Protocol Number: APX005M-006

Official Title: A Phase 2 Study of APX005M in Combination with Concurrent Chemoradiation as Neoadjuvant Therapy for Resectable Esophageal and Gastroesophageal Junction Cancers

NCT Number: NCT03165994

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CLINICAL PROTOCOL APX005M-006

A Phase 2 Study of APX005M in Combination with Concurrent Chemoradiation as Neoadjuvant Therapy for Resectable Esophageal and Gastroesophageal Junction Cancers

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Date of Version 11:
12 August 2021

The information contained in this document is the confidential and proprietary information of Apexigen, Inc.

This study will be conducted in accordance with Protocol APX005M-006, the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

SPONSOR APPROVAL PAGE

DocuSigned by:

[redacted]

17-Aug-2021 | 10:20 PDT

Date

Clinical Development
Apexigen, Inc.

DOCUMENT HISTORY

Version	Date	Replaces	Description of Changes
Original Protocol (Version 1.2) to Version 8	22 Nov 2016 to 28 Oct 2019	N/A	• This study was conducted under an Investigator-sponsored IND ([redacted], University of California, San Francisco; and previous versions of the study protocol through Version 8 have been submitted to FDA by [redacted]
Version 9	16 Mar 2020	Version 8	• Apexigen, Inc has replaced [redacted] as IND Sponsor; the Sponsor has been changed to reflect Apexigen, Inc. throughout the protocol • Clarified the visit schedule to detail the follow-up visits after APX005M administration • Simplified the exploratory objectives to possible predictive molecular or immune-based efficacy biomarkers • Clarified correlative biomarker sample collection and Central Lab shipment location in Appendix 2 (previously Appendix 3) • Changed safety oversight by the DSMP (with deletion of the plan in Appendix 2) to the Sponsor and the Sponsor's Medical Monitor or designee • Revised the number of subjects to be enrolled ([redacted]), the total number of clinical sites enrolling (approx. 4-5), as well as the time period of enrollment (changed from 18 months to ~3 years [9 months from the start of enrollment under Version 9]) and expected overall study duration (changed from 24 months total to 19 months from the start of enrollment under Version 9) • Clarified the duration of patient participation in the study (changed from 11–17 weeks [first dose to completion of surgery] to 9 months [first dose to completion of post-surgery follow-up])
Version 10	30 Dec 2020	Version 9	• Updated IND number to reflect APX005M-006 added under Apexigen IND 122725 • Updated List of Abbreviations to reflect terminology specific to proton beam radiation • Revised the number of subjects to be enrolled [redacted] • Increased number of sites from 4–5 to 8–12 • Added rationale for protocol Version 10 to Section 2.4 • Clarified timing of administration for oral and intravenous pre-medications • Modified Schedule of Assessments, Study Procedures and corresponding sections of the protocol to reflect revised chemoradiation and APX005M dosing schedules. Chemotherapy will occur from Weeks 1–5, radiation from Weeks 1–6 and APX005M will be administered at Weeks 1, 2, 4, and 6. • Modified Schedule of Assessments, Study Procedures, and Appendix 2 to allow archival tissue samples to be

Version	Date	Replaces	Description of Changes
			submitted at Screening if a subject is unable to complete the endoscopic biopsy • Modified Schedule of Assessments, Study Procedures, and Appendix 2 to reflect modifications to Blood and Plasma sample collection for Immune Correlatives and Cytokines • Corrected Study Schema to reflect change to Chemoradiation, APX005M, sample collection, and Endoscopic biopsy schedule • Modified Inclusion Criterion 3 to state that T1-3 Nx determination is preferred to be determined by endoscopic ultrasound [EUS] • Modified Section 6.2.1 to reflect Endoscopic Ultrasound historical results within 56 days of Screening to be used • Added exclusion criteria regarding history of organ transplant and/or concurrent immunosuppressive medication. These subjects must be discussed with Medical Monitor or designee prior to consent • Added guidance under Prohibited Concomitant Medications regarding Influenza and COVID-19 vaccines • Modified CT-PET at Screening to allow historical CT-PET if completed within 28 days prior to first dose of APX005M • Strongly recommended that chemotherapy is completed on Mondays during treatment Weeks 1, 2, and 4 and administration of APX005M is scheduled on Wednesday or Thursday to allow for a 2-3 day-period between administration of chemotherapy and infusion of APX005M to ensure the least remaining effect of the steroid component of the chemo premedication on therapeutic activity of APX005M • Clarified that timing of pre-surgery CT-PET scan is recommended to be scheduled no earlier than 4 weeks after completion of chemoradiation • Added guidance regarding use of proton beam radiation therapy • Updated title of Section 8.1 from Sample Size and Accrual Rate to Sample Size and the following language was added: A minimum number of [redacted] evaluable patients with adenocarcinoma histology will allow to test the null hypothesis that the true pCR is 23% against a 1-sided alternative of 53% with a Type 1 error rate of 0.05 and power of 77%. All language regarding Accrual rate was removed. • Section 8.2 was updated to outline the safety analysis of the first 6 patients enrolled under protocol Version 10 (or a later protocol version)

Version	Date	Replaces	Description of Changes
Version 11	12 Aug 2021	Version 10	• 1.1 Abbreviated Synopsis was updated to note the correct treatment period of 6 weeks • 1.1 Abbreviated Synopsis, 1.2 Full Synopsis updated Estimated Enrollment Period to reflect current duration of enrollment • 1.1 Abbreviated Synopsis, 1.2 Full Synopsis Duration of Participation updated to include overall survival • 1.1 Abbreviated Synopsis, 1.2 Full Synopsis updated to add Overall Survival • 1.2 Full Synopsis, 3.3 Exploratory Objective, 8.3.4 Exploratory Endpoints updated to add Overall Survival as an exploratory objective • 1.2 Full Synopsis, Trial Design, 5.1 Study Overview, Figure 1 Study Schema updated reflect Overall Survival period • 2.2 Background on APX005M updated per the current version of the Investigator Brochure • 4.3.3 Inclusion Criteria was updated for creatinine clearance to make this assessment required and updated measured creatinine clearance requirement from ≥30 to ≥60 mL/min • 4.3.4 Exclusion Criteria was updated to add criteria for exclusion of subjects who concurrently participate in an interventional trial • 4.5 Duration of Follow-Up updated to reflect total follow up period from post-surgical follow up through overall survival • 4.6 Study Timeline updated to reflect current enrollment timeline • 6.2.1 Screening Endoscopic Ultrasound updated to note historical test results are to be obtained within 56 days of first administration of APX005M instead of Screening • 6.2.4 Follow-Up Visits updated to include overall survival • 6.2.5 End of Study Visit, 6.6 Subject Withdrawal/Study Discontinuation Criteria clarified to note that subjects withdrawing or being discontinued prior to the 6- month post-operative follow up visit should attend the EOS Visit • 5.2 Systemic Treatment, 6.2.2.3 Visit 2, and Table 7 Schedule of Assessments were updated to reduce the frequency of the 4-hour post APX005M infusion monitoring from Weeks 1, 2, 4, and 6 to after the first two infusions of APX005M. • 6.2.3Visit 3, and Table 7 Schedule of Assessments were updated to allow for visit to be conducted remotely if sample collection is not required. Vitals signs at Visit 3 are required if the visit is conducted in clinic.

SIGNATURE PAGE OF THE INVESTIGATOR

Title: A Phase 2 Study of APX005M in Combination with Concurrent Chemoradiation as Neoadjuvant Therapy for Resectable Esophageal and Gastroesophageal Junction Cancers

Protocol Number: APX005M-006

Version: 11

Date: 12 August 2021

IND Number: 122725

Sponsor: Apexigen, Inc.

I have read and agreed to the protocol of the above-mentioned clinical study. I agree to conduct this study in compliance with procedures detailed in this document and according to the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki and applicable local regulations. This study will not be initiated without prior Institutional Review Board (IRB) or Ethics Committee approval.

I agree to maintain adequate records in accordance with GCP and that source data will be attributable, legible, contemporaneous, original, accurate, and complete. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting the above commitments and I agree to provide adequate oversight of study personnel involved in this study.

_____
Signature

_____
Name, title and affiliation of Investigator

_____
Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
4DCT	4-dimensional computed tomography
ABC	Active breathing control
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Antigen presenting cell
AST	Aspartate aminotransferase
AUC	Area under the curve
AveIP	Average intensity pixel
bsPTV	Beam specific Planning Target Volume
CBC	Complete blood count
CBC diff	Complete blood count with differential
CR	Complete response
CRF	Case report form
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA	Cytotoxic T-lymphocyte-associated protein
CTV	Clinical Target Volume
DC	Dendritic cell
DLT	Dose limiting toxicity
eCRF	Electronic case report form
EDC	Electronic data capture
EKG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study
EUS	Endoscopic ultrasound
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GE	Gastroesophageal
GEJ	GE junction
GTV	Gross tumor volume
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

Abbreviation	Definition
IgG	Immunoglobulin G
IND	Investigational New Drug application
IMRT	Intensity modulated radiation therapy
IRB	Institutional Review Board
IRR	Infusion related reaction
ISR	IND safety report
IV	Intravenous
LAO	Left anterior-posterior oblique
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MFO	Multiple field optimization
OS	Overall survival
NCI	National Cancer Institute
PBS	Pencil beam scanning
PD-1	Programmed death 1 (PD-1)
PD-L1	Programmed death-ligand 1 (PD-L1)
PET	Positron emission tomography
pCR	Pathologic complete response
PSPT	Passively scattered proton therapy
PTV	Planning Target Volume
RAO	Right anterior-posterior oblique
RECIST	Response Evaluation Criteria in Solid Tumors
RO	Robust optimization
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAR	Suspected adverse reaction
SFO	Single field optimization
SOC	Standard-of-care; standard of care
SSAR	Serious suspected adverse reaction
ULN	Upper limit of normal
V	Visit
W	Week
WOCBP	Women of childbearing potential
XRT	External radiation therapy

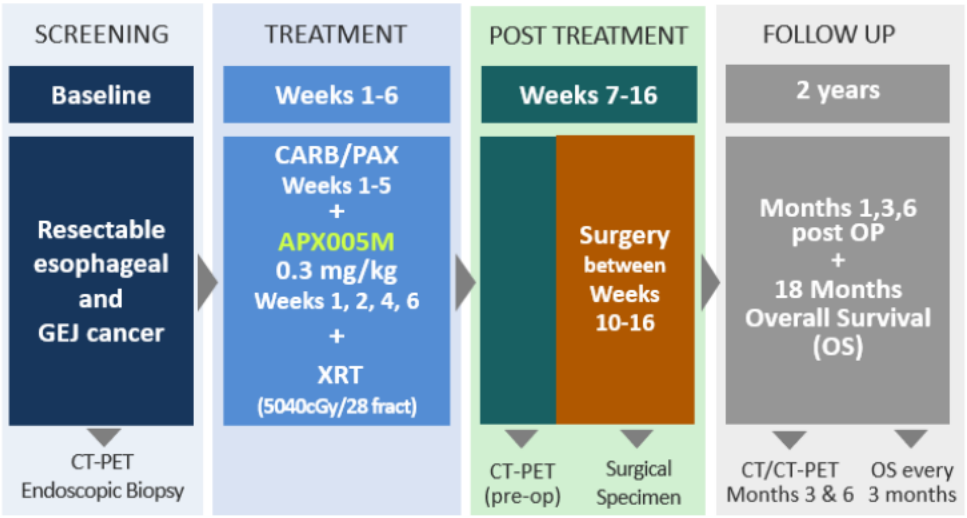
1. SYNOPSIS

1.1 Abbreviated Synopsis

Title	A Phase 2 Study of APX005M in Combination with Concurrent Chemoradiation as Neoadjuvant Therapy for Resectable Esophageal and Gastroesophageal Junction Cancers
Trial Phase	2
Clinical Indication	Patients with resectable (T1-3Nx, excluding T1N0) cancers of the esophagus and gastroesophageal (GE) junction, including both squamous cell and adenocarcinomas
Trial Type	Open-label, single arm, Phase 2 study
Type of Control	Historical control
Route of Administration	Intravenous (IV) APX005M
Trial Blinding	None
Treatment Groups	Single arm study
[redacted]	[redacted]
Estimated Enrollment Period	Approximately 3 years (13 months from the start of enrollment under protocol Version 9)
Treatment Period	6 weeks
Post–treatment Period (ending on the date of surgery)	4–10 weeks (between Study Weeks 7 and 16)
Post-operative Follow-up Period	6 months
Overall Survival Follow-up Period	18 months
Duration of Participation	Planned study duration from first dose to completion of the overall survival follow-up period is approximately 28 months
Estimated Duration of Trial	Approximately 41 months from the start of enrollment under protocol Version 9

1.2 Full Synopsis

Title	A Phase 2 Study of APX005M in Combination with Concurrent Chemoradiation as Neoadjuvant Therapy for Resectable Esophageal and Gastroesophageal Junction Cancers.
Patient Population	Patients with resectable (T1-3Nx, excluding T1N0) cancers of the esophagus and GE junction, including both squamous cell and adenocarcinomas.
Rationale for Study	Immunotherapeutic approaches have demonstrated clear evidence of therapeutic activity in a subset of patients with advanced gastroesophageal cancers. CD40 agonistic antibodies represent an attractive and novel form of immunotherapy that stimulate an immune response by activating antigen processing and presentation, recruiting immune effectors such as natural killer cells and macrophages, and additionally have direct cytotoxic effects on tumor cells. However, the activity of this class of agents in esophageal/GE junction cancers is unknown and will be evaluated in the context of this study by combining it with standard chemoradiation in the neoadjuvant setting, with serial collection of tissue and blood along the way for correlative purposes to monitor on-target treatment and pharmacodynamics effects.

	This study represents the first of its kind to evaluate the safety and preliminary efficacy of combining a CD40 agonist antibody with standard chemoradiation in patients with resectable disease.
Primary Objective	To assess the efficacy of this novel combination, as measured by the **pathologic complete response (pCR) rate**
Secondary Objectives	(1) To further characterize the **safety** and **feasibility** of combining APX005M with standard-of-care (SOC) chemoradiation (external beam radiation in daily fractions, with concurrent weekly low-dose carboplatin/paclitaxel) in the neoadjuvant setting for patients with resectable esophageal and GE junction cancers (2) To assess the efficacy as measured by **rates of R0 resection**; **pathologic stage at time of surgery**; and **radiographic/metabolic response** to neoadjuvant treatment on computed tomography-positron emission tomography (CT-PET)
Exploratory Objective	(1) To identify possible predictive molecular or immune-based efficacy biomarkers for this novel combination (2) To characterize and assess overall survival
Study Design	This is a non-comparative open-label multi-site Phase 2 study of APX005M in patients with resectable (T1-3Nx, excluding T1N0) cancers of the esophagus and GE junction, including both squamous cell and adenocarcinomas. [redacted] evaluable patients will be enrolled to this Phase 2 study., at an estimated rate of 2-3 patients every month. [redacted] patients with histologically proven squamous cell carcinoma will be enrolled in the study. The null hypothesis that the true pCR is 29% will be tested against a 1-sided alternative of 53% with a Type 1 error rate of 0.05 and power of 81%. Safety and toxicity will be assessed on a continuous basis throughout the course of study treatment. Adverse events will be described and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. Regular clinical assessments will be performed throughout the course of study treatment, including physical exams, CT-PET scan at the completion of chemoradiation, and assessment of pathologic response at the time of surgery. **Trial Diagram** below presents a schematic of the study design. 
[redacted]	[redacted]

Duration of Participation	Planned study duration, from first dose to completion of the overall survival follow-up period is approximately 28 months.
Treatment Period	6 weeks
Post Treatment Period (up to the date of surgery)	4-10 weeks (between Study Weeks 7 and 16)
Duration of Post-operative Follow up	6 months
Overall Survival Follow-up Period	18 months
Estimated Duration of Trial	The study will reach completion approximately 41 months from the start of enrollment under protocol Version 9
Study Drug/ Investigational Product	APX005M, a CD40 agonist antibody

2. BACKGROUND AND RATIONALE

2.1 Background on Esophageal Cancer

There are an estimated 17,000 incident cases of esophageal cancer in the United States annually, with a yearly mortality rate that almost approximates the incidence rate.[1] This number may in fact underestimate the true number of cases, depending on how GE junction adenocarcinomas (which can be categorized as either esophageal or gastric) are classified. Trends for histologic subtypes have been shifting, with the incidence of adenocarcinomas steadily climbing over the past several decades in Western countries, with a concomitant decline in squamous cell carcinomas (which still comprise the majority of cases globally).[1,2]

The most commonly accepted treatment approach for patients with localized or locoregional esophageal/GE junction cancers consists of **trimodality therapy**. The CROSS trial, a Dutch Phase 3 trial, established the combination of **preoperative low-dose weekly carboplatin, paclitaxel, and daily radiation** over a 5-week course as the current standard of care (SOC) in this disease setting.[3] In this trial, 92% of patients undergoing trimodality therapy underwent successful R0 resection, **pathologic complete response (pCR; ypT0N0) rate was 29%,** and median overall and disease-free survival rates were 49.4 months and (not yet reached), respectively.

2.2 Background on APX005M

CD40 and its role in tumor immunity. CD40 is a member of the tumor necrosis factor receptor superfamily and plays an important role in induction of tumor apoptosis and regulation of immune activation, especially in crosstalk between T cells and antigen presenting cells (APCs).[4] CD40 is expressed by dendritic cells (DCs), B cells, monocytes, and other non-lymphoid cells.[5] CD40 ligand (CD40L), also known as CD154, is the chief ligand described for CD40 and is expressed primarily by activated T lymphocytes and platelets. CD40-agonistic antibodies can substitute for the function of CD40/CD154 on activated T cells to boost immunity. Signaling through CD40 on APCs, including DCs, B cells, and monocytes, results in improved antigen processing and presentation, and cytokine release from activated APCs, which in turn enhance T-cell response.[6,7] Therefore, a CD40-agonistic antibody can activate and stimulate both innate and adaptive immunity.

CD40 is also expressed on many tumor cells and can mediate a direct cytotoxic effect. In addition to B-cell lymphoma, CD40 expression has been reported in 30−70% of primary human solid tumor samples, including melanoma and carcinomas.[8] Activation of CD40 on tumor cells results in tumor cell apoptosis and inhibition of tumor growth.[9] CD40-agonistic antibodies have demonstrated potent anti-tumor immune response in both animal models and cancer patients. Due to its action on both immune and tumor cells, CD40 is being studied as a target for novel cancer immunotherapy; agonistic anti-CD40 antibodies have been demonstrated to be potent stimulators of tumor immune responses in both animal models and cancer subjects.[10-13]

A human or humanized immunoglobulin G (IgG) 1 antibody that can utilize Fc receptors to cluster CD40 and enhance CD40-agonistic effects, like APX005M, might be preferable both in terms of potential decreased immunogenicity and increased anti-tumor activity for use in cancer immunotherapy.

Development of APX005M and preclinical data. To develop a potent CD40 agonist with antibody effector functions, Apexigen initially generated a humanized IgG1 anti-CD40 agonistic antibody named “APX005” using Apexigen’s proprietary rabbit monoclonal antibody (mAb) technology and mutational linkage guided humanization technology. This antibody binds to CD40 with high affinity and induces activation of antigen-presenting cells (APCs). In 2011, Li and Ravitch demonstrated that CD40 agonistic activities and its adjuvant effect on tumor vaccination could be enhanced by increasing the binding affinity of a CD40 agonistic antibody to FcγIIb receptors through a point mutation at position 267 from serine to aspartic acid (S267E).[14] To further enhance the agonistic activities of APX005, the same S267E mutation was introduced onto APX005 to create APX005M where “M” stands for mutation. APX005M is the drug candidate to be evaluated in human clinical trials.

APX005M is a humanized IgG1 mAb. In vitro, APX005M binds to both human and cynomolgus monkey CD40 with high affinity, triggering activation of APCs, including B cells, monocytes, and DCs and stimulating cytokine release from both human and monkey lymphocytes and monocytes. APX005M does not bind to rodent CD40. Through activation of APCs, APX005M is capable of stimulating antigen-specific T-cell responses to alloantigens, viral antigens, and tumor antigens.

In vivo, APX005M demonstrated potent anti-tumor activity in multiple human CD40-expressing lymphoma xenograft models. Treatment with APX005M resulted in dose-dependent inhibition of tumor growth, tumor regression, and significant prolongation of survival in lymphoma xenograft models. The in vivo APX005M anti-tumor activity is possibly mediated through the mechanisms of antibody-dependent cell-mediated phagocytosis and induction of apoptosis. Further details regarding the preclinical data of APX005M are provided in the Investigator's Brochure.

Clinical data to date with APX005M. Study APX005M-001 is a first in human Phase 1 dose escalation study of APX005M with 8 pre-planned dose levels. APX005M was administered to study subjects at doses up to [redacted]. At the [redacted] dose level, 1 out of 6 dose limiting toxicity (DLT)-evaluable subjects experienced a DLT [(Grade 4 cytokine release syndrome (CRS)]. Two additional subjects at the [redacted] dose level experienced serious adverse events (SAEs) in later cycles (Grade 3 CRS and Grade 4 thrombocytopenia). On 02 May 2016 Apexigen decided to discontinue dose escalation and enroll up to 6 subjects in dose level [redacted] (originally designed as an intermediate de-escalation dose level) and an additional 3 subjects at the previously completed dose level [redacted] to better characterize the safety and pharmacodynamics of APX005M and to help establish the single agent recommended Phase 2 dose (RP2D).

As of 03 April 2020, [redacted] subjects had received at least one dose of APX005M across 4 company sponsored trials (APX005M-001, APX005M-002, APX005M-006 and APX005M-010) (130 males [61%], age range 28–86 years):

- [redacted] (28.6%) received monotherapy
- [redacted] (65.3%) received systemic combination therapy with nivolumab
- [redacted] (83.1%) received APX005M at the RP2D [redacted]
- [redacted] (11.3%) at doses lower than the RP2D
- [redacted] (5.6%) at doses higher than the RP2D

Across the 4 CSTs, a total of 3643 TEAEs, including 140 SAEs, have been reported in the safety population of [redacted] subjects. Almost all subjects (95.3%) experienced at least one TEAE. About half of all TEAEs (47.1%) were considered by the investigator to be related to APX005M (regardless of the relationship to other study treatments where applicable, i.e., nivolumab in Study APX005M-002).

APX005M demonstrated a dose-dependent activation of APCs (as demonstrated by increases in expression of activation markers such as CD54, CD70, CD80, CD86, HLA-DR), T cell activation and increases in circulating levels of IL-12, IFN-γ, TNF-α and IL-6.

For further details on the completed APX005M-001 study and the other ongoing company sponsored studies please refer to latest version of the APX005M Investigator's Brochure.

2.3 Rationale for the Proposed Study

Immunotherapeutic approaches have demonstrated clear evidence of therapeutic activity in a subset of patients with advanced gastroesophageal cancers. The KEYNOTE-012 and -028 trials evaluated the immune checkpoint inhibitor pembrolizumab (10 mg/kg every 2 weeks) in advanced gastric and esophageal (squamous cell and adenocarcinomas), respectively, selected for programmed death-ligand 1 (PD-L1) positivity (approx. 40% of screened patients). Objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was similar in both of these studies, in the 22–23% range.[15,16]

To date, the activity of CD40 agonistic antibodies in esophageal/GE junction cancers is unknown.

Patients with esophageal/GE junction cancers who have their primary tumors intact are in some ways ideal candidates for correlative study purposes, as they can readily undergo repeated endoscopic biopsies for serial tumor tissue acquisition in order to monitor on-target treatment and pharmacodynamic effects.

2.4 Rationale for the Proposed Doses Used in This Study

The decision on appropriate starting dose of APX005M follows discussions with Apexigen and is based on the available safety data in the ongoing Phase 1 trial, as well as the desire to maintain a biologically active dose. It is recognized that the administration of study drug concurrently with chemoradiation has not been formally evaluated to this point and may theoretically lead to potentiation of toxicities, such as pneumonitis that can develop related to both thoracic radiation and immunotherapy.

One conservative approach that could be undertaken would be to conduct separate dose-finding studies to test each combination separately. However, CD40 agonist antibodies have already been shown to be safe when combined with full-dose chemotherapy[17], and a suitable clinical context in which to examine APX005M in combination with radiation to a primary tumor site (sans chemotherapy) is elusive. Also of note, clinical experience with other immune checkpoint inhibitors (anti-programmed death 1 [PD]-1/PD-L1 and anti-cytotoxic T-lymphocyte-associated protein [CTLA]4 mAbs) in combination with radiation in a variety of disease settings have suggested no major safety concerns, with immune-related AEs occurring at an observed rate

similar to that expected at baseline, and none that appeared specifically associated with the particular site irradiated.[18]

Therefore, we have instead elected to test this novel combination in the neoadjuvant setting, using full doses of chemotherapy (carboplatin/paclitaxel) plus radiation as informed by the CROSS trial. Given that this is being administered in a potentially curative disease setting, we are employing the following strategies to maximally address safety concerns:

- The starting dose of APX005M will be **0.3 mg/kg**, which is two dose levels below the maximum tolerated dose identified in the ongoing Phase 1 study ([redacted]), and 1 dose level below the RP2D ([redacted]). The AEs observed at the [redacted] dose level (7 patients enrolled; 5 evaluable) are shown in Table 1 below; with only 1 exception (Grade 3 hyperuricemia) these represent Grade 1/2 (mostly Grade 1) toxicities.

Table 1 AEs Observed with APX005M at Dose Level [redacted]

MedDRA System Organ Class	Number (%) of Patients per Maximum Reported CTCAE Grade					
- Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
BLOOD AND LYMPHATIC SYSTEM DISORDERS						
- Thrombocytopenia	1 (20.0)	-	-	-	-	1 (20.0)
- Leukocytosis	1 (20.0)	-	-	-	-	1 (20.0)
CODE PENDING						
- Code Pending	-	1 (20.0)	-	-	-	1 (20.0)
GASTROINTESTINAL DISORDERS						
- Vomiting	1 (20.0)	-	-	-	-	1 (20.0)
- Constipation	1 (20.0)	-	-	-	-	1 (20.0)
- Ascites	1 (20.0)	-	-	-	-	1 (20.0)
- Abdominal Distension	1 (20.0)	-	-	-	-	1 (20.0)
- Dry Mouth	1 (20.0)	-	-	-	-	1 (20.0)
- Rectal Haemorrhage	1 (20.0)	-	-	-	-	1 (20.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
- Fatigue	-	2 (40.0)	-	-	-	2 (40.0)
- Chills	-	1 (20.0)	-	-	-	1 (20.0)
- Asthenia	-	1 (20.0)	-	-	-	1 (20.0)
- Oedema Peripheral	1 (20.0)	-	-	-	-	1 (20.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
- Infusion Related Reaction	-	1 (20.0)	-	-	-	1 (20.0)
INVESTIGATIONS						
- Alanine Aminotransferase Increased	1 (20.0)	-	-	-	-	1 (20.0)
- Aspartate Aminotransferase Increased	1 (20.0)	-	-	-	-	1 (20.0)
- Body Temperature Increased	1 (20.0)	-	-	-	-	1 (20.0)

MedDRA System Organ Class	Number (%) of Patients per Maximum Reported CTCAE Grade					
- Preferred Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
- Platelet Count Decreased	1 (20.0)	-	-	-	-	1 (20.0)
- Transaminases Increased	-	1 (20.0)	-	-	-	1 (20.0)
METABOLISM AND NUTRITION DISORDERS						
- Decreased Appetite	1 (20.0)	-	-	-	-	1 (20.0)
- Hyperuricaemia	-	-	-	1 (20.0)	-	1 (20.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
- Neck Pain	1 (20.0)	-	-	-	-	1 (20.0)
NERVOUS SYSTEM DISORDERS						
- Seizure	-	-	1 (20.0)	-	-	1 (20.0)
PSYCHIATRIC DISORDERS						
- Insomnia	1 (20.0)	-	-	-	-	1 (20.0)
RENAL AND URINARY DISORDERS						
- Acute Kidney Injury	-	-	2 (40.0)	-	-	2 (40.0)
RESPIRATORY DISORDERS						
- Dyspnoea	1 (20.0)	-	-	-	-	1 (20.0)
- Hiccups	1 (20.0)	-	-	-	-	1 (20.0)
SKIN/SUBCUTANEOUS DISORDERS						
- Pruritus	1 (20.0)	-	-	-	-	1 (20.0)
- Rash	1 (20.0)	-	-	-	-	1 (20.0)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities.

- All patients will also start with a single dose of APX005M by itself, to ensure no significant toxicities from administration of study drug alone (i.e. CRS) prior to initiating concurrent chemoradiation.
- Stringent early stopping rules/interim safety analyses will be performed after the first 6 patients have been enrolled, to ensure that patient safety is being maintained and that subjects are able to proceed to their curative resection in timely fashion.
- Version 6 (7/24/2018): Review of the first 3 patients treated on this protocol, all of whom proceed to surgical resection in timely fashion, was notable for intraoperative findings of a significant inflammatory response and "lymphatic weeping" per description of the operating surgeon. Of note, 1 of these patients developed a postoperative chylous leak and eventually died from progressive respiratory failure; however, as this represents a known complication associated with esophagectomy (occurring in 3–4% of individuals), this was deemed unlikely related to study treatment. However, based on these findings, in order to mitigate the potential greater operative challenges associated with such an inflammatory response, the protocol is being amended to eliminate the 4th and final dose

of APX005M that had originally been administered 2 weeks following completion of chemoradiation.

- Version 10 (12/30/2020) integrates the first dose of APX005M in the chemoradiation treatment period so all doses of APX005M are given concurrently with chemoradiation. This significantly reduces the time between screening and start of chemoradiation, which is especially beneficial for patients who suffer from dysphagia and pain. One additional dose of APX005M has been added early during the treatment phase so that patients now receive APX005M [redacted] at Weeks 1, 2, 4, and 6, which should optimize the therapeutic effect of the combination regimen. The increase in the frequency of APX005M administration should not result in significantly increased toxicity. Two-week and 1-week administration schedules have been evaluated in the FIH Study APX005M-001 and no significant increase in toxicity or cumulative toxicity have been observed, while the 1-week schedule provided a more sustained T cell activation comparative to every 3-week schedule. The recommended time period between the last dose of APX005M and the surgery is the same as in the last protocol version so any theoretical concern of a potential greater operative challenge associated with an APX005M-dependent inflammatory response remains mitigated. A safety analysis of this APX005M administration schedule will be performed after the first 6 patients treated under protocol Version 10 complete the neoadjuvant treatment period.
- For further details on the overall safety of APX005M please refer to latest version of the APX005M Investigator's Brochure.

3. OBJECTIVES OF THE STUDY

3.1 Primary Objective

To assess the efficacy of this novel combination, as measured by the **pathologic complete response (pCR) rate**

3.2 Secondary Objectives

(1) To further characterize the **safety** and **feasibility** of combining APX005M with SOC chemoradiation (external beam radiation in daily fractions, with concurrent weekly low-dose carboplatin/paclitaxel) in the neoadjuvant setting for patients with resectable esophageal and GE junction cancers.

(2) To assess the efficacy of combining APX005M with SOC chemoradiation as measured by **rates of R0 resection**; **pathologic stage at time of surgery**; and **radiographic/metabolic response** to neoadjuvant treatment on CT-PET.

3.3 Exploratory Objectives

(1) To identify possible predictive molecular or immune-based efficacy biomarkers for this novel combination

(2) To characterize and assess overall survival

4. STUDY DESIGN

4.1 Characteristics

This is a non-randomized, single-arm, open-label study.

4.2 Number of Subjects

[redacted] evaluable patients will be enrolled across multiple (approx. 8–12) clinical sites within the US. A patient is considered evaluable for the purpose of the primary analysis if she/he meets study eligibility criteria and have undergone surgical resection.

4.3 Entry Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.3.1 Diagnosis/Condition for Entry into the Trial

Patients with resectable (T1-3Nx, excluding T1N0) cancers of the esophagus and GE junction, including both squamous cell and adenocarcinomas.

4.3.2 Administrative Procedures

4.3.2.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form (ICF), any subsequent revised written ICF, and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

4.3.3 Inclusion Criteria

1. Age ≥18 years of age
2. Histologically proven squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma of the esophagus or GE junction. No more than 50% patient with squamous cell carcinoma should be included in the study
3. Surgically resectable (T1-3 Nx preferably by endoscopic ultrasound [EUS]). Excluded are:
    a. Very early stage tumors (T1N0)
    b. Cervical esophageal tumors
    c. Tumors invading the tracheobronchial tree or associated with tracheoesophageal fistula
    d. Any evidence of distant metastases (as determined by EUS or CT/PET)
    e. Cervical, supraclavicular, or other nodal disease that is either not included in the radiation field or is not able to be resected at the time of esophagectomy
4. Eastern Cooperative Oncology Group (ECOG) performance status 0–1
5. Adequate hematological, renal, and hepatic parameters defined as follows:

a. Absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L in absence of growth factor support
b. Platelet count $\geq 150\times10^9$/L
c. Hemoglobin >9 g/dL
d. Serum creatinine ≤1.5 mg/dL, and calculated (using the formula of Cockcroft and Gault) or measured creatinine clearance ≥60 mL/min
e. Aspartate aminotransferase and alanine aminotransferase (ALT) ≤2.5× the upper limit of normal (ULN)
f. Total bilirubin ≤1.5× ULN

6. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within the 7 days prior to investigational product administration and a negative urine pregnancy test within the 3 days prior to the first investigational product administration, or a negative serum pregnancy test within the 3 days prior to the first investigational product administration
7. WOCBP and male subjects who are sexually active with WOCBP must agree to use 2 highly effective methods of contraception (including a physical barrier) during the study and for 30 days following the last dose of investigational product
8. Ability to understand a written informed consent document, and the willingness to sign it

4.3.4 Exclusion Criteria

1. Any history of or current hematologic malignancy
2. History of a second primary cancer is allowed in the event the cancer is curatively resected and there is no evidence of recurrence/metastatic disease x 1 year. Subjects who have a history of cervical or breast carcinoma in situ, localized prostate cancer, adequately treated basal cell or squamous cell carcinoma of the skin, or superficial bladder tumors [Ta, Tis & T1] are also allowed
3. Major surgery within 4 weeks of first dose of investigational product
4. Prior or concurrent treatment with any anticancer agent for the same cancer diagnosis
5. Prior exposure to any immuno-oncology agents, including CD40/PD-1/PD-L1/CTLA-4 inhibitors (if any ambiguity, should be discussed with the Apexigen Medical Monitor or designee)
6. History of bone marrow transplantation
7. History of organ transplant and/or concurrent immunosuppressive medication. Subjects with a history of organ transplant and/or concurrent immunosuppressive medication must be discussed with the Medical Monitor or designee prior to consent
8. Uncontrolled diabetes or hypertension
9. History of autoimmune disorders with the exception of vitiligo or autoimmune thyroid disorders

10. Chronic steroid dependency (prednisone equivalent >10 mg/day). Any steroid use should be discontinued at least 2 weeks prior to initiation of study treatment.
11. History of sensitivity or allergy to mAbs or IgG
12. History of severe hypersensitivity reaction to Cremaphor EL.
13. Pre-existing > Grade 2 peripheral sensory neuropathy.
14. Congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, or myocardial infarction within 6 months before first dose
15. History of any arterial thromboembolic event within 3 months prior to first dose of investigational product
16. Active coagulopathy
17. Active known clinically serious infections (> Grade 2 National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 4.03)
18. Known HIV infection
19. Subjects of reproductive potential who do not use effective methods of birth control
20. Pregnant or actively breastfeeding women
21. Any clinically significant psychiatric, social, or medical condition that, in the opinion of the Investigator, could increase subject's risk, interfere with protocol adherence, or affect a subject's ability to give informed consent.
22. Concurrent participation in any interventional trial

4.4 Duration of Treatment

Treatment will continue until:

- The patient has completed all protocol-specified aspects of study therapy.
- Disease progression.
- Inter-current illness prevents further administration of treatment.
- Unacceptable AE(s)
- Patient decides to withdraw from the study.
- Significant patient non-compliance with protocol.
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the Investigator.

4.5 Duration of Follow-Up

Patients will be followed up to 24 months after completion of all components of study treatment.

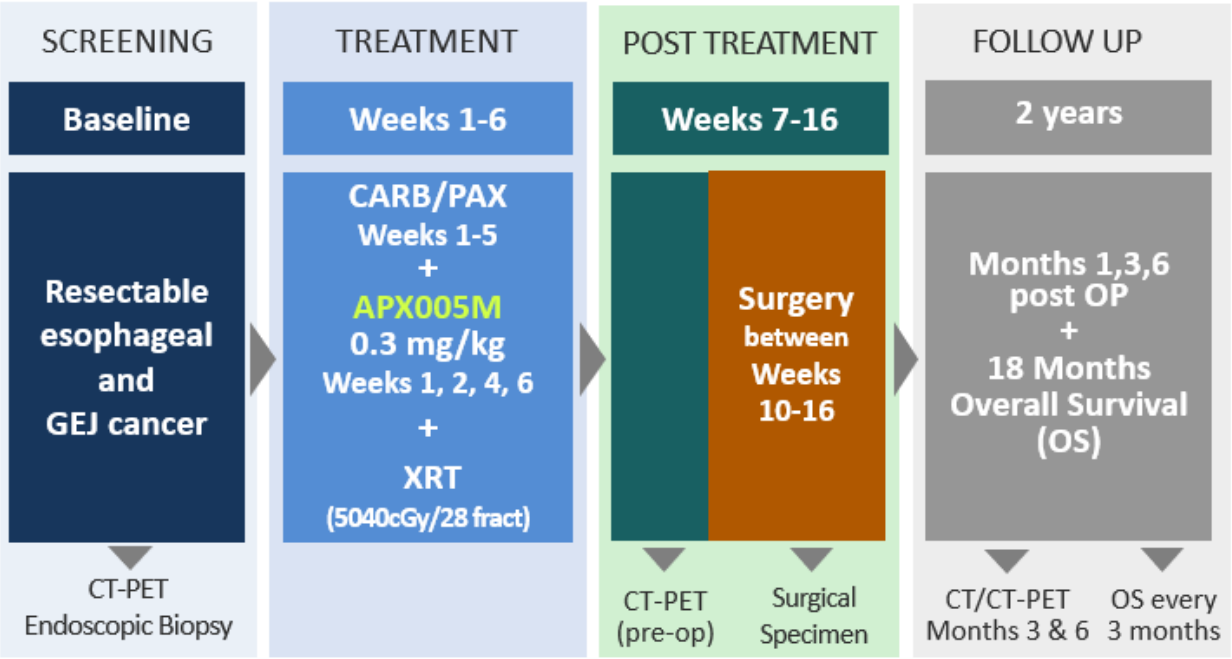
4.6 Study Timeline

This study is anticipated to accrue patients over a 3-year period (13 months from the start of enrollment under protocol Version 9.

5. TREATMENT PLAN

5.1 Study Overview

Figure 1 Study Schema



Abbreviations: CT-PET = computed tomography-positron emission tomography; GEJ = gastroesophageal junction; XRT = external radiation therapy.

5.2 Systemic Treatment

Treatment will be administered on an outpatient basis.

Weekly low-dose carboplatin/paclitaxel will be administered as per SOC (Table 2) on the first visit (V1) of Study Weeks 1–5 (see Section 5.3).

Pre-medication for carboplatin and paclitaxel will be administered according to institutional standards, typically consisting of anti-emetics, dexamethasone, and an H2 blocker.

Table 2 Regimen Description: Systemically Administered Agents

Drug	Dose	Route	Schedule
Paclitaxel	50 mg/m^2	IV over 1 hour	On the first visit (V1) of Study Weeks 1–5
Carboplatin	AUC = 2	IV over 1 hour	On the first visit (V1) of Study Weeks 1–5
APX005M	0.3 mg/kg	IV over 1 hour	On the second visit (V2) of Weeks 1, 2, 4 and 6 (2–3 days after chemotherapy)

Abbreviations: AUC = area under the curve; IV = intravenous.

During concurrent treatment (Study Weeks 1, 2, 4 and 6), APX005M will be administered on second visit (V2) offset by 2–3 days, from carboplatin/paclitaxel (Table 2). For example, patients traditionally receive their chemotherapy on a Monday, in which case APX005M would be administered on a Wednesday or Thursday of that same week.

APX005M is diluted in sterile 0.9% sodium chloride solution and will be administered via an intravenous (IV) infusion set-up over 60 minutes. A window between –5 minutes and +10 minutes is permitted (i.e., infusion time is 55 minutes to 70 minutes). The infusion can be interrupted in the case of infusion-related reaction (IRR)/CRS. Once patient symptoms resolve infusion should be restarted at half the initial infusion rate.

An appropriate pre-medication regimen, to be administered approximately 30 ± 5 minutes before any administration of APX005M, [redacted]

Administration of any intravenous formulations of these medications should be completed 10 ± 5 minutes before administration of APX005M.

After completion of the first 2 infusions of APX005M, patients will be monitored for 4 hours in the infusion center and will be asked to return for an outpatient follow-up the next day.

5.2.1 Study Drug - Description, Supply and Storage of Investigational Product

5.2.1.1 APX005M

APX005M is a humanized mAb of the immunoglobulin G1 (IgG1) CD40 agonist and activates APCs (e.g., DCs, monocytes, and B cells) that stimulates cancer-specific T-cell responses.

Packaging and Labeling

APX005M investigational product is supplied in 20 mL Type 1 clear glass vials for IV injection. Each depyrogenated vial contains [redacted] APX005M in a sterile, clear to slightly opalescent, colorless to slightly yellow, preservative-free solution (pH 5.5) [redacted] for injection with a target fill volume of 16.9 mL per vial. Glass vials are plugged with Teflon®-coated rubber stoppers and sealed with aluminum seals. The 20 mL vials (16.9 mL/vial) are intended for single use.

Additional APX005M details including labeling, storage, and preparation information are provided in the Pharmacy Manual. It should be noted that the Pharmacy Manual may be updated/revised as additional information becomes available.

APX005M will be labeled and packaged according to Good Manufacturing Practice and product manufacturing specifications, adhering to applicable local and federal laws.

Storage and Dispensing

The APX005M investigational product should be stored in a secure location with limited access under controlled temperature conditions of 2–8°C and in accordance with local regulations. Vials should be stored in their original folding carton to protect from light. If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product and contact the sponsor immediately.

The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. It is the responsibility of the Investigator to ensure that the investigational product is only dispensed to study subjects. APX005M must be administered to study subjects by qualified personnel.

Safety Precautions

When handling investigational product, wear laboratory coats and disposable protective gloves. Avoid contact with eyes, skin, and clothing. Protect it from light and contamination.

Drug Accountability

It is the responsibility of the Investigator to ensure that a current record of APX005M disposition is maintained at each study site where APX005M is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines and should include:

- Quantity of APX005M received and placed in storage area
- Quantity of APX005M currently in storage area
- APX005M label information

- Dates and initials of person responsible for each APX005M inventory entry/movement
- Quantity of APX005M dispensed to each subject, including unique subject identifiers
- Non-study disposition of APX005M (e.g., lost, wasted, and/or broken)
- Quantity of APX005M returned to Apexigen or designee for destruction
- Quantity of APX005M destroyed at study site, if applicable

Apexigen or designee will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

Upon completion or termination of the study, all unused and/or partially used APX005M must be returned to Apexigen or designee if not authorized by Apexigen or designee to be destroyed at the site. All APX005M returned to Apexigen or designee must be accompanied by the appropriate documentation and clearly identified by protocol number and study site number on the outermost shipping container. Returned supplies should be in the original containers (e.g., kits that have clinical labels attached). Empty containers should not be returned. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures and appropriate records of disposal are kept.

If APX005M vials are to be destroyed onsite, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Apexigen or designee, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused APX005M can only be destroyed after being inspected and reconciled by the responsible Apexigen or designee Study Monitor. Complete and updated AE information is available in the Investigator's Brochure.

Each participating site/institution is responsible for site management of drug accountability records.

Drug Ordering

Each participating site will obtain APX005M directly from Apexigen as study supply. The details for initial and resupply will be described in the pharmacy manual.

5.3 Radiotherapy

Summary: Total dose of radiation will be 5040 cGy in 180 cGy fractions (Table 3).

Table 3 Regimen Description: Radiation

Radiation Therapy	Dose	Schedule
	5040 cGy in 28 fractions of 180 cGy	28 daily fractions administered Weeks 1–6

Technical Factors: Linear accelerators with a minimum energy of 6-15 MV will be used. A multiple field 3-D conformal technique or intensity modulated radiation therapy (IMRT) will be used. All fields will be treated each day. The patient will be treated in the supine position. Radiation will be delivered up to 5 days/week, once per day.

CT-based conformal planning is required on this study. In accordance with current guidelines for use of IMRT in clinical trials (see http://qarc.org/), IMRT may be used only if the degree of tumor motion is assessed and can be limited to 1.0 cm or techniques are used to compensate for respiratory motion.

Protocol Treatment Volumes: A volumetric treatment planning CT study will be required for this study. Each patient will be positioned in an individualized immobilization device in the treatment position on a flat table. Contiguous CT slices, with 3-5 mm thickness, will be obtained starting from the level of the cricoid cartilage and extending inferiorly through the liver. A measurement scale for the CT image shall be included.

Gross Tumor Volume (GTV): The GTV is based on the pre-chemotherapy extent of disease using the initial PET/CT scan, endoscopy report, and CT scan. The entire esophageal wall, including any disease that has extended through the wall should be contoured as the GTV as well as any PET/CT-avid or enlarged lymph nodes.

Clinical Target Volume (CTV): The intent of pre-operative treatment is to include the tumor plus the nodal groups at risk (whether clinically positive or negative). The CTV should encompass the peri-esophageal lymph nodes, mediastinal lymph nodes for mid- and upper- thoracic esophageal tumors, and the submucosal spread longitudinally along the esophagus. This is generally a 3–4 cm expansion on the GTV superiorly and inferiorly and 1.0 cm expansion radially. For distal esophageal tumors and GE junction tumors, the CTV should include the celiac lymph nodes. For tumors above the carina, the supraclavicular lymph nodes should be included in the CTV.

Planning Target Volume (PTV): The PTV is established by expanding the CTV by 0.5 cm in all directions. This will result in a margin of up to 5 cm superior and inferior and approximately 1.0–2 cm radially to the extent of tumor (GTV). For distal esophageal and GE junction tumors where motion management is not being used, the superior-inferior expansion can be 0.7–1.0 cm to account for the respiratory motion.

Target Dose Constraints:

Dose Prescription: The prescribed dose to the PTV is 5040 cGy delivered in 180 cGy/day over 28 fractions, to be administered during Weeks 1–6, ideally, 5 fractions from Monday to Friday during Weeks 1–5 and Monday to Wednesday during Week 6.

Dose Uniformity: The dose to 99% of the PTV must be at least 93% of the prescribed dose, and a contiguous volume of no more than 2cc inside the PTV may exceed 20% of the prescribed dose.

Tissue Heterogeneity: Calculation shall take into account the effects of tissue heterogeneities. Planning must be performed using an approved dose calculation algorithm. Approved algorithms include: convolution superposition, collapsed cone convolution, and Monte Carlo.

Normal tissue Dose Constraints: The normal structures to be contoured will depend on the level of the esophagus involved, but can include left and right lungs, heart, esophagus, brachial plexus, left and right kidneys, liver, stomach, small intestine, and spinal canal. The dose to normal tissues must be kept within the parameters described below.

1. Lungs
    a. V20Gy ≤20%
    b. and V30Gy ≤15%
    c. and V40Gy ≤10%
    d. V10Gy ≤40%
    e. V5Gy <60%
2. Cord
    a. Max ≤4500 cGy
3. Bowel
    a. Max bowel dose < Max PTV dose
    b. and D05 ≤45 Gy
4. Heart
    a. V40Gy ≤50%
    b. Mean <3000 cGy
5. L and R kidney:
    a. No more than 33% of the volume can receive 1800 cGy
6. Liver
    a. V20Gy ≤30 %
    b. V30Gy ≤20
    c. mean <21 Gy

7. Stomach
    a. Mean <3000 cGy (if not within PTV)
    b. Max dose <54 Gy

Treatment Planning:

Simulation: Patients will be positioned supine with arms above the head. A CT simulation will be performed using 3–5 mm slice thickness. In patients for whom treatment will be delivered using respiratory gating or tracking, the planning CT scan should be performed with the patient in a breath-hold in end expiration.

Motion Management: For distal esophageal and GE junction tumors, respiratory motion can be significant, requiring an assessment of the degree of tumor motion at the time of simulation. To determine the extent of respiratory motion, a respiratory correlated CT scan may be obtained at the time of simulation. This scan will be performed throughout the breathing cycle (i.e., 4-dimensional CT) so that separate CT data sets associated with each phase of respiration can later be reconstructed. Treatment delivery can be done using the motion management technique available at the institution and can include treatment during free-breathing as long as an internal target volume has been designed based on the motion of the tumor on the 4D-CT.

Beam Arrangements:

1. 3D Conformal Beam Arrangements: Beam arrangement selection for 3D conformal treatment will vary based on the shape, size, and location of the CTV and the resulting PTV in relation to normal organs.
2. IMRT - Beam Arrangement: A five-field beam arrangement is preferred to minimize the low dose distributed to the lungs. Suggested beam arrangements are:
    a. For distal esophagus the following beam arrangement is useful for minimizing dose to the heart and lungs: left posterior-anterior oblique (155), left anterior-posterior oblique (LAO; 70–80), anteroposterior (0), right anterior-posterior oblique (RAO; 280–290), right posterior-anterior oblique (205)

        Note that the range of gantry angles for the LAO and RAO fields is due to the fact that one needs to find the best compromise between the amount of heart and lung in the field.

    b. For GE-junction esophagus, the following beam arrangement may be substituted if it is better for minimizing dose to the kidney. All beams are 15 MVx: posteroanterior (180º), close to left lateral (90º±10º), LAO (30–35º), RAO (325–330º), close to right lateral (270º±10º). All beams are 15 MV X-ray beams.

        These recommended beam arrangements may be changed to one more fitting for the patient's particular anatomy.

Field Verification: As a minimum requirement, verification images are obtained at the start of treatment and at least each week thereafter. Patients treated with IMRT should have daily planning. Prior to the first treatment, images that verify the position of the isocenter placement must be obtained. Imaging can consist of portal or orthogonal images, or cone beam CT.

Definitions of Deviations in Protocol Performance

Prescription Dose

- No Deviation: ≥99% of the PTV receives ≥93% of the prescribed dose, and a contiguous volume of no more than 2cc inside PTV exceeds 20% of the prescribed dose.
- Minor Deviation: Deviations of this magnitude are not desirable, but are acceptable. Coverage that is equal to 93% of the prescribed dose and falls between 99% and 95% of the PTV, or a contiguous volume of no more than 2cc inside the PTV exceeds 20–25% of the prescribed dose.
- Major Deviation: Doses in this region are not acceptable. More than 1 cm^3 of tissue outside the PTV receives ≥120% of the prescribed dose, or 93% of the prescribed dose falls below 95% of the PTV, or a contiguous volume of no more than 2cc inside the PTV exceeds 25% of the prescribed dose.

Volume

- Minor Deviation: Margins less than specified, or field(s) 1–3 cm greater than specified.
- Major Deviation: Fields transect tumor or specified target volume(s), or fields are more than 3 cm greater than specified.

Critical Organ

- Major Deviation: The maximum dose to the spinal cord exceeds 4500 cGy; the heart mean dose exceeds 3000 cGy; the lung V20 exceeds 30% or the V10 exceeds 50%
- Minor Deviation: The lung V20 exceeds 20% or the V10 exceeds 40%

Treatment Interruption

- Minor Deviation: Treatment interruptions between five and nine normally scheduled treatment days.
- Major Deviations: Treatment interruptions totaling more than nine normal scheduled treatment days.

For centers that prefer to use proton beam therapy prescription dose, target and organ at risk volumes, field verification, and other radiation procedures for proton beam therapy will be similar to IMRT, unless defined otherwise.

Proton Simulation and Motion Management

A motion management technique-specific treatment planning CT (e.g., 4DCT, breath-hold, gating, Active Breathing Control (ABC) etc.) will be required for every patient.

Proton Planning Procedures

Free-breathing CT that is generated from a 4DCT, such as an average intensity pixel CT (AveIP), mid-ventilation CT, the breath-hold/gated CT, or the free-breathing CT acquired with no other motion management will be the primary dataset for dose calculation. Passively scattered proton therapy (PSPT) or pencil beam scanning (PBS) proton beams will be used for patients enrolled in the proton arm, but PBS is recommended when available.

For proton planning, each beam has an individual and unique beam specific PTV (bsPTV) expansion from the CTV. In the plane perpendicular to the beam axis, the bsPTV expansion from the CTV is according to the method used for photons. The CTV expansion along the distal and proximal margins of the beam axis will be based on established algorithms to account for range uncertainty of the beam. The PTV is only used for evaluation purposes.

For PSPT planning, two or three beam approaches have been most commonly used, using posterior-anterior, left lateral oblique +/- left posterior-lateral oblique beams. For PBS planning, two or three beam approaches have also been most commonly utilized, using a pair of right and left posterior-oblique beams +/- posterior-anterior beam.

For PSPT planning the compensator will be smeared based on accepted algorithms.

For PBS, single field optimization (SFO) and multi field optimization (MFO) are permitted. Robust optimization (RO) is recommended. Robust evaluation for setup and range uncertainties should be performed and the dose on the worst case scenario should meet planning criteria for GTV and CTV. The plan should be recalculated and evaluated on both inhale and exhale phases if a 4DCT is used and dose to GTV and CTV on both phases should meet planning criteria.

5.4 Surgical Considerations

All patients will be evaluated by a surgeon at the pre-registration visit and at the end of their neoadjuvant therapy. It is recommended that patients have surgery no earlier than 4 weeks and no greater than 10 weeks after last dose of APX005M (Study Weeks 10 to 16). Determination of resectability after completion of neoadjuvant therapy will be at the discretion of the treating team.

Any of the following surgical approaches are deemed acceptable, as long the approach includes the surgical removal of any lymph nodes felt to be suspicious:

- Ivor Lewis esophagogastrectomy
- Thoracoabdominal esophagectomy
- 3-hole esophagectomy (McKeown procedure)
- Transhiatal esophagectomy
- Minimally invasive esophagectomy

A gross surgical margin of at least 5 cm both proximally and distally are recommended. A frozen section of both the proximal and distal surgical margin should be obtained to confirm a negative microscopic surgical margin. Surgeons are encouraged to dissect the entirety of each lymph node station as opposed to sampling individual lymph nodes. Cumulative pathologic evaluation of at least 15 lymph nodes, with a preferred target of 18 lymph nodes, is recommended to allow for complete staging and accurate prediction of prognosis.

5.5 Dose Modifications and Dosing Delays

Management of suspected AEs may require temporary interruption and/or dose reduction of 1 or more components of study treatment, as shown in Table 4. Toxicity will be described and graded according to the NCI-CTCAE Version 4.03. If a patient experiences several toxicities, the recommended dose adjustment should be based on the highest grade toxicity. Up to 2 dose reductions of each agent are permissible; beyond this, the subject will be discontinued from treatment.

Table 4 Dose Levels

	Starting Dose	Dose Level –1	Dose Level –2
APX005M	0.3 mg/kg	[redacted]	
Carboplatin	AUC 2	AUC 1.5	AUC 1
Paclitaxel	50 mg/m^2	40 mg/m^2	30 mg/m^2

Abbreviations: AUC = area under the curve.

5.5.1 Hematologic Toxicity

During concurrent chemoradiation, given the known potential for cytopenia associated with carboplatin and paclitaxel, these chemotherapy agents will be first to be modified with any episode of clinically relevant hematologic toxicity (Table 5).

Table 5 Dose Modifications Due to Hematologic Toxicity

Hematologic Toxicity	Chemotherapy (carboplatin/paclitaxel)	APX005M
≥ Grade 3 ANC	Interrupt chemotherapy* until ANC improves to ≤ Grade 2, then resume treatment at 1 dose level lower of carboplatin and paclitaxel	Maintain dose level For neutropenic fever (body temperature >38.3ºC (oral) and ANC <1000/mm^3) consider reducing the APX005M dose following discussion with the Apexigen Medical Monitor or designee.
≥ Grade 3 platelets	Interrupt chemotherapy* until platelets improve to ≤ Grade 2, then resume treatment at 1 dose level lower of carboplatin and paclitaxel	Maintain dose level. Reduce by 1 dose level for platelets Grade ≥3 with bleeding or requiring blood transfusion

Abbreviations: ANC = absolute neutrophil count.

* Investigator will defer to the radiation oncologist as to whether an interruption of the radiation therapy is also indicated.

Any scheduled dose of **APX005M** should also be held while chemoradiation is being held.

5.5.2 Non-Hematologic Toxicity

During concurrent chemoradiation, non-hematologic toxicities may prompt dose reductions of either or both chemotherapy agents (carboplatin and paclitaxel) and/or APX005M, depending on the treating physician's adjudication of which agents are most likely to be contributing to the specific toxicity(ies). As a general rule, for known common side effects associated with carboplatin and paclitaxel such as nausea, fatigue, and/or peripheral sensory neuropathy, these agents may be reduced first while the dose of APX005M remains unchanged. However, in specific instances, it may be appropriate to simultaneously consider a dose reduction of APX005M, including Grade 3 nausea, vomiting, or diarrhea lasting >72 hours despite optimal medical management.

Table 6 Dose Modifications Due to Non-Hematologic Toxicities

Toxicity	Severity	Carboplatin/paclitaxel	APX005M
Neurologic toxicity (peripheral neuropathy)	**Grade 2**	Reduce paclitaxel by 1 dose level for all subsequent doses. No change in carboplatin dosing.	Maintain dose level.
	Grade 3	Permanently discontinue paclitaxel. No change in carboplatin dosing.	Maintain dose level.
	Grade 4	Discontinue study treatment.	Discontinue study treatment.

Toxicity	Severity	Carboplatin/paclitaxel	APX005M
Hepatic dysfunction	Total bilirubin 1.5–3 × ULN AND AST/ALT ≤2.5 × ULN	Decrease paclitaxel by 1 dose level for all subsequent doses. No change in carboplatin dosing.	Maintain dose level.
	Total bilirubin ≤1.5 × ULN AND AST/ALT 2.5–10 × ULN	Decrease paclitaxel by 1 dose level for all subsequent doses. No change in carboplatin dosing.	Maintain dose level.
	Total bilirubin 1.5–3 × ULN, AND AST/ALT 2.5–10 × ULN	Decrease paclitaxel by 2 dose levels for all subsequent doses. No change in carboplatin dosing.	Maintain dose level.
	Total bilirubin >3 × ULN OR AST/ALT >10 × ULN	Permanently discontinue paclitaxel. No change in carboplatin dosing.	Decrease by 1 dose level for all subsequent doses
IRR to paclitaxel	**Grade 1-2**	Stop infusion. Administer H1 and/or H2 blockers, and/or steroids according to institutional policy. Restart the infusion when symptoms resolve and pretreat before all subsequent doses.	Maintain dose level. Delay APX005M to the following week if steroids were used to treat the infusion reaction.
	Grade 3-4	Stop infusion and permanently discontinue paclitaxel; may continue with carboplatin for remaining doses.	Maintain dose level. Delay APX005M to the following week if steroids were used to treat the infusion reaction.
IRR/CRS to APX005M	**Grade 1-2**	Maintain dose level.	Stop infusion Symptomatic treatment. Maintain dose level.
	Grade 3	Maintain dose level.	Decrease by 1 dose level for all subsequent doses.
	Grade 4	Maintain dose level.	Permanently discontinue.
Nausea/vomiting	**Grade 3** (≥6 episodes of vomiting in 24 hours) for 3 days or more, despite optimal medical management	Interrupt chemotherapy* until improves to ≤ Grade 2, then resume treatment. 1st incidence: Maintain dose level 2nd incidence +: Reduce by 1 dose level	Treat at same time as chemoradiation is resumed. 1st and 2nd incidence: Maintain dose level ≥3rd incidence: Reduce by 1 dose level
	Grade 4	Discontinue study treatment.	Discontinue study treatment.

Toxicity	Severity	Carboplatin/paclitaxel	APX005M
Diarrhea	**Grade 3** (≥7 stools per 24 hours over baseline) for 3 days or more, despite optimal medical management	Interrupt chemotherapy* until improves to ≤ Grade 2, then resume treatment. 1st incidence: Maintain dose level 2nd incidence +: Reduce by 1 dose level	Treat at same time as chemoradiation is resumed. 1st and 2nd incidence: Maintain dose level ≥3rd incidence: Reduce by 1 dose level
	Grade 4	Discontinue study treatment.	Discontinue study treatment.
Other	**Grade 3**	Interrupt chemotherapy* until improves to ≤ grade 2, then resume treatment at 1 reduced dose level.	Treat at same time as chemoradiation is resumed; consider reducing the APX005M dose following discussion with the Apexigen Medical Monitor or designee
	Grade 4	Discontinue study treatment.	Discontinue study treatment (unless discussed and approved by the Apexigen Medical Monitor or designee)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

* Investigator will defer to the radiation oncologist as to whether an interruption of the radiation therapy is also indicated.

6. STUDY PROCEDURES AND OBSERVATIONS

6.1 Participant Registration

A written, signed ICF and a Health Insurance Portability and Accountability Act authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

6.2 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section. Any safety laboratory results falling outside of the reference ranges may be repeated at the discretion of the Investigator. Please refer to the Table 7 for a summary of all study procedure and assessments.

6.2.1 Screening

The Screening procedures and assessments must be completed within 28 days of Day 1 of the treatment period unless otherwise stated:

- Physical examination
- Vital signs
- Complete medical history and demographics
- ECOG performance status
- Baseline medications/concomitant medication (conmeds)
- Baseline AE assessment
- CT-PET scan (historical test results for CT-PET may be acceptable if within 28 days prior to first administration of APX005M)
- Endoscopic ultrasound confirming appropriate T and N staging for study eligibility is recommended (historical test results for endoscopic ultrasound obtained within 56 days prior to first administration of APX005M may be acceptable)
- Laboratory evaluation per local laboratory assessment including:
    - Complete blood count (CBC) with differential (CBC diff)
    - Chemistry panel
    - Coagulation assessments (PT/INR, PTT)
- Serum and urine pregnancy test for WOCBP
- Urinalysis
- Electrocardiogram
- Upper endoscopy with biopsy for immune correlates completed within 14 days prior to Day 1 of study treatment (archival tissue samples from initial diagnosis may be acceptable if the patient is unable to complete an endoscopy)

6.2.2 Treatment Period (Week 1-6)

Every effort should be made to adhere to this schedule, acknowledging there may be delays or treatment interruptions due to AEs that produce some deviations in schedule.

6.2.2.1 Radiotherapy

Twenty-eight daily fractions of radiotherapy administered up to 5 times/week (recommended Monday-Friday during Weeks 1–5 and Monday–Wednesday during Week 6).

6.2.2.2 Visit 1 (Chemotherapy Visit, Week 1–5)

Visit strongly recommended to be scheduled on Monday.

- Vital signs
- ECOG performance status
- Conmeds
- AE assessment
- Laboratory evaluation including:
    - CBC diff
    - Chemistry panel
    - Weeks 1, 3 and 5 only, Coagulation panel (PT/INR, PTT)
- Week 1 prior to chemotherapy dosing only, Blood/plasma samples for molecular or immune-based correlates (Appendix 2)
- Administration of carboplatin + paclitaxel

6.2.2.3 Visit 2 (Immunotherapy Visit, Week 1, 2, 4, 6)

Visit during Weeks 1, 2, and 4 is strongly recommended to be scheduled on a Wednesday or Thursday (2–3 days after carboplatin + paclitaxel administration).

Visit during Week 6 can be scheduled Monday or Tuesday.

- Vital Signs
- Conmeds
- AE assessment
- Week 6 only, ECOG performance status
- Week 6 only, laboratory evaluation including:
    - CBC diff
    - Chemistry panel
- Week 1 prior to APX005M dosing only, Plasma samples for cytokines (Appendix 2)
- Week 6 prior to APX005M dosing only, Blood/plasma samples for molecular or immune-based correlates (Appendix 2)
- **Infusion of APX005M**
- Monitor the patient for 4 hours after APX005M infusion (first 2 infusions only)

6.2.2.4 Visit 3 (Safety Follow-up, Week 1, 2, 4, 6)

Visit should be scheduled 24 hours ± 6 hours after infusion of APX005M and may be conducted remotely if no sample collection is required.

- Vital signs (required if visit is conducted in clinic)
- Conmeds
- AE assessment
- Week 1 24 hours ± 6 hours post APX005M dosing only, Plasma samples for cytokines (Appendix 2)

6.2.3 Post Treatment Period (Weeks 7-16)

Prior to Surgery

- CT-PET scan (no earlier than 4 weeks after last dose of APX005M)
- Vital signs
- ECOG performance status
- Conmeds
- AE assessment
- Laboratory evaluation including (after CT-PET/prior to surgery):
    - CBC diff
    - Chemistry panel
    - Coagulation panel (PT/INR, PTT)
- Blood/plasma samples for molecular or immune-based correlates (Appendix 2) prior to CT-PET scan
- **Surgical Resection** (recommended no earlier than 4 weeks and no later than 10 weeks after last dose of APX005M (Study Weeks 10 to 16).
- Tissue collection (surgical specimen) for molecular or immune-based correlates (Appendix 2)

6.2.4 Follow-Up Visits

Post-Operative Follow-Up

Three post-operative visits should be scheduled at Months 1, 3, and 6 post-operatively. The following procedures should be performed at those time points:

- Vital signs
- ECOG performance status
- Conmeds
- AE assessment
- Laboratory evaluation including:

  - CBC diff
  - Chemistry panel
- Blood/plasma samples for molecular or immune-based correlates (Appendix 2) at the 3-month follow up prior to CT/CT-PET scan
- CT or CT-PET scan at 3 and 6 months post-operatively (or at End of Study visit)

Overall Survival Follow-Up

After the 6 months post-operative follow up visit, patients will be contacted approximately every 3 months for approximately 18 months to determine survival status. When contacting the patient, the following will be determined:

- Subject status
- Disease progression (as determined by routine CT/CT-PET, if available)
- Subsequent anti-cancer therapy

6.2.5 End of Study Visit

All patients who discontinue study or withdraw consent (see Section 6.6) prior to the 6 months post-operative follow up visit should attend an End of Study (EOS) visit:

- Vital signs
- ECOG performance status
- Conmeds
- AE assessment
- Laboratory evaluation including:
  - CBC diff
  - Chemistry panel
- Blood/plasma samples for molecular or immune-based correlates (Appendix 2) prior to CT/CT-PET scan
- CT or CT-PET scan

6.3 Schedule of Assessments

Table 7 Schedule of Assessments

	SCREENING	TREATMENT PERIOD													POST-TREATMENT (ending on the date of surgery)	FOLLOW-UP	
																Postop (x3) / EOS	Overall Survival
	Days| (–28 to 0)	Week													Between Weeks 7–16[1]	Months 1, 3, 6[2]	~ Every 3 Months[16]
		W1			W2			W3	W4			W5	W6				
Visit		V1	V2	V3	V1	V2	V3	V1	V1	V2	V3	V1	V2	V3			
Informed consent	X																
Inclusion/exclusion criteria	X																
Medical history, demographics	X																
Serum/urine pregnancy test[3]	X																
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE/SAE assessment	X	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X[4]			X			X	X			X	X		X	X	
Physical exam	X																
CBC diff	X	X[4]			X			X	X			X	X		X	X	
Chemistry panel	X	X[4]			X			X	X			X	X		X	X	
Coagulation panel	X	X[4]						X				X			X		
Urinalysis	X																
EKG	X																
CT-PET scan	X[5]														X[6]	X[7]	
Endoscopic ultrasound[8]	X																
Endoscopy with biopsy[9]	X																
APX005M administration[10, 11]			X			X				X			X				
Carboplatin/paclitaxel[11]		X			X			X	X			X					
XRT[12]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Surgical resection (tissue)[13]															X		

	SCREENING	TREATMENT PERIOD													POST-TREATMENT (ending on the date of surgery)	FOLLOW-UP	
																Postop (x3) / EOS	Overall Survival
	Days| (–28 to 0)	Week													Between Weeks 7–16[1]	Months 1, 3, 6[2]	~ Every 3 Months[16]
		W1			W2			W3	W4			W5	W6				
Visit		V1	V2	V3	V1	V2	V3	V1	V1	V2	V3	V1	V2	V3			
Blood/plasma samples for molecular or immune-based correlates[14]		X											X		X	X	
Plasma sample for cytokines[15]			X	X													
Subject Status																	X

Abbreviations: AE = adverse event; CBC = complete blood count; CT-PET = computed tomography-positron emission tomography; ECOG = Eastern Cooperative Oncology Group; EKG = electrocardiogram; EOS = End of Study; EUS = endoscopic ultrasound; SAE = serious adverse event; SOC = standard of care; V = visit; W = week; WOCBP = women of childbearing potential; XRT = external radiation therapy.

1. Visit and labs during this period should be performed at least once (more frequent per Investigator's discretion) and ideally be scheduled after CT-PET and prior to surgery.
2. Following first postop visit, f/u visits and tests will be done per institutional practice.
3. WOCBP must have a negative serum pregnancy test within the 7 days prior to investigational product administration and a negative urine pregnancy test within the 3 days prior to the first investigational product administration, or a negative serum pregnancy test within the 3 days prior to the first investigational product administration.
4. Does not need to be repeated if performed as part of screening assessment within previous 14 days prior to dosing any study drug.
5. CT-PET historical test results may be acceptable if completed within 28 days prior to dosing any study drug.
6. CT-PET post-chemoradiation should be performed no earlier than 4 weeks after completion of APX005M treatment period.
7. CT or CT-PET post-op should be performed at Months 3 and 6 (SOC) or at EOS visit.
8. Historical test results may be acceptable if within 56 days prior to first administration of APX005M
9. Endoscopic biopsy should be performed within 14 days prior to first dose of study drug. Biopsy tissue samples to be collected for assessment of molecular or immune correlates. Archival tissue samples from initial diagnosis may be acceptable if the patient is unable to complete an endoscopy.
10. Monitor the patient for 4 hours after the first 2 APX005M infusions.
11. During Weeks 1, 2, and 4 chemotherapy should be scheduled on a Monday and administration of APX005M should be scheduled on a Thursday
12. 28 daily fractions of 180 cGy to be administered ideally in 5 daily fractions from Monday to Friday during Weeks 1–5 and Monday to Wednesday during Week 6
13. Tissue samples from the primary tumor or dissected lymph nodes to be collected for assessment of immune correlates
14. Blood and Plasma samples to be collected at Week 1 Visit 1 (prior to chemotherapy dosing), at Week 6 Visit 2 (prior to APX005M dosing), post treatment period prior to CT-PET scan and at the 3-month follow-up visit or EOS visit prior to CT/CT-PET.
15. Plasma samples for cytokines to be collected at Week 1 Visit 2 before first APX005M infusion and 24 hours after APX005M infusion (Visit 3)
16. Overall Survival subject contact will assess subject status, disease progression, and subsequent anti-cancer therapy.

6.4 Usage of Concurrent/Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for 1 of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The Investigator should discuss any questions regarding this with the Apexigen Medical Monitor or designee. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the subject's primary physician.

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of APX005M and 30 days after the last dose of APX005M should be recorded. Concomitant medications administered after 30 days after the last dose of APX005M should be recorded for SAEs.

The following medications are optional and are allowed during the study:

- Anti-nausea and anti-emetics: per institutional standards
- Antidiarrheals: For subjects developing Grade 1–2 diarrhea, loperamide (2 mg every 2 hours) is strongly recommended at the first onset of symptoms. For subjects with persistent diarrhea despite the use of loperamide, the use of octreotide is recommended. Other antidiarrheal agents may be used if necessary; a work-up for other etiologies is suggested for subjects who progress to Grade 3 or 4 diarrhea while taking loperamide
- Myeloid growth factors (e.g., granulocyte-colony stimulating factor) may be used if neutropenia occurs, in accordance with American Society of Clinical Oncology Guidelines [34], but are not to be given prophylactically and should not be substituted for a required dose reduction
- Red blood cell transfusions, erythropoietic-stimulating agents, or platelet transfusions, if clinically indicated in accordance with institutional guidelines
- Treatment with non-conventional therapies (e.g., acupuncture), and vitamin/mineral supplements is acceptable provided that they do not interfere with treatment and the study endpoints
- Subjects may receive SOC for any underlying illness or treatment emergent AEs

6.4.1 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-CR relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy for either palliative or therapeutic intent
- Herbal medicine for anticancer treatment should be stopped 1 week prior to 1st dose of investigational product.
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than APX005M
- Radiation therapy not specified in this protocol
- Live vaccines within 30 days prior to the first dose of APX005M and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, intranasal influenza vaccines and typhoid vaccine. Seasonal influenza vaccines for injection and COVID-19 vaccines are allowed as long as they can be administered 6–7 days prior and after a dose of APX005M (minimum 6–7 days prior to treatment period, Week 3 or 5 of treatment period, minimum 6–7 days after end of treatment period).
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology (excluding standard pre-medication for paclitaxel and management of acute AEs). The use of physiologic doses of corticosteroids may be approved after consultation with the Medical Monitor or designee.

Subjects who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the Investigator deems to be medically necessary.

6.4.2 Management of Infusion Related Reaction/Cytokine Release Syndrome

Subjects should be instructed that symptoms associated with IRR/CRS can occur at any time following the administration of the APX005M, and if such symptoms develop while they are at home, they should contact the study doctor/study team and/or seek emergency medical care if appropriate.

Steroids should not be used routinely to prevent or treat IRR/CRS as steroidal therapy may significantly impair the therapeutic benefit, however, these suggestions do not contraindicate the use of any medicine clinically needed under emergency circumstances including epinephrine,

diphenhydramine, methylprednisolone or other steroids, nebulized albuterol, or any other medicine needed including additional narcotics to manage treatment-related symptoms as clinically indicated.

In the event of toxicities consistent with IRR/CRS consider the recommendations in Table 8:

Table 8 Management of IRR/CRS

<table>
<tr><th colspan="2">Toxicity Suspected to be Related to Infusion/ Cytokine Release</th><th>Recommended Treatment</th></tr>
<tr><td colspan="2">• Mild toxicity requiring symptomatic treatment only (e.g., fever with or without constitutional symptoms, nausea, fatigue, headache, myalgia, malaise)</td><td>• Vigilant supportive care
• Maintain adequate hydration
• Antipyretics, nonsteroidal anti-inflammatory drugs, antihistamines, anti-emetics, analgesics as needed
• In case of mild symptoms persisting for >48 hours assess for infection, empiric treatment of concurrent bacterial infections</td></tr>
<tr><td rowspan="2">• Symptoms or clinical findings requiring and responding to moderate intervention, such as:
o O_2 requirement <40%
o Hypotension responsive to fluids ± low dose of 1 vasopressor (e.g., <50 mg/min phenylephrine)
o CTCAE Grade 2 organ toxicity</td><td>No extensive comorbidities</td><td>• All of the above
• Monitor cardiac and other organ functions closely</td></tr>
<tr><td>Extensive comorbidities
Age ≥70 years</td><td rowspan="2">• All of the above
• Administer tocilizumab first
• Administer corticosteroids if symptoms worsen or do not improve in <4 hours</td></tr>
<tr><td colspan="2">• Symptoms or clinical findings requiring aggressive intervention, such as:
o O_2 requirement ≥40%
o Hypotension requiring high dose or multiple vasopressors
o Ventilator support required</td></tr>
</table>

Abbreviations: CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion related reaction.

6.5 Diet/Activity/Other Considerations

6.5.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

6.5.2 Contraception

The effect of APX005M on a fetus in utero is unknown. It is also not known if APX005M has transient adverse effects on the composition of sperm.

Carboplatin has been shown to be embryotoxic and teratogenic in rats. Paclitaxel caused embryo- and fetotoxicity in rabbits. There are no adequate and well-controlled studies of carboplatin or paclitaxel in pregnant women. Carboplatin or paclitaxel may cause fetal harm when administered to a pregnant woman. WOCBP participating in this study must avoid becoming pregnant.

It is not known whether carboplatin or paclitaxel is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to carboplatin or paclitaxel treatment of the mother, breast-feeding must be discontinued if the mother is treated with carboplatin/paclitaxel.

The human embryo and fetus are sensitive to ionizing radiation. As such, radiation exposure to an embryo/fetus may increase the risk of cancer in the developing baby or even increase the probability of miscarriage depending on the radiation dose.

Subjects must agree to use an adequate method of contraception starting prior to the first dose of study therapy through 90 days after the last dose of study therapy, and their partners should be encouraged to use adequate method of contraception as well. The following are considered adequate barrier methods of contraception: condom, spermicide (by the partner), diaphragm (by the partner), copper intrauterine device (by the partner), sponge (by the partner), or spermicide. Appropriate hormonal contraceptives (for the partner) will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents). Male subjects must agree to not donate sperm during the period of the study and for a period of 90 days after the last dose of study therapy.

Subjects must be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study by the subject's partner. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject must not be enrolled into the study.

6.6 Subject Withdrawal/Study Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be taken off the trial at the discretion of the Investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures are provided in Section 6.2.5. A subject withdrawing or being discontinued prior to the 6-month post-operative follow up visit should attend the EOS Visit, if feasible.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent
- Confirmed radiographic disease progression
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed the study follow-up period.
- Administrative reasons

6.7 Replacement Policy

All patients who receive at least 1 dose of APX005M will be analyzed for safety. A patient is considered evaluable for the purpose of the primary analysis if she/he meets study eligibility criteria and have undergone surgical resection. Patients who are not evaluable for the purpose of the primary analysis or who discontinue from study participation prior to receiving any study therapy may be replaced after discussion with the Apexigen Medical Monitor or designee.

6.8 Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

- Quality or quantity of data recording is inaccurate or incomplete
- Poor adherence to protocol and regulatory requirements
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
- Plans to modify or discontinue the development of the study drug

In the event of the Sponsor's decision to terminate the study notification will be provided to sites so that appropriate adjustments to patient treatment can be made.

7. REPORTING AND DOCUMENTATION OF RESULTS

7.1 Evaluation of Efficacy

Subjects are not expected to have RECIST measurable disease; therefore, response and progression in this study will be evaluated as follows:

a) **Post-treatment CT-PET**: Results will be based on combination of change in wall thickening, size of regional lymph nodes, and metabolic activity of involved areas, and will be categorized as 1 of the following:

   i) Responding

   ii) Stable/unchanged

   iii) Progressing

   iv) Not evaluable.

   Responses will be assessed by the Investigator. Raw standardized uptake values will also be entered into electronic data capture (EDC).

b) **pCR** at surgery: yes/no

   Responses will be assessed by the Investigator. The pathology report will also be submitted to the Sponsor.

7.2 Assessing and Recording Adverse Events

The AE definitions and reporting procedures provided in this protocol comply with the current Code of Federal Regulations for IND safety reporting (21CFR312.32). The Apexigen Medical Monitor (or designee) must promptly review all information relevant to the safety of the investigational product received from any source. The Investigator or appropriately qualified designee (e.g., a certified nurse practitioner or physician's assistant properly listed on the Form FDA 1572) will carefully monitor each subject throughout the study for possible AEs.

7.2.1 Definitions of Adverse Events

Adverse Event

AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction

Suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Serious AE or Serious SAR

An AE or SAR is considered "serious" (SAE or serious SAR [SSAR]) if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent any of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening

An AE or SAR is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.

Unexpected AE or Unexpected SAR

An AE or SAR is considered "unexpected" if it is not listed in the Investigator’s Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator’s Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator’s Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator’s Brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or SARs that are mentioned in the Investigator’s Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Overdose of APX005M

For this trial, an overdose will be defined as APX005M >1 mg/kg body weight.

No specific information is available on the management of an overdose of APX005M. It is expected that an overdose of APX005M will be associated with severe CRS. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive

treatment should be provided if clinically indicated. Retreatment after an overdose must be discussed with Apexigen Medical Monitor or designee.

7.3 Adverse Event Classification

7.3.1 Relationship to Study Treatment

The Investigator will assess the possible attribution of the each of the different modalities of study treatment (APX005M and/or chemotherapy [carboplatin/paclitaxel] and/or radiation) to the event; this information will be entered into EDC system using the classification as *related* or *unrelated* as defined listed below:

The event is suspected to be related if:

- There is a clinically plausible time sequence between the AE onset and study treatment
- There is a biologically plausible mechanism for the study treatment to cause or contribute to the AE
- The event improves or diminishes upon temporary interruption of the study treatment without the initiation of any specific treatment for the event (dose delay) and/or recurs or worsens when resuming treatment after criteria for retreatment are met
- The AE cannot be reasonably attributed to concurrent or underlying illness, other drugs, or procedures

The Apexigen Medical Monitor (or designee) will review all Investigator-reported assessments of relationship and confirm.

The event is not suspected to be related if:

- The AE is more likely to be explained by the subject's underlying disease, clinical state, concomitant medication, or study or non-study procedure
- The time occurrence of the AE is not reasonably related to study treatment
- The event is not related to study treatment

7.3.2 Severity

The NCI-CTCAE, v4.03, will be used to describe the event and to assess the severity of AEs. For AEs not adequately addressed in the NCI-CTCAE Version 4.03, Table 9 should be used.

Table 9 General Toxicity Grading of AEs

Severity	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of ADL*
Grade 3	Severe; medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Abbreviations: ADL = activities of daily living; AE = adverse event.

Semi-colon indicates "or" within the description

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Abnormal laboratory findings should be reported as AEs only if they are clinically relevant.

AE will be reported at the highest grade experienced. An AE that completely resolves and then recurs will be recorded as a new AE.

7.4 Collection and Reporting

7.4.1 General AE Reporting

All AEs will be collected from the time the subject receives any investigational product through 30 days after receiving the last dose of investigational product, death, or initiation of new anticancer therapy, whichever occurs first. SAEs and AEs with potential immunologic etiology will be recorded up to 100 days and pregnancies up to 120 days after the last dose of investigational product, death, or initiation of new anticancer therapy, whichever occurs first.

Events that occur after the subject signs the informed consent but prior to the first dose of investigational product will be recorded as past medical history; events that start after the first dose of investigational product will be recorded as AEs. In addition, the Investigator should report any AEs that may occur after this time period which are assessed to have a reasonable possibility of being associated with investigational products.

All AEs must be promptly documented on the AE electronic CRF (eCRF). The minimum information required for each AE includes event, duration (start and end dates), start time (for events occurring within 48 hours after the start of APX005M infusion) severity, seriousness, causality to investigational product, action taken, and outcome. Whenever possible, reporting specific diagnosis is preferred when reporting AEs in the AE eCRF rather than reporting individual signs and symptoms except for infusion related reactions and CRS.

All AEs that are considered related to investigational products must be followed to resolution, stabilization, until improvement is not expected, 30 days after receiving the last dose of investigational product, death, or initiation of new anticancer therapy, whichever occurs first. SSARs will be followed until resolution, stabilization, or until resolution is not anticipated.

If an office visit is not possible, a follow-up of ongoing AEs should be attempted by telephone and documented in the subject's source file. AEs continuing at 30 days after the last dose of investigational product should have a comment in the source file by the Investigator that the event has stabilized or is not expected to improve.

The Investigator is responsible for evaluating all AEs, obtaining supporting source documents, and determining that documentation of the event is adequate. The Investigator may delegate these duties to sub-investigators and must ensure that these sub-investigators are qualified to perform these duties under the supervision of the Investigator and that they are listed on the Form FDA 1572.

7.4.2 Disease Progression

Disease progression will be documented in an eCRF intended to capture such information. Signs and symptoms related to disease progression should be reported in the appropriate eCRF as an AE or as a SAE if applicable. Verbatim terms such as "disease progression," "progressive disease," etc. should not be reported as AEs or SAEs unless the Investigator considers the progression to be atypical, accelerated, or caused by the investigational products. Similarly, death occurring as a result of disease progression should be reported on the eCRF intended to capture death information and should not be reported as an SAE.

7.4.3 Serious AEs or Serious SARs

Apexigen (or designee) must be notified of the occurrence of any SAE/SSAR within 24 hours of Investigator's knowledge of the event. The SAE/SSAR will be reported by completing and submitting the SAE/SSAR report form by:

Email: [redacted]

If only limited information is initially available, follow-up reports are required and must be submitted in a timely fashion as additional information becomes available. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses.

The Investigator should also comply with the applicable regulatory requirements related to the reporting of SAEs/SSARs to the regulatory authorities and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The sponsor may request additional source documentation pertaining to the SAE/SSAR from the investigational site. If a subject is

permanently withdrawn from the study due to an SAE/SSAR, this information must be included in the initial or follow up SAE/SSAR report in the eCRF.

The sponsor is responsible for notifying the appropriate health authorities of unexpected SSARs through expedited IND safety reports (ISR) in accordance with applicable laws and regulations.

7.4.4 Handling of Expedited Safety Reports

Apexigen (or designee) will notify Investigators of all ISRs. Upon receiving an ISR from Apexigen (or designee), the Investigator must review and retain the ISR with the Investigator's Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, Apexigen (or designee) will submit the ISR to the appropriate IRB/IEC. The Investigator and IRB/IEC will determine if the informed consent requires revision. The Investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

7.4.5 Non-serious AEs

The collection of AE information begins after subject's written consent to participate in the study; AEs that occur after consent, but prior to the first dose should be recorded as medical history. If an ongoing AE changes in its intensity or in its perceived relationship to investigational product, a new AE entry for the event should be completed. AEs should be followed to resolution, stabilization, a minimum of 30 days after the discontinuation of the investigational product or reported as SAEs if they become serious.

7.4.6 Laboratory Test Abnormalities

Laboratory test values captured as part of the study should be recorded on the appropriate pages of the eCRF. Laboratory abnormalities that meet any of the following criteria will also be captured on the AE or SAE reporting eCRF page as appropriate:

- Require the subject to have any of the investigational products discontinued, delayed, or interrupted
- Require the subject to receive specific corrective therapy
- Are clinically significant
- Meet the definition of an SAE/SSAR.

7.5 Pregnancy Reporting

Subjects will be instructed to notify the Investigator as soon as possible after becoming pregnant or learning of the pregnancy of a partner. If a subject or partner of a subject becomes pregnant during treatment or up to 120 days following the last study drug administration, the Investigator will notify Apexigen (or designee) within 24 hours of learning of the pregnancy.

If the subject becomes pregnant while receiving study treatment, the study treatment should be permanently discontinued. Exceptions to the discontinuation may be considered for life-threatening conditions only after consultation with the sponsor. The Investigator will discuss the risks and concerns of study treatment to a developing fetus and counsel the subject and/or pregnant partner (or ensure that such counseling is provided).

Pregnancies will be followed through the outcome of the pregnancy. Newborns should be followed for a minimum of 8 weeks.

The Investigator will complete a Pregnancy Surveillance Form and report the information regarding the pregnancy, outcome, and status of the newborn, as appropriate.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated.

8. STATISTICAL CONSIDERATIONS AND EVALUATION OF RESULTS

8.1 Sample Size

The primary objective of this study is to assess the efficacy of combining APX005M with SOC chemoradiation (carboplatin/paclitaxel/radiation therapy), as measured by the pCR rate.

[redacted] evaluable patients will be enrolled to this Phase 2 study. The null hypothesis that the true pCR is 29% will be tested against a 1-sided alternative of 53% using an Exact Binomial Test with a Type 1 error rate of 0.05 and power of 81%. A minimum number of [redacted] evaluable patients with adenocarcinoma histology will allow to test the null hypothesis that the true pCR is 23% against a 1-sided alternative of 53% with a Type 1 error rate of 0.05 and power of 77%.

8.2 Interim Analyses and Stopping Rules

Due to this study being conducted in the neoadjuvant setting, this trial will have to following safeguards in place to ensure that study treatment does not compromise patients' ability to make it to their planned (potentially) curative operation in a timely fashion:

The study will be halted to accrual for analyses of safety/tolerability after the first 6 patients have been enrolled. Enrollment may continue once this cohort of patients has completed their neoadjuvant therapy.

The first 6 patients enrolled under protocol Version 10 or later will undergo a safety assessment.

If $\geq$2 of the first 6 patients enrolled in the study and if $\geq$2 of the first 6 patients enrolled after the implementation of protocol Version 10 or later experience unacceptable toxicities attributable to

the addition of APX005M to standard chemoradiation, then enrollment will be halted and the trial design will be reconsidered, including but not limited to the possibility of amending the study to use a lower starting dose of APX005M (while maintaining an unchanged fixed dose of chemoradiation) or reverting to APX005M administration schedule in Version 9 of the protocol. Unacceptable toxicities include:

- Grade 3 or higher non-hematologic toxicity, *excluding* the following:
  - Grade 3 nausea, vomiting or diarrhea lasting <48 hours after providing optimal supportive care
  - Grade 3 anorexia
  - Grade 3 fatigue
  - Grade 3–4 IRR to paclitaxel
- Grade 3–4 IRR to APX005M or Grade 3-4 CRS
- If any AE(s) (of any grade) attributable to study treatment leads to a delay in the patient being able to make it to surgery within 20 weeks of starting study treatment, the study will be suspended and the trial design reconsidered. Scheduling conflicts, patient preference, or other logistic reasons unrelated to toxicity do not count.

8.3 Analyses Plans

8.3.1 Populations for Analyses

All subjects receiving APX005M will be included in the safety population.

Primary efficacy population include patients who meet all study eligibility criteria and have undergone surgical resection. Secondary efficacy population include patients who meet all study eligibility criteria and have a post-treatment CT-PET scan.

8.3.2 Primary Endpoint

The primary efficacy measure is the proportion of patients who achieve a pCR (pCR rate). These data will be reported both for the entire study cohort and for each histologic subgroup. An exact Clopper-Pearson lower 95% confidence limit will be used to test the null hypothesis that the pCR rate is ≤30%. If the lower 95% confidence limit is above 30%, the null hypothesis will be rejected and it will be concluded that the pCR rate is higher than 30%.

8.3.3 Secondary Endpoints

Other efficacy data (secondary endpoints) that will be captured include rates of R0 resection; pathologic stage at time of surgery; and radiographic/metabolic response to neoadjuvant treatment on CT-PET. As this patient population does not typically have measurable disease by RECIST, the radiographic/metabolic response will be described in qualitative terms

(i.e., improved/stable/worse). This data will be reported both for the entire study cohort and for each histologic subgroup.

The assessment of safety (secondary endpoint) will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges. AEs will be summarized by presenting, at each dose level, the number and percentage of patients having any AE, having an AE in each body system and having each individual AE. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate. Toxicities will be tabulated by grade and organ system using the NCI-CTCAE v4.03. Number of patients with dose modifications and reason for dose modification will be tabulated.

In the CROSS trial establishing this preoperative chemoradiation regimen as SOC, the overall incidence of non-hematologic Grade 3–4 toxicity was 13%. We hypothesize that the experimental treatment being evaluated in the current protocol will be safe and tolerable, which we define as not substantially increasing the incidence of non-hematologic Grade 3–4 toxicity (or operative delays) in this patient population.

Feasibility: This study will be considered feasible if no patients require a delay in their planned surgery for reasons of toxicity attributable to investigational product.

8.3.4 Exploratory Endpoints

Descriptive statistics will be used for the exploratory studies, as this work should be considered preliminary in nature and the sample size inadequate to clearly demonstrate the predictive utility of any of the correlatives being evaluated or their changes in response to treatment. This will include:

(1) Identification of possible predictive molecular or immune-based efficacy biomarkers for this novel combination

(2) Characterization and assessment of overall survival

Exploratory readouts will be summarized by descriptive statistics for each time point. Wilcoxon singed-rank test will be used to compare the measurements between baseline and post-induction with APX005M alone/post-APX005M/chemoradiation, separately to assess if there is any change from baseline to post-treatment. In addition, the baseline measurements will be compared between the pCR patients vs. non-pCR patients by Wilcoxon rank-sum test.

9. ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Compliance with the Protocol and Protocol Revisions

This study will be conducted in accordance with this study protocol and with ICH GCP guidelines, the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50), as well as all other applicable country and regional legal and regulatory requirements. The Investigator is responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to potential subjects are reviewed and approved by the appropriate IRB/IEC prior to the enrollment of any study subjects.

If a protocol revision substantially alters the study design or increases the potential risk to the subject:

1. The consent form must be revised and submitted to the IRB/IEC for review and approval/favorable opinion
2. The revised consent form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the revision
3. The new consent form must be used to obtain consent from new subjects prior to enrollment

If the revision is an administrative letter, Investigators must inform their IRB/IEC.

9.2 Institutional Review Board/Independent Ethics Committee

The Investigator must obtain written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., subject leaflets), and any other written information to be provided to subjects. The Investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator's Brochure or product labeling, information to be provided to subjects and any updates. Revisions to the protocol must also be approved by the IRB/IEC prior to the implementation of changes in this study.

The Investigator or sponsor should provide the IRB/IEC with reports, updates, and other information (e.g., expedited safety reports, protocol revisions, and administrative letters) according to regulatory requirements or institution procedures.

9.3 Informed Consent

Written informed consent is required from each subject prior to any testing under this protocol, including screening tests and evaluations. The ICF, as specified by the clinical site's IRB/IEC, must follow the Protection of Human Subjects regulations listed in the CFR, Title 21, Part 50.

Investigators must ensure that subjects or, in those situations where consent cannot be given by subjects, their legally acceptable representative, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding this clinical study in which they volunteer to participate. The information that is given to the subject or the representative shall be in a language understandable to the subject or representative. Freely given written informed consent prior to clinical study participation must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written ICF and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form, and any other written information, was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

Preparation of the consent form is the responsibility of the Investigator and must include all elements required by ICH, GCP and applicable regulatory requirements as well as adhere to GCP and ethical principles that have their origin in the Declaration of Helsinki. The consent form must also include a statement that sponsor and Regulatory Authorities have direct access to subject records. Apexigen (or designee) will provide the Investigator with a sample consent form.

Prior to the beginning of the study, the Investigator must have the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the subjects. The Investigator must provide the subject or legally acceptable representative with a copy of the consent form and allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the trial.

9.4 Monitoring

The Investigator/institution must agree to the inspection of study-related records by the regulatory authority/Apexigen (or designee) representative and must allow direct access to source documents to the regulatory authority/Apexigen (or designee) representative/IRB/IEC. Apexigen (or designee) representative will review onsite study records and directly compare them with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

The Investigator must notify Apexigen (or designee) promptly of any inspections by regulatory authorities and forward promptly copies of inspection reports to Apexigen (or designee).

9.5 Confidentiality

All records identifying the subject will be kept confidential to the full extent of the law.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded on the eCRF. If the subject name appears on any other document (e.g., pathologist report) or study materials (e.g., biopsy tissue slides), then that information must be redacted before a copy of the document is supplied to Apexigen (or designee). Study data stored on a computer will be stored in accordance with local data protection laws and regulations. Subjects will be informed in writing that representatives of the sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws and regulations.

If the results of the study are published, the subject's identity will remain confidential.

The Investigator will maintain a list to enable subjects' records to be identified in accordance with applicable laws and regulations and according to the terms and agreed upon in such subjects' signed consent forms.

9.6 Investigational Site Training

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure or debarment).

Systems with procedures that assure the quality of every aspect of the study will be implemented.

If necessary, Apexigen (or designee) will provide investigational staff training prior to study initiation. Training topics will include, but are not limited to, GCP, AE reporting, study details and procedure, study documentation, informed consent, and enrollment of WOCBP.

9.7 Data Collection and Handling

9.7.1 Case Report Forms

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include subject diaries, laboratory reports, and other documents. Apexigen (or designee) will supply the eCRF, which will be completed in English.

Data collection will involve the use of the EDC system, to which only authorized personnel will have access.

The Investigator or designee must enter all results collected during the clinical study into eCRFs. Guidelines for completion of eCRFs will be reviewed with study site personnel at the site initiation visits. Investigators are responsible for approval of the entered/corrected data. Detailed instructions may be found in the other study-specific documents.

All entries made on the eCRF must be verifiable against source documents. In addition to periodic monitoring occurring within the system by study monitors, programmatic edit checks and data listings will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks and queries may be electronically issued to the clinical study sites and electronically resolved by those sites.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure subject confidentiality in accordance with the legal and regulatory requirements applying to protected health information. Study records (e.g., copies of eCRFs and regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data should be retained for the time period required by applicable regulatory requirements and will not be destroyed until written notification is given by Apexigen (or designee) for destruction.

9.8 Publications

The data collected during this study are confidential and proprietary to Apexigen. Any publications or abstracts arising from this study require approval by Apexigen prior to publication or presentation and must adhere to Apexigen's publication requirements (as set forth in the approved clinical trial agreement). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission. Apexigen shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

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11. APPENDICES

Appendix 1: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Abbreviations: ECOG = Eastern Cooperative Oncology Group.

Appendix 2: Immune Correlative Tissue and Blood Sample Collection

A. Tumor tissue collection

Patients will undergo upper endoscopy with tissue biopsy at screening. When a patient is unable to complete an endoscopy a formalin fixed paraffin embedded historical tissue sample may be acceptable after consultation with the Medical Monitor or designee. Details about the number of core biopsies and procedure specific recommendation are provided in the laboratory manual. In general, the size and the number of cores collected is determined by patient safety, accessibility and size of lesion at the discretion of the physician performing the procedure.

Patients will undergo surgical resection of their primary tumor and associated lymph nodes. Tissue samples should be collected from primary tumor or from dissected lymph nodes that could contain tumor tissue. If available, normal tissue form the proximal and distal surgical margins could be collected.

Three to four core biopsies/tissue fragments will be collected and processed separately with the following priority:

- Formalin fixed paraffin embedded (FFPE)
- Fresh frozen tumor specimen for RNA analysis
- Fresh frozen tumor specimen for DNA analysis

B. Blood samples collection

Whole blood and plasma samples for molecular or immune-based correlates will be collected at the following time points:

- Treatment Period Week 1 Visit 1 (prior to chemotherapy dosing)
- Treatment Period Week 6 Visit 2 (prior to APX005M dosing)
- Post Treatment Period, prior to CT-PET scan
- At the 3-month follow-up visit or EOS visit prior to CT/CT-PET

Additional plasma samples for cytokines will be collected at the following time points:

- Treatment Period Week 1 Visit 2 (prior toAPX005M dosing)
- Treatment Period Week 1 Visit 3 (24 hours ± 6 hours post APX005M dosing)

Details about collection procedure, volumes, and processing and shipping of tissue, whole blood and plasma samples are provided in the Laboratory Manual.