases in analytes related to APC, NK, and T cell activation. Average Fold Change (FC): TNF-α, FC = 16.26; IL-12, FC = 18.8; sCD83, FC = 4.9; IFN-γ, FC = 4.99; and IL-15, FC = 1.6 (all p< 0.0001, two-sided t test). Soluble CD4 (sCD4), FC = 1.5 (p< 0.001).
- Increased expression of these immune mediators and markers is consistent with activation of DCs, NK and T cells.

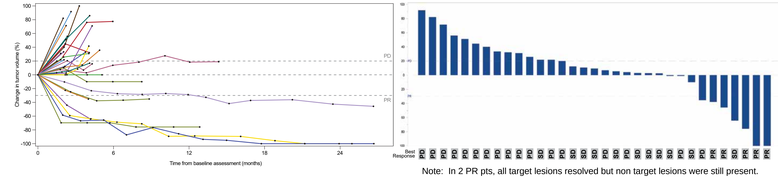
Clinical Characteristics and Response Outcomes

Duration prior anti-PD-1 (mos)	Prior anti-CTLA4	Elevated baseline LDH
10	No	Yes
4 to 5		
12.5	Yes	Yes
2.4		Yes
2.7		
1.8		
5.9	Yes	Yes
10.4		
11.7	Yes	
12		
10.7		
13.3		
10.5		
28.7		Yes
4	Yes	Yes
37.8		
21.2	Yes	Yes
~14	Yes	Yes
15.4		
~10 & 6*	Yes	
11		
4.1		Yes
~1.5 & 7*	Yes	Yes
7.7		
4.6		Yes
10.5		
12.1		
1.8		Yes
11.1		
10.4		
5.9		Yes
3.7		Yes
2.6		



All pts who achieved a PR had relapsed/refractory disease while receiving anti-PD-1 therapy for several months (~3 to 12.5 months) and were not expected to have delayed tumor responses to continued anti-PD-1 therapy. The majority of PR pts started sotigalimab/nivolumab therapy within a few months of stopping pre-study anti-PD-1; 1 pt with primary resistant/refractory disease had a delay of 11 months. Two PR pts had received prior anti-CTLA4/anti-PD-1 therapy but stopped the anti-CTLA4 component ~6 to 12 months before study start.
*Pts had 2 courses of anti-PD-1 with durations shown separated by >2.5 months.

Best Change (%) in Tumor Size From Baseline Sum of the Diameters of All Target Lesions



Note: In 2 PR pts, all target lesions resolved but non target lesions were still present.

V. Summary

- Melanoma pts refractory to anti-PD-1/PD-L1 therapy are poorly responsive to SOC treatment and have an unmet medical need.
- This study demonstrates that the combination of sotigalimab and nivolumab can be administered repeatedly >1 year with a reasonable safety profile and a low reported incidence of infusion reactions and no reported CRS in this patient population.
- The combination was active in anti-PD-1 refractory melanoma pts (ORR 15.2%, SD 33.3%), many of whom had progressed after prolonged durations of anti-PD-1 therapy (Median ~10 months) and/or had elevated LDH at baseline (42%), a poor prognostic indicator of response to anti-PD1/PD-L1 therapy.
- Durable responses up to 25+ months observed and 4 of 5 pts remained in PR without further systemic therapy. SD observed up to 14.8 months.
- The combination of sotigalimab and nivolumab resulted in treatment benefits (tumor response or prolonged disease control) in anti-PD-1 refractory melanoma pts with an overall favorable safety and tolerability profile. These results are encouraging and warrant further investigation.
- In addition, sotigalimab's activity and safety support investigations of combinations with other immuno-oncology therapeutics in other clinical settings.

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