Phase 1b/2 Study of CD40 Agonistic Antibody APX005M in Combination with Nivolumab (Nivo) in Subjects with Metastatic Melanoma (M) and Subjects with Non-Small Cell Lung Cancer (NSCLC)

Sarah A. Weiss[1,*], Harriet Kluger[1,*], Anthony J. Olszanski[2], Lynn Schuchter[3], Gerald P. Linette[3], Linda Garland[4], Nicholas O. Iannotti[5], Melissa Johnson[6], Emin Avsar[7], Minu K. Srivastava[8], Ovid C. Trifan[8], Martin J. Edelman[2]

[1]Yale Cancer Center, [2]Fox Chase Cancer Center, [3]Abramson Cancer Center of the University of Pennsylvania, [4]University of Arizona Cancer Center, [5]Hematology Oncology Associates, [6]Sarah Cannon Research Institute, [7] Bristol-Myers Squibb, [8]Apexigen, Inc. *These two authors contributed equally.

Abstract

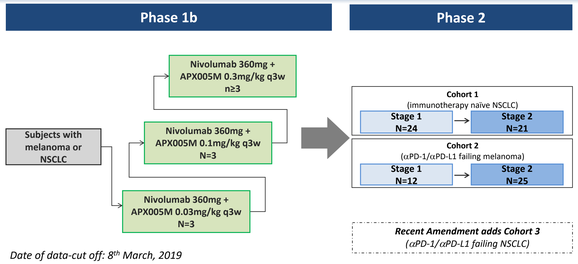
Background: Despite recent success with checkpoint inhibitors such as anti-PD-1, the majority of patients with M or NSCLC have transient response or no response to checkpoint blockade. Preclinical data suggest that CD40 agonist antibodies can be combined with anti-PD-1 antibodies to trigger effective T cell immunity. We are conducting a multi-center, open label Phase 1b/2 clinical trial to evaluate the combination of APX005M with Nivo in subjects with M or NSCLC. We report safety and efficacy from the completed Phase 1b portion of the study and the 1st stage of the Phase 2 M cohort.

Methods: Phase 1b followed a 3+3 design and enrolled adult subjects with M and disease progression (PD) while receiving anti-PD-1 therapy (anti-CTLA-4 more than 3 months prior to study entry was allowed) and subjects with immunotherapy naïve NSCLC, in 3 dose levels of APX005M (0.03, 0.1 and 0.3 mg/kg) combined with a fixed dose of Nivo (360mg) every 3 weeks. Primary objectives in phase 1b were to evaluate safety and determine the phase 2 dose (P2D) of APX005M. Phase 2 is enrolling subjects with M or NSCLC in two parallel Phase 2 cohorts, each following a Simon 2-stage design. Primary objective in phase 2 is to evaluate the tumor response in each cohort. Phase 1b analyses were performed on dose limiting toxicity (DLT)-evaluable subjects. Phase 2 analyses were performed on all treated subjects.

Results: Phase 1b: No DLTs were observed in the 9 subjects enrolled in Phase 1b and the P2D for APX005M is 0.3 mg/kg. Four subjects experienced Grade 3 AEs considered related to study drugs (non-DLTs) with no grade 4 AEs reported. Of the 5 subjects with M, 1 had a confirmed PR, 2 had prolonged SD (>8 months) and 2 had PD as best overall response. Of the 4 subjects with NSCLC, 1 had a robust confirmed PR, 2 had SD (on study lesion biopsies histology negative) and 1 had PD as best overall response. Phase 2: The 1st stage of the M cohort enrolled 10 additional subjects. One subject experienced a Grade 3 AE considered related to study drugs with no grade 4 AEs reported. Of these 10 subjects, 2 had confirmed PR, 2 had SD, and 6 had PD as best overall response. The overall toxicity profile of the combination is consistent with the profiles of individual agents. NanoString analysis of paired tumor biopsies revealed high tumor-infiltrating lymphocytes, and increased expression of IFNγ inducible cytokines (CXCL9 and CXCL10) in response to treatment. Increased tumor T cell infiltration was further confirmed by immunohistochemistry.

Conclusions: APX005M + Nivo demonstrated a good safety profile and promising antitumor activity in M subjects with PD while receiving anti-PD-1 therapy and potential activity in NSCLC. The study is currently enrolling subjects in the 2nd stage of the Phase II M cohort and the 1st stage of the Phase II NSCLC cohort. Clinical trial information: NCT03123783.

APX005M-002 Study Design



Date of data-cut off: 8th March, 2019

Key Eligibility Criteria

Phase 1b: subjects that met eligibility criteria for Phase 2 Cohort 1 or Cohort 2

Phase 2 Cohort 1: immunotherapy naïve non-small cell lung cancer

- Histologically or cytologically confirmed NSCLC
- Metastatic or locally advanced not amenable to curative treatment
- Patients may be treatment naïve or could have received one prior platinum-based chemotherapy
- Patient with a driver mutation (EGFR, ALK or ROS) should have received appropriate TKI and progressed before enrollment.

Phase 2 Cohort 2: metastatic or unresectable melanoma progressing on anti-PD-1/PD-L1 therapy

- Histologically or cytologically confirmed unresectable or metastatic melanoma that had progressive disease during treatment with anti-PD-1/PD-L1 therapy documented by 2 consecutive tumor assessments (at least 4 weeks apart)
- Patients with BRAF activating mutation could have also received a BRAF inhibitor and/or MEK inhibitor regimen prior to anti-PD-1/PD-L1 therapy
- Patients could have received anti-CTLA-4 therapy provided they did not have disease progression while on therapy and they discontinue treatment with anti-CTLA-4 therapy at least 3 months prior to first dose of investigational product

General

- age ≥ 18
- measurable disease per RECIST 1.1,
- ECOG performance status of 0 or 1
- Normal bone marrow, kidney and liver function

Study Demographics

Safety/Efficacy Population		Phase 1b DL1 (N=3)	Phase 1b DL2 (N=3)	Phase 1b DL3 (N=3)	Phase 1b Total (N=9)	Phase 2 Melanoma Cohort Total (N=12)
Site						
Yale University	n (%)	0 (0.0)	1 (33.3)	3 (100.0)	**4 (44.4)**	**10 (83.3)**
Fox Chase Cancer Center	n (%)	1 (33.3)	1 (33.3)	0 (0.0)	**2 (22.2)**	
University of Pennsylvania	n (%)	0 (0.0)	1 (33.3)	0 (0.0)	**1 (11.1)**	**1(8.3)**
Tennessee Oncology, PLLC	n (%)	1 (33.3)	0 (0.0)	0 (0.0)	**1 (11.1)**	
The University of Arizona Cancer Center	n (%)	1 (33.3)	0 (0.0)	0 (0.0)	**1 (11.1)**	
Hem-Onc Associates of the Treasure Coast	n (%)					**1 (8.3)**
Primary Diagnosis						
Metastatic melanoma progressing on anti-PD-1	n (%)	1 (33.3)	2 (66.7)	2 (66.7)	**5 (55.6)**	**12 (100.0)**
Immunotherapy naïve NSCLC	n (%)	2 (66.7)	1 (33.3)	1 (33.3)	**4 (44.4)**	
Gender						
Female	n (%)	0 (0.0)	1 (33.3)	1 (33.3)	**2 (22.2)**	**3 (25.0)**
Male	n (%)	3 (100.0)	2 (66.7)	2 (66.7)	**7 (77.8)**	**9 (75.0)**
Age (years)						
	n	3	3	3	**9**	**12**
	Median [Min, Max]	72.0 [61.0, 77.0]	64.0 [55.0, 76.0]	58.0 [53.0, 67.0]	**64.0 [58.0, 72.0]**	**59.5 [34.0, 79.0]**
Race						
Black or African American	n (%)	0 (0.0)	1 (33.3)	0 (0.0)	**1 (11.1)**	
White or Caucasian	n (%)	3 (100.0)	2 (66.7)	3 (100.0)	**8 (88.9)**	**12 (100.0)**
ECOG PS at Baseline						
0	n (%)	1 (33.3)	1 (33.3)	3 (100.0)	**5 (55.6)**	**11 (91.7)**
1	n (%)	2 (66.7)	2 (66.7)	0 (0.0)	**4 (44.4)**	**1 (8.3)**

Phase 1b/2 Safety Data

	Phase 1b DL1 (N=3)	Phase 1b DL2 (N=3)	Phase 1b DL3 (N=3)	Phase 1b Total (N=9)	Phase 2 Melanoma Cohort Total (N=12)
Subjects with AEs [N(%)]	3(100)	3(100)	3(100)	9(100)	12(100)
Subjects with Grade 3-4 AEs [N(%)]#	3(100)	2(66.7)	0	5(55.7)	2(16.7)
Subjects with APX005M-related Grade 3 Events[N(%)]*	2(66.7)	2(66.7)	0	4 (44.4)	1(8.3)
Subjects with Nivo-related Grade 3 Events[N(%)]*	2(66.7)	1(33.3)	0	3(33.3)	1 (8.3)
Subjects with SAE [N(%)]	1(33.3)	1(33.3)	0	2(22.22)	2(16.7)
Subjects with Drug-related SAE (APX005M & Nivo) [N(%)]		0(0)		0(0)	0(0)

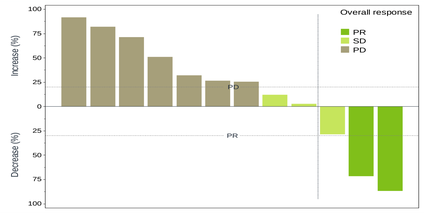
 # No DLTs were observed in Phase 1b; * No Grade 4 drug related AEs were observed in the study

Most Frequent(≥ 2pts) all Grade AEs Related to:	Phase 1b	Phase 2
APX005M	Pyrexia, pruritus, rash, nausea, influenza like illness	pyrexia, chills, fatigue, nausea, pruritus, rash
Nivolumab	pruritus, rash	fatigue, rash, chills, pruritus, dry skin, nausea, dry mouth

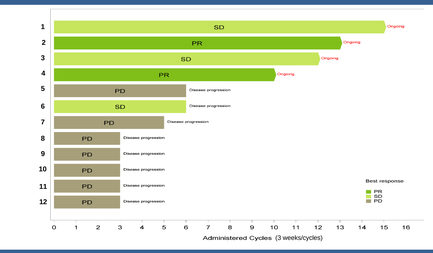
Summary of Best Overall Response

Best Confirmed Overall Response		Phase 1b NSCLC DL1 (N=2)	Phase 1b NSCLC DL2 (N=1)	Phase 1b NSCLC DL3 (N=1)	Phase 1b NSCLC Total (N=4)	Phase 1b Melanoma DL1 (N=1)	Phase 1b Melanoma DL2 (N=2)	Phase 1b Melanoma DL3 (N=2)	Phase 1b Melanoma Total (N=5)	Phase 2 Melanoma Cohort Total (N=12)
PR	n (%)	**1**	**0**	**0**	**1 (25.0)**	**0**	**1**	**0**	**1 (20.0)**	**2 (16.7)**
SD	n (%)	**0**	**1**	**1**	**2 (50.0)**	**0**	**1**	**1**	**2 (40.0)**	**3 (25.0)**
PD	n (%)	0	0	0	0	0	0	1	1 (20.0)	7 (58.3)
NE	n (%)	1	0	0	1 (25.0)	1	0	0	1 (20.0)	0

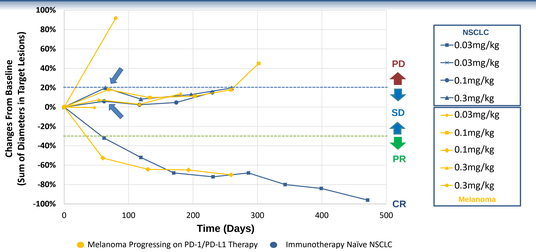
Phase 2 Melanoma Cohort: Percent Change in Sum of Target Lesions (Best Response)



Phase 2 Melanoma Cohort: Time on Treatment

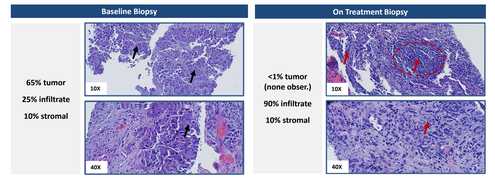


Phase 1b: Percent Change in Sum of Target Lesions



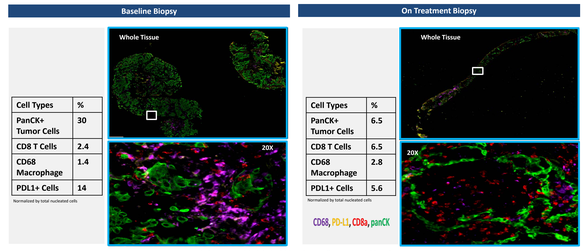
Preliminary data reflective of ongoing clinical trial. Arrow indicates no tumor tissue on tumor biopsy

Tumor Eradication by APX005M + Nivo in Subject with NSCLC



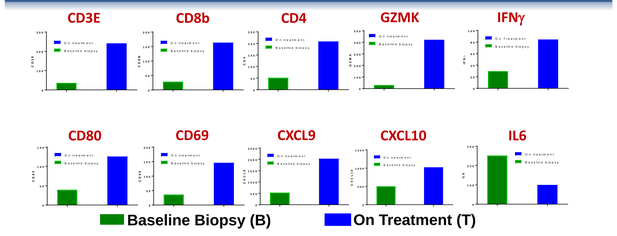
Histopathology for Subject X, NSCLC (APX005M 0.1mg/kg + Nivo 360mg)

Treatment Induced Immune Cell Infiltration at Tumor Site (Multicolor IHC)



Subject X, NSCLC (APX005M 0.1mg/kg + Nivo 360mg)

Treatment Induced Changes in Gene Expression (NanoString)



Subject X, NSCLC (APX005M 0.1mg/kg + Nivo 360mg)

Conclusions

- APX005M combined with Nivolumab demonstrated an acceptable safety profile.
- APX005M combined with Nivolumab demonstrated promising clinical activity in subjects with melanoma with active disease progression while receiving anti-PD-1/PD-L1 therapy.
- The combination showed preliminary antitumor activity in subjects with NSCLC previously treated with a platinum containing regimen.
- Nanostring analysis of paired tumor biopsies from 2 of 4 subjects with NSCLC showed a trend toward increased expression of IFNγ inducible cytokines (CXCL9 and CXCL10) following treatment relative to baseline. A trend toward increased tumor CD8 T cell infiltration was observed by immunohistochemistry.
- The study is currently enrolling subjects in all Phase 2 cohorts. Clinical trial information: NCT03123783

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Apexigen