A Multicenter Phase 2 Study of Sotigalimab (CD40 Agonist) in Combination With Neoadjuvant Chemoradiation for Resectable Esophageal and Gastroesophageal Junction (GEJ) Cancers

Andrew H. Ko[1], Marcus Smith Noel[2], Joseph Chao[3], Davendra Sohal[4], Mary Crow MD[5], Paul Eliezer Oberstein[6], Aaron James Scott[7], Autumn Jackson McRee[8], Caio Max Sao Pedro Rocha Lima[9], Lawrence Fong[1], Bridget P Keenan[1], Erin Filbert[10], Frank J. Hsu[10], Veena Shankaran[11]

[1]University of California San Francisco, San Francisco, CA; [2]Georgetown University Hospital, Washington, DC; [3]City of Hope Comprehensive Cancer Center, Duarte, CA; [4]University of Cincinnati, Cincinnati, OH; [5]Renovatio Clinical, Houston, TX; [6]Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY; [7]University of Arizona Cancer Center, Tucson, AZ; [8]Univ of North Carolina, Chapel Hill, NC; [9]Wake Forest University Baptist Medical Center, Winston-Salem, NC; [10]Apexigen, Inc., San Carlos, CA; [11]University of Washington School of Medicine, Seattle, WA

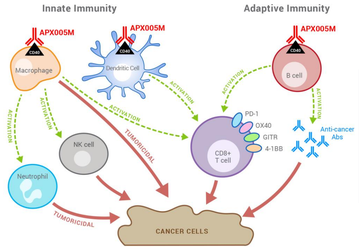
Poster #1229P

I. RATIONALE / BACKGROUND

- Esophageal/GEJ cancers are the seventh most common cancer worldwide.
- Trimodality therapy (neoadjuvant chemotherapy and radiation followed by surgery) represents the current gold standard for patients with resectable tumors, resulting in higher R0 resection rates and prolonged overall survival (OS) compared to surgery alone.
- Achieving a pathologic complete response (pCR) to neoadjuvant therapy is associated with a significantly improved OS.
  - Data from the CROSS trial and other studies show a pCR rate of 19-23% in adenocarcinomas (AC) and 42-49% in squamous cell carcinomas (SCC) following standard chemoradiation (CRT).
- Immunotherapeutic agents have now been integrated into treatment paradigms for esophageal/GEJ cancers in the advanced and postoperative adjuvant setting.
- Sotigalimab (sotiga) is a high affinity, potent CD40 agonist mAb capable of inducing and expanding anti-tumor immune responses by activating dendritic cells (DCs), T cells, NK cells, B cells, and M1 macrophages.
- This study examined the safety and efficacy of combining sotiga with neoadjuvant CRT in pts with esophageal/GEJ cancers with the goal of inducing anti-tumor responses and providing clinical benefit in these cancers.

Sotigalimab (APX005M)

- APXiMAB™ derived, humanized IgG1 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
- Undetectable binding to FcγRIIIa eliminating ADCC effects on CD40-expressing antigen presenting cells (APCs)
- Single-agent activity in immunotherapy näive pts with advanced melanoma
- Reasonable safety profile allowing combinations with other oncology therapeutics in multiple indications without additive/synergistic toxicities



- Stimulates both innate and adaptive immune responses
- Activates APCs to process and present antigens to T cells and prime anti-tumor T cell responses
- Modulates TME by targeting TAMs and inducing immune cell activation and infiltration converting "cold" tumors to "hot"

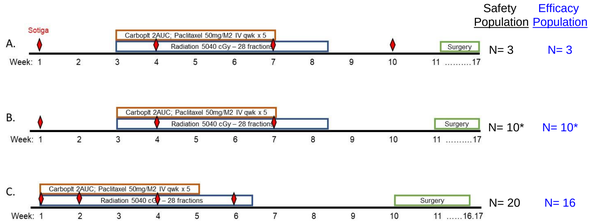
(APXiMAB™ is Apexigen's proprietary rabbit-based antibody discovery platform.)

II. PATIENT ELIGIBILITY

- Adenocarcinoma, squamous cell carcinoma, or undifferentiated carcinoma of the esophagus or GE junction
- Surgically resectable (T1-3 Nx by endoscopic U/S)
  - T1N0 and cervical tumors excluded
- ECOG PS 0-1
- Adequate hematologic, renal, and hepatic parameters
- No contraindications to immunotherapy (e.g. active autoimmune disorders)
- No chronic steroid dependency

III. STUDY DESIGN

- Multicenter, non-randomized study design
- Primary efficacy endpoint: pCR rate
- Study treatment: carboplatin (AUC 2) + paclitaxel (PTX) (50 mg/m2) weekly x 5 concurrent with radiation 5040 cGy, plus up to 4 doses of sotiga 0.3mg/kg IV, followed by Ivor-Lewis esophagectomy
  - Protocol underwent sequential amendments (for pragmatic and clinical reasons) over time, leading to adjustments in treatment administration according to 1 of the 3 schedules below:



*1 pt was enrolled on Schedule A but reconsented to Schedule B and did not receive a 4th dose of sotiga.

IV. PATIENT AND TUMOR CHARACTERISTICS[1]

- ITT population: n = **34** pts enrolled between Feb 2018 and Dec 2021
- Safety population (pts receiving at least 1 dose of sotiga): n = **33** (1 pt did not tolerate paclitaxel and withdrew prior to first dose of sotiga & not part of Safety pop.)
- Efficacy population (pts completing all planned neoadjuvant therapy and going on to surgery): n = **29**
  - 4 pts did not go on to surgery and were not evaluable for 1º study endpoint (3 declined surgery, 1 died prior to surgery 2º to complications a/w mechanical fall and then cancer)

SAFETY POPULATION (n=33)	N (%)
Age	Median 67 y.o. [range, 38-75]
Sex: Female/Male	7 (21) / 26 (79)
Race: Caucasian / Asian / African American / Other	25 (76) / 5 (15) / 1 (3) / 2 (6)
ECOG PS at baseline	
0 1	23 (70) 10 (30)*
Histology	
Adenocarcinoma	25 (76)
Squamous cell carcinoma	8 (24)
Disease Stage at Diagnosis	
II IIB III IVA	2 (6) 1 (3) 22 (67) 8 (24)
Tumor Location	
Upper Third / Middle Third / Lower Third / GEJ	2 (6) / 8 (24) / 8 (24) / 15 (45)

* 1 subject did not have ECOG assessed at Screening; Week 1 Visit 1 Pre-treatment ECOG was 1.

[1]Presentation based on data as of July2022

V. SAFETY

Treatment-Related Adverse Events Observed in ≥20% of patients

Adverse Event (Preferred Term)	Sotiga Related		Carboplatin Related		Paclitaxel Related		Radiation Related		All N=33	
	All Gr (%)	Gr 3+ N (%)	All Gr N (%)	Gr 3+ N (%)	All Gr N (%)	Gr 3+ N (%)	All Gr N (%)	Gr 3+ N (%)	All Gr N (%)	Gr 3+ N (%)
Nausea	17 (51.5)	1 (3.0)	18 (54.5)	1 (3.0)	18 (54.5)	1 (3.0)	10 (30.3)	1 (3.0)	24 (72.7)	1 (3.0)
Fatigue	16 (48.5)	1 (3.0)	18 (54.5)	1 (3.0)	19 (57.6)	1 (3.0)	11 (33.3)	1 (3.0)	23 (69.7)	1 (3.0)
Chills	16 (48.5)	0	3 (9.1)	0	2 (6.1)	0	-	-	16 (48.5)	0
Diarrhea	7 (21.2)	0	11 (33.3)	0	11 (33.3)	0	4 (12.1)	0	14 (42.4)	0
Neutropenia	-	-	14 (42.4)	8 (24.2)	14 (42.4)	8 (24.2)	3 (9.1)	2 (6.1)	14 (42.4)	8 (24.2)
AST increase	8 (24.2)	0	2 (6.1)	0	8 (24.2)	0	1 (3.0)	0	14 (42.4)	0
Thrombocytopenia	7 (21.2)	2 (6.1)	13 (39.4)	2 (6.1)	13 (39.4)	2 (6.1)	6 (18.2)	0	13 (39.4)	3 (9.1)
Leukopenia	4 (12.1)	0	13 (39.4)	8 (24.2)	13 (39.4)	8 (24.2)	3 (9.1)	1 (3.0)	13 (39.4)	8 (24.2)
ALT increase	6 (18.2)	1 (3.0)	2 (6.1)	0	8 (24.2)	1 (3.0)	1 (3.0)	0	13 (39.4)	2 (6.1)
Vomiting	9 (27.3)	1 (3.0)	9 (27.3)	1 (3.0)	9 (27.3)	1 (3.0)	8 (24.2)	1 (3.0)	11 (33.3)	1 (3.0)
Cytokine Rel. Syn.	11 (33.3)	3 (9.1)	-	-	-	-	-	-	11 (33.3)	3 (9.1)
Esophagitis	-	-	5 (15.2)	2 (6.1)	5 (15.2)	2 (6.1)	9 (27.3)	3 (9.1)	10 (30.3)	3 (9.1)
Pyrexia	9 (27.3)	0	-	-	-	-	-	-	9 (27.3)	0
Infusion Rel Rxn	5 (15.2)	0	-	-	2 (6.1)	0	-	-	7 (21.2)	0

Other AE considered related to sotiga >10% include: hypotension, pruritis 6 (18.2%); arthralgia 5 (15.2%); alkaline phosphatase increased, flushing, myalgia 4 (12.1%).

- No AEs considered related to sotiga directly led to withdrawal of planned sotiga treatment.
  - Unrelated AEs prevented the completion of sotiga in 2 pts.
- 16 pts (48.5%) experienced at least 1 SAE (34 events) with 6 considered at least possibly related to sotiga (3 CRS, 1 nausea and vomiting, 1 dysphagia and 1 Guillain-Barré Syndrome).
- Transient Gr 3 CRS occurred in 3 pts. Overall, CRS symptoms were prevented or mitigated by an extended premedication regimen of NSAIDs and antihistamines. Tocilizumab was used in only 2 pts.
- No AE leading to fatal outcome was related to study neoadjuvant CRT/sotiga.
  - Of 7 reported deaths: 5 were due to disease progression, 1 to surgery related complications (Chyle leak and pneumonia), and 1 to unrelated medical condition.

VI. EFFICACY

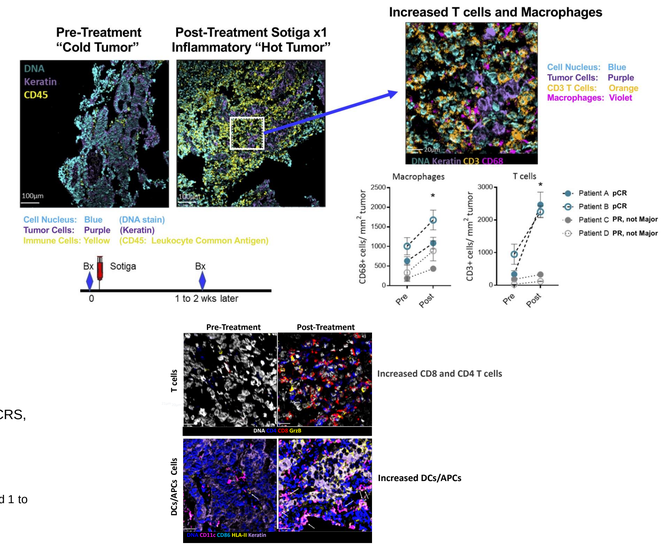
	Efficacy population N= 29 % (n/total)	Histologic subtype		Location
		Adenocarcinoma n= 24 % (n/total)	Squamous Cell Ca n= 5 % (n/total)	GEJ Ca, n= 14 % (n/total)
R0 resection	86% (25/29)	83% (20/24)	100% (5/5)	79% (11/14)
Pathologic response				
Complete response (pCR)	**38% (11/29)**	**33% (8/24)**	**60% (3/5)**	**29% (4/14)**
Major path response*	66% (19/29)	63% (15/24)	80% (4/5)	57% (8/14)
PD (before or at surgery)	7% (2/29)	8% (2/24)	0% (0/5)	14% (2/14)
Historical CRT pCR rate		19 – 23%	42 – 49%	--

* Defined as <10% viable tumor – includes pathologic CR and PR

- Sotiga plus neoadjuvant CRT led to encouraging rates of pCR in the overall pt population and in the histologic subgroups of adenocarcinoma and squamous cell carcinoma.
- R0 resection and major pathologic responses were achieved in the majority of pts.
- pCR rate by treatment administration schedule: A = 66.7% (2/3), B = 30% (3/10), C = 37.5% (6/16).
  - pCR rate by #doses: Sotiga 4 doses = 41.2% (7/17); 3 doses = 33.3% (4/12) [Note: 2 pts did not receive their scheduled 4th dose]
- Relapse-free and overall survival data are being collected and still pending at the time of this analysis.

VII. CORRELATIVE FINDINGS

Run-in Dose of Sotiga Alone Turns "Cold" Tumor "Hot"



- On treatment schedules A & B, pts had tumor biopsies collected pre- and 1-2 wks following a single run-in dose of sotiga alone. Samples were analyzed by IonPath for markers of immune cells including CD45, T cells, monocytes and DCs/APCs. Following this single dose of sotiga, a significant inflammatory response was observed, which was quantitatively higher in pts achieving a pCR.

VIII. SUMMARY / FUTURE DIRECTIONS

- Sotiga was generally safe and well-tolerated when combined with standard of care chemoradiation in the neoadjuvant setting for patients with resectable esophageal/GE junction cancer surgery.
- Sotiga in combination with chemoradiation conferred favorable pathologic CR rates compared to historical data.
  - Promising results observed for both squamous cell and adenocarcinoma histologies
  - Awaiting mature data on relapse-free and overall survival in the study population
- A single run-in dose of sotiga as monotherapy induced an inflammatory response in the tumor – changing the immune microenvironment from "cold" to "hot", validating the MOA of this agent.
- In total, these results are encouraging and warrant further investigation in a larger and randomized prospective study design.
- Sotiga's activity and safety support investigations of combinations with other oncology therapeutics in other clinical settings.

References

Filbert et al, *Cancer Immunol Immunother* (2021); Klevebro F. et al, *Ann Onc* (2016); Samson, P. et al, *J Thor Onc* (2016); Van Hagen P. et al, *N Eng J Med* (2012).