An Early Phase Randomized Trial of APX005M in BRCAwt Patients with Recurrent Ovarian Cancer

ENGOT-OV64/NSGO-CTU-SOLERO

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of Daily Living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CA125	Cancer Antigen 125
CI	Confidence Interval
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ENGOT	European Network of Gynaecological Oncological Trial Groups
FSH	Follicle stimulating hormone
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GM-CSF	Granulocyte-macrophage-colony-stimulating factor
HB	Hemoglobin-b
HRD	Homologous Recombination Deficient
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International normalized ratio
IRB	Institutional Review Board
LD	Longest Diameter
LDH	Lactic dehydrogenase
LH	Luteinizing hormone
mAb	Monoclonal antibody

NCI	National Cancer Institute
NE	Not evaluable
NSGO-CTU	Nordic Society of Gynaecological Oncology – Clinical Trial Unit
OS	Overall survival
ORR	Overall Response Rate
PARP	Poly (ADP-ribose) polymerases
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PRO	Patient reported outcomes
PS	Performance Status
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-OV28	Quality of Life Questionnaire Ovarian 28
QoL	Quality of life
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal
WCC	White Cell Count
ITT	Intention to treat
BRCAwt	BRCA wild type

1 PROTOCOL SUMMARY

1.1 Synopsis

Version & date: Final Version 1.1 – 27-October-2021

Study Title: An Early Phase Randomized Trial of APX005M in BRCAwt Patients with Recurrent Ovarian Cancer

EudraCT Number: 2020-005990-29

Study phase: 2

Study duration: Estimated to be 36 months

Investigational Product and Reference Therapy: APX005M ± RT and Carboplatin/PLD

Indication: Relapsed ovarian cancer where platinum combination therapy is an option.

Sponsor: Nordic Society of Gynaecological Oncology – Clinical Trial Unit (NSGO-CTU)

Principal Investigator: Mansoor Raza Mirza

1.2 Study Design

This multicenter, prospective, open-label, randomized phase II study is evaluating the preliminary efficacy of APX005M (+/-RT) with carboplatin-PLD for BRCAwt patients with relapsed ovarian cancer.

1.3 Planned Number of Subjects: 90 subjects

1.4 Scientific Study Objectives

	Objectives	**Endpoints**
Primary	To evaluate the preliminary efficacy of APX005M-carboplatin-PLD and APX005M-radiotherapy-carboplatin-PLD combinations	Overall Response Rate (ORR) at 12 wks

Secondary	To evaluate safety	Overall Response Rate (ORR) at 24 wks Progression-free survival (PFS) in each treatment arm at 24 months DCR at 12 wks and 24 wks
		Safety until 30 days after last dose of study drug(s)
	To evaluate Patient Reported Outcomes (PROs) in treatment arms	PROs: EORTC QLQ C30 and OV28 overall measures and single items at baseline and every 12 wks for 24 months
Exploratory/ translational research	To describe genetic, molecular, and immunological mechanisms in blood and tumor	Evaluation of changes in molecular and immunological markers of response and/or resistance over time
	To explore the efficacy of APX005M in combination in the molecular and immunological subgroups.	Correlation between changes in molecular and immunological markers and efficacy and/or resistance to treatment in defined subgroups

1.5 Study arms, dosing and duration of treatment:

Arm A: Subjects will receive the following:

• Carboplatin (AUC = 5, day 1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², day1) IV q4 wks x 6 cycles or until progressive disease or unacceptable toxicity.

Arm B: Subjects will receive the following:

• Carboplatin (AUC = 5, day 1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², day 1) IV q4 wks x 6 cycles or until progressive disease or unacceptable toxicity.

• APX005M (0.3 mg/kg, days 1 & 15) IV q4 wks x 6 cycles concomitant with chemotherapy

Arm C: Subjects will receive the following:

• Carboplatin (AUC = 5, day 1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², day 1) IV q4 wks x 6 cycles or until progressive disease or unacceptable toxicity.

• APX005M (0.3 mg/kg, days 1 & 15) IV q4 wks x 6 cycles concomitant with chemotherapy

• External beam radiation therapy; a dose of 0.5 Gy per fraction. (administered as single fractions prior to APX005M administration) days 1 & 15 q4 wks x 6 cycles or until progressive disease or unacceptable toxicity. Maximum 24 wks of therapy; total dose 6 Gy.

Radiation therapy should be discontinued in case of CR at wk 12 (at first tumor assessment).

Re-planning of target lesions is permitted at wk 12.

If it is impossible to draw target lesions due to diffuse character of disease, radiation therapy can be omitted.

1.6 Randomization:

1:2:2 randomization (arm A:B:C):

Arm A: 18 subjects

Arm B: 36 subjects

Arm C: 36 subjects

1.7 Stratification:

Subject population will be stratified according to:

• Planned to receive relapse surgery

• Previous use of PARP inhibitor (yes/no)

1.8 Inclusion Criteria

A subject will be eligible for inclusion only if all the following criteria are fulfilled:

1. Have signed an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation.
2. Histologically diagnosed epithelial ovarian, fallopian tube or primary peritoneal cancer.

3. Radiological or histological confirmation of relapse disease ≥ 6 month after last chemotherapy
4. Known BRCAwt
5. Have completed at least one line of platinum-containing chemotherapy (maximum three previous lines of therapy are permitted). Earlier PARPi and earlier bevacizumab therapies are permitted
6. Must have measurable or evaluable disease according to RECIST 1.1.
7. Baseline biopsy: Tissue biopsy for submission to central laboratory prior to study treatment should be from a newly obtained metastatic biopsy, if there is a lesion suitable for biopsy and the subject consents to this procedure. If a metastatic biopsy is not feasible, or patient is unwilling to provide new biopsy, archival tissue samples should be submitted. Archival tissue sample from metastatic site is preferred; however, archival tissue sample of primary tumor is acceptable.
8. Must consent to undergo mandatory tumor biopsy of at least one metastatic site at day 84 (±7). Biopsy at day 84 (±7) is only applicable if surgery is not performed.
9. Age ≥ 18 years
10. Body weight > 30 kg
11. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
12. Must have a life expectancy ≥ 12 weeks.
13. Must have normal Left Ventricular Ejection Fraction (LVEF > 50%) measured by MUGA scan or echocardiography.
14. Must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below (5% deviation for hematological parameters and 10% deviation for biochemistry is permitted):

    a. Haemoglobin ≥ 10.0 g/dL (≥ 6.2 mmol/L) with no blood transfusion in the past 28 days
    b. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    c. Platelet count ≥ 100 x 10^9/L
    d. Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
    e. Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) /Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case, they must be ≤ 5 x ULN
15. Must have creatinine clearance estimated ≥ 50 mL/min using the Cockcroft-Gault formula
16. A participant is eligible to participate, if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:
    - Is not a woman of childbearing potential (WOCBP)

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in [Appendix 5] during the intervention period and for at least 90 days after the last dose of APX005M and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (i.e., noncompliance, recently initiated) prior to the first dose of study intervention.

- A WOCBP must have a negative urine or serum pregnancy test within 28 days of study treatment and a confirmed negative highly sensitive pregnancy test within 24 hours before the first dose of study intervention.

Additional requirements for pregnancy testing during and after study intervention are in Section 1.10: Table 6: Schedule of Assessments

1.9 Exclusion Criteria

A Subject will not be eligible for inclusion if any of the following criteria are fulfilled:

1. Previous immunotherapy (for example anti-PD-1/L1).
2. Other malignancy unless curatively treated with no evidence of disease for ≥ 3years, except adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS) and stage 1 grade 1 endometrial carcinoma.
3. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g. unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or subjects with congenital long QT syndrome.
4. Subjects with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.
5. Subjects with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.
6. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Subjects who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) or physiologic replacement doses (i.e. prednisone 5 - 7.5 mg/day) for adrenal insufficiency may be enrolled in the study. Inhaled or topical steroids, and

adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

7. Prior radiation therapy.
8. Planned concomitant therapy with any other anticancer therapy
9. Conditions requiring ongoing therapy with antibiotics
10. History of any arterial thromboembolic event within 3 months prior to first dose of APX005M
11. Active coagulopathy
12. Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation
13. History of organ transplant
14. Major surgery or significant traumatic injury within 4 weeks prior to first dose of study drugs
15. Pregnant or breastfeeding women.
16. Subjects with a known hypersensitivity to any of the excipients of the product.
17. Any unresolved toxicity NCI CTCAE Grade ≥ 2 from previous anticancer therapy, except alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
    a. Subjects with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the **Lead Principal Investigator (PI) of the respective collaborative group**
    b. Subjects with irreversible toxicity not reasonably expected to be exacerbated by treatment with study drugs may be included only after consultation with the **Lead PI of the respective collaborative group**.
18. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    a. Subjects with vitiligo or alopecia
    b. Subjects with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement
    c. Any chronic skin condition that does not require systemic therapy
    d. Subjects without active disease in the last 5 years may be included, but only after consultation with the **Lead PI of the respective collaborative group.**
    e. Subjects with celiac disease controlled by diet alone
19. Subjects considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, recent (within 3 months), uncontrolled major seizure disorder, serious

chronic gastrointestinal conditions associated with diarrhea, interstitial lung disease or any psychiatric disorder/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the Subject to give written informed consent.

20. Immunocompromised subjects, e.g. subjects who are known to be serologically positive for human immunodeficiency virus (HIV).
21. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg)), **hepatitis C.** Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
22. Receipt of live attenuated vaccine within 30 days prior to the first dose of Investigational Product (IP). Note: Subjects, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP. COVID-19 vaccination must be performed minimum 7 days prior to first dose of APX005M.

2. INTRODUCTION

2.1 Background

Ovarian cancer is a malignancy arising from surface epithelium in the ovaries. It is the second most common gynaecologic malignancy and is the leading cause of death from gynaecological cancer. Approximately 239,000 new cases of ovarian cancer and 152,000 deaths are annually reported worldwide [1]. Most patients are diagnosed with advanced disease and the population-based 5-year relative survival rate is below 40 %. [2]

The etiology of the disease is unknown in 85-90 %. Women with BRCA gene mutations have a greatly increased risk of ovarian and breast cancer. The estimated lifetime risk of ovarian cancer is 35 to 46 % for *BRCA*1 mutation carriers and 13 to 23 % for *BRCA*2 mutation carriers. Population-based studies in North America have reported that about 15 % of women with invasive ovarian carcinoma have a germline *BRCA* mutation.

Most ovarian cancers are diagnosed at an advanced stage and despite initial therapy, most women with advanced-stage ovarian cancer will relapse and require additional treatment. Relapsing disease is divided into relapsed disease where platinum is and is not an option.

Due to the poor prognosis of recurring ovarian cancer, and the substantial symptom burden for these patients, there is an urgent need for novel therapeutic options. Introduction of PARP inhibitors have considerably improved progression-free survival, however most of the patients will relapse on PARPi therapy with not many following options in hand. Thus, novel treatment modalities are needed.

Among the promising approaches to activating therapeutic antitumor immunity is the modulation of host immune system. Immune modulation includes inhibitory or stimulatory pathways in the immune system, which are crucial for activating the immune response, maintaining self-tolerance, and modulating the duration and amplitude of physiological immune responses. Modulation of immune checkpoints, by antibodies against immune inhibitory molecules, has shown clinical benefits for patients with various solid tumors such as melanoma, lung cancer, bladder cancer, renal cell carcinoma [3-5]. Currently, both antagonistic monoclonal antibodies (mAb) against immune inhibitory molecules, such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed death receptor-1 (PD-1)/programmed death-ligand 1 (PD-L1), and agonistic antibodies against immune costimulatory molecules, such as CD40 and OX40, are under active development for different cancer indications [6].

Apexigen has developed the mAb APX005M (APX005M), which binds and activates CD40, a costimulatory molecule expressed by antigen presenting cells (APC). As such, APX005M is a CD40 agonistic antibody. The cell surface molecule CD40 is a member of the tumor necrosis factor receptor (TNFR) superfamily and plays an important role in induction of tumor apoptosis and regulation of immune activation, especially in crosstalk between T cells and APCs [7]. CD40 is expressed by dendritic cells (DC), B cells, monocytes, and some non-lymphoid cells [8]. The natural ligand (CD40L) for CD40 is CD154, which is expressed on activated T cells and provides a major component of T cell "help" for immune response. Agonistic CD40 antibodies can substitute for the function of CD154 on T cells to boost immunity. Signaling through CD40 on APCs, including dendritic cells (DCs), monocytes, and B cells, can, in turn, enhance the T cell response via improvement in antigen processing and presentation, upregulation of costimulatory molecules and through the release of cytokines from activated APCs [9,10]. Therefore, an agonistic CD40 antibody can activate and stimulate both innate and adaptive immunity.

CD40 is expressed on many tumor cells and can mediate a direct cytotoxic effect. CD40 expression has been reported in 30−70% of primary human solid tumor samples including B cell lymphoma, melanoma and carcinomas [11]. Activation of CD40 on tumor cells results in tumor cell apoptosis and inhibition of tumor growth [12]. Due to its action on both immune and tumor cells, CD40 has been 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 patients [13-16].

The potential mechanisms of action for an agonistic anti-CD40 antibody, depending on its isotype, include stimulation of immune response by activating antigen processing and presentation, recruitment of immune effectors such as natural killer (NK) cells and macrophages, and direct cytotoxic effects on tumor cells. All of these could lead to therapeutic effects in tumors with high mutational burden, such as melanoma. Thus, the desired therapeutic CD40 agonist antibody should have these functionalities.

A few CD40 agonistic antibodies have been evaluated in human clinical trials. Many of the clinical studies in cancer subjects with solid tumors have been conducted with the fully human IgG2 CD40 antibody CP-870,893. In a Phase 1 clinical trial, CP-870,893 was well tolerated; the MTD was found to be 0.2 mg/kg. The main toxicity of CP-870,893 was cytokine release syndrome (CRS) of

mild to moderate severity. Single agent antitumor activity was observed in several melanoma subjects treated with CP-870,893 [17, 18].

2.2 Study Drug (APX005M)

Apexigen has developed the monoclonal antibody (mAb) APX005M (APX005M), which binds and activates CD40, a costimulatory molecule expressed by antigen presenting cells (APC). As such, APX005M is a CD40 agonistic antibody. The cell surface molecule CD40, a member of the tumor necrosis factor receptor (TNFR) superfamily, plays an important role in induction of tumor apoptosis and regulation of immune activation, especially in crosstalk between T cells and APCs [7]. CD40 is expressed by dendritic cells (DC), B cells, monocytes, and some non-lymphoid cells [8]. The natural ligand (CD40L) for CD40 is CD154, which is expressed on activated T cells and provides a major component of T cell "help" for immune response. Agonistic CD40 antibodies can substitute for the function of CD154 on T cells to boost immunity. Signaling through CD40 on APCs, including dendritic cells (DCs), monocytes, and B cells, can, in turn, enhance the T cell response via improvement in antigen processing and presentation, upregulation of costimulatory molecules and through the release of cytokines from activated APCs [9,10]. Therefore, an agonistic CD40 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 [11]. Activation of CD40 on tumor cells results in tumor cell apoptosis and inhibition of tumor growth [12]. Due to its action on both immune and tumor cells, CD40 has been 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 [13-16].

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2.3. APX0005M

2.3.1 Pharmacology

APX005M is an IgG1 humanized mAb with the S267E mutation at the Fc region. APX005M binds with high affinity to human CD40 (Kd = 1.2 × 10-10 M) and monkey CD40 (Kd = 3.5 × 10−10 M) but does not cross-react with mouse or rat CD40. APX005M blocks the binding of CD40 to CD40L. The APX005M binding epitope has been mapped to 2 specific regions on CD40. These are 92TSEACESCVLHRSCSP107 and 125PCPVGFFSNVSSAFEKCHPW144. The region 92TSEACESCVLHRSCSP107 is known as a CD40L binding domain. It has been shown that CD40L-blocking antibodies tend to have more potent CD40 agonistic activities than CD40L-non-blocking antibodies [19].

Preclinical experiments with APX005M showed that it activates the CD40 signaling pathway, leading to APC activation, as demonstrated by an increased expression of CD80, CD83, and CD86, and by expression and release of cytokines from human DCs and lymphocytes. As a result of APC activation, APX005M enhances T-cell proliferation to alloantigen, triggers production of IFN-γ in response to viral antigens and enhances T-cell response to tumor antigens. APX005M combined with a TLR 4 agonist, or an antibody against programmed death ligand 1 (PD-L1), synergistically enhance T-cell responses. In comparison with other CD40-agonistic antibodies, such as CP-870,893, SGN-40, and ADC-1013 analogues, APX005M is the most potent CD40 agonist. APX005M did not appear to have a substantive effect on normal human DC and T-cell counts but could partially reduce B cell counts in vitro. The potential for APX005M to induce expression of cytokines was evaluated with peripheral blood mononuclear cells (PBMC) obtained from normal humans and treatment naïve cynomolgus monkeys, including anti CD3 antibody as a positive control. Cytokine secretion differed significantly between species with much less secretion from monkey PBMCs compared with human PBMCs. These data suggest that APX005M is a strong CD40-agonistic antibody that can activate APCs (DCs, B cells, and monocytes) and in turn stimulate T-cell response.

In cancer patients APX005M induces 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 IL12, INF-γ, TNF-α and IL6.

For more detailed and comprehensive information regarding non-clinical pharmacology, please refer to the current APX005M IB.

2.3.2 Pharmacokinetics

Non-clinical pharmacokinetics (PK) of APX005M was determined in a Good Laboratory Practice (GLP) repeat-dose toxicology study using cynomolgus monkeys. Weekly intravenous (IV) administration of 5 doses of APX005M was well tolerated at 0.3, 3, and 30 mg/kg. The PK properties of APX005M are typical of other mAbs and comprise low clearance (average range of 0.401–7.27 mL/h/kg), small volume of distribution (average range of 57–80.1 mL/kg), and long terminal half-life (average > 66 hours at 3 mg/kg and 30 mg/kg). Positive anti-drug antibodies (ADA) titers were observed in all animals in the low-dose group (0.3 mg/kg) but not in the high-dose group (30 mg/kg) [20]. Based on these results, the no observed adverse effect level (NOAEL) was considered 30 mg/kg.

Cancer patients' exposure to every 3-week and every 2-week IV administration of APX005M (at dose levels of 0.03 mg/kg or less), were for the most part below the limit of quantitation (BLOQ). Administration of APX005M (at dose levels between 0.1 and 1 mg/kg) lead to rapid increase in serum concentrations, reaching a maximum just after the end of the infusion. Concentrations declined rapidly thereafter and were for the most part BLOQ between 24 and 168 hours after the start of dosing. Increase in the dose of APX005M (0.1 mg/kg to 1 mg/kg) led to approximately dose proportional increase in maximum serum concentration (C_{max}) and area under the curve at the last measurable time point (AUC_{0-t}). No accumulation of APX005M was observed with every 21- or 14-days dosing. For more detailed and comprehensive information regarding non-clinical pharmacology, please refer to the current APX005M IB.

2.3.3 Clinical Experience

APX005M has been administered to cancer patients with heavily pretreated solid tumors at doses ranging from 0.0001 mg/kg to 1 mg/kg body weight every 3 weeks, 0.1 mg/kg and 0.3 mg/kg every 2 weeks and 0.1 mg/kg and 0.3 mg/kg every 1 week. In all 3 administration schedules, the dose of 0.3 mg/kg body weight was well tolerated, with toxicities ≤ Grade 2, which is the recommended phase 2 dose. In all 3 administration schedules, APX005M demonstrated a dose-dependent activation of APCs, T-cell activation, and increases in circulating levels of cytokines. For more detailed and comprehensive information regarding nonclinical pharmacology, please refer to the current APX005M IB.

Details of completed and ongoing studies are described briefly below. Additional information is provided in the APX005M IB. As of 03 April 2021, the clinical program for the evaluation of the safety and efficacy of APX005M either as monotherapy or in combination with other agents is comprised of 4 company sponsored trials (CST) (Table 1) and 9 investigator sponsored trials (IST) conducted under non-Apexigen (third-party) INDs (Table 2).

Table 1: Overview of APX005M Clinical Trials Sponsored by Apexigen (For the most up-to-date clinical information regarding APX005M, refer to the current version of the Investigator's Brochure)

Study ID APX005M	NCT Number	Title	Enrolled, N	Patient Population	Study Status
001	02482168	Phase 1 Study to Evaluate the Safety and Tolerability of the CD40-agonistic Monoclonal Antibody APX005M in Subjects with Solid Tumors	43	Advanced solid tumors	Completed
002	03123783	A Study to Evaluate the Safety and Efficacy of the CD40 Agonistic Antibody APX005M Administered in Combination with Pembrolizumab in Subjects with Non-small Cell Lung Cancer and Subjects with Metastatic Melanoma	140[a]	NSCLC, metastatic melanoma	Ongoing as of cutoff date – Database lock on 20 Apr 2021
006	03165994	A Phase 2 Study of APX005M in Combination with Concurrent Chemoradiation as Neoadjuvant Therapy for Resectable Esophageal and Gastroesophageal Junction Cancers	13	Adults with resectable (T1-3Nx, excluding T1N0) cancers of the esophagus and gastroesophageal (GE) junction, including both squamous cell and adenocarcinomas	Ongoing
010	04337931	A Phase II, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of the CD40 Agonistic Antibody APX005M With or Without Stereotactic Body Radiation in Adults with unresectable or Metastatic Melanoma	18	Non-resectable or metastatic melanoma	Ongoing

[a] Safety population N=139 (one subject did not receive APX005M)

Table 1 from APX005M IB edition 8

Table 2: Overview of APX005M Clinical Trials Under Third-party INDs (For the most up-to-date clinical information regarding APX005M, refer to the current version of the Investigator's Brochure)

Study ID APX005M-	Sponsor Study ID	NCT Number	Study Description	Enrolled, N
003	2015-0654	02706353	APX005M in Combination with Systemic Pembrolizumab in Patients with Metastatic Melanoma	25
004	PICI0002	03214250	APX005M in Combination with Gemcitabine and nab-Paclitaxel with or without Nivolumab in Previously Untreated Metastatic Pancreatic Adenocarcinoma	108[a]
005	PBTC 051	03389802	Phase I Study of APX005M in Pediatric Subjects with Recurrent/Refractory Brain Tumors and Newly Diagnosed Brain Stem Glioma	25
007	NT-003	03597282	An Open-label, Phase 1B Study of NEO-PV-01 + CD40 Agonist Antibody (APX005M) or Ipilimumab with Nivolumab in Patients with Advanced or Metastatic Melanoma	7
008	HIC #2000021757	03502330	A Phase I/Ib Study of APX005M in Combination with Nivolumab and Cabiralizumab in Patients with Advanced Melanoma, NSCLC or Renal Cell Carcinoma Whose Disease has Progressed on Anti-PD-1/PD-L1 Therapy	37
009	AAAS0095	03719430	A Phase II Trial Evaluating APX005M (a CD40 Agonistic Monoclonal Antibody) in Combination with Standard-of-care Doxorubicin for Treatment of Advanced Sarcomas	17
011	STU-2019-1492	04130854	Immunotherapy during neoadjuvant therapy for rectal cancer, a Phase II randomized multi-center trial with and without APX005M, an anti-CD40 agonist	11
012	HIC #2000026830	04495257	A Phase I Study of APX005M in combination with nivolumab and ipilimumab in treatment naïve patients with advanced melanoma or renal cell carcinoma	6
013	2014-1029	02600949	Pilot Study of The Feasibility and Safety of a Personalized Peptide Vaccine in Patients with Advanced Pancreatic Ductal Adenocarcinoma or Colorectal Adenocarcinoma	0

Abbreviations: NSCLC = non-small cell lung cancer
[a] Safety population N=74 (one arm of the study did not include treatment with APX005M)

Table 2 from APX005M IB edition 8

2.3.4 Risks and Possible Side Effects

This section summarizes:

• AEs reported in the CSTs as captured in the study clinical databases and the central safety data base as of the data cut-off date (03 April 2021).

• SAEs reported to Apexigen for all studies (CSTs and ISTs) as captured in the central safety data base as of the time of the data cut-off date (03 April 2021).

All AEs reported in this section are graded by CTCAE (Common Terminology Criteria for Adverse Events) version 4.03.

Table 3 below lists the preferred terms of Treatment Emergent Adverse Events (TEAEs) reported as related to APX005M in the 4 CSTs (Studies APX005M-001, -002, -006 and 010; safety population N=213). This list includes the related TEAEs from Study APX005M-002 (safety population N=139) regardless of the relatedness to the co-administered nivolumab.

Table 3: TEAEs Reported as Related to APX005M in ≥2 Subjects (For the most up-to-date clinical information regarding APX005M, refer to the current version of the Investigator's Brochure)

Related TEAE Preferred Term	Subjects (N=212)	
	N	%
Pyrexia	97	45.75%
Chills	95	44.81%
Nausea	72	33.96%
Fatigue	66	31.13%
Pruritus	53	25.00%
AST Increased	49	23.11%
Vomiting	45	21.23%
ALT Increased	44	20.75%
Infusion-related Reaction	31	14.62%
Diarrhea	29	13.68%
Asthenia	29	13.68%
Headache	27	12.74%
Blood AP Increased	25	11.79%
Rash	24	11.32%
Decreased Appetite	24	11.32%
Gamma-GT Increased	23	10.85%
Cytokine Release Syndrome	22	10.38%
Flushing	21	9.91%
Hypotension	20	9.43%
Arthralgia	18	8.49%
Dyspnoea	18	8.49%
Myalgia	17	8.02%
Blood Bilirubin Increased	16	7.55%
Anaemia	15	7.08%
Hypertension	14	6.60%
Tachycardia	11	5.19%
Malaise	10	4.72%
Platelet Count Decreased	9	4.25%
Blood Creatinine Increased	8	3.77%
Amylase Increased	7	3.30%
Cough	7	3.30%
Weight Decreased	7	3.30%
Thrombocytopenia	7	3.30%
Abdominal Pain	7	3.30%
Lipase Increased	6	2.83%
Constipation	6	2.83%
Dizziness	6	2.83%
Dysgeusia	6	2.83%
Chest Discomfort	5	2.36%
Hyperhidrosis	5	2.36%

Related TEAE Preferred Term	Subjects (N=212)	
	N	%
Urticaria	5	2.36%
Dry Mouth	5	2.36%
Rash Maculo-papular	4	1.89%
Lymphocyte Count Decreased	4	1.89%
Rash Macular	4	1.89%
Sinus Tachycardia	4	1.89%
Insomnia	4	1.89%
Hypothyroidism	4	1.89%
Oedema Peripheral	4	1.89%
Colitis	4	1.89%
Influenza Like Illness	4	1.89%
Dry Skin	4	1.89%
Pneumonitis	3	1.42%
Neutrophil Count Decreased	3	1.42%
Blood Thyroid Stimulating Hormone Increased	3	1.42%
Hyponatraemia	3	1.42%
Fall	3	1.42%
Back Pain	3	1.42%
Hyperthyroidism	3	1.42%
Dysphagia	3	1.42%
Acute Kidney Injury	3	1.42%
Chromaturia	2	0.94%
Haemoglobin Decreased	2	0.94%
Syncope	2	0.94%
Blood Lactate Dehydrogenase Increased	2	0.94%
Musculoskeletal Pain	2	0.94%
Pruritus Generalised	2	0.94%
Wheezing	2	0.94%
Abdominal Distension	2	0.94%
Pain	2	0.94%
Vitreous Floaters	2	0.94%
Abdominal Pain Upper	2	0.94%
Arthritis	2	0.94%
Night Sweats	2	0.94%
Hot Flush	2	0.94%
Pleural Effusion	2	0.94%
Hyperglycaemia	2	0.94%

Related TEAE Preferred Term	Subjects (N=212)	
	N	%
Tremor	2	0.94%
White Blood Cell Count Decreased	2	0.94%
Muscle Spasms	2	0.94%
Hypoaesthesia	2	0.94%
Dyspepsia	2	0.94%
Hypoxia	2	0.94%
Pain in Extremity	2	0.94%
Erythema	2	0.94%
Lethargy	2	0.94%
Localised Oedema	2	0.94%
Blood Alkaline Phosphatase	2	0.94%

Abbreviations: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase
Data cutoff date 03 April 2021

Table 3 from APX005M IB edition 8

Individual discussions of the AEs in the CSTs are provided in the APX005M IB. A summary of related SAEs across all clinical studies is provided in Table 4.

2.3.5 Serious Adverse Events

According to the central SAE database, 238 SAEs were reported in 138 subjects of the SAE safety population (430 subjects [all CST and IST study subjects having received at least one dose of APX005M]). The majority of SAEs (189, 79,4%) were considered unrelated to APX005M by the investigator. The number of subjects with SAEs considered related to APX005M at any dose level is summarized in table 4 by CTCAE Grade.

Table 4: Number of Subjects with Related SAEs (For the most up-to-date clinical information regarding APX005M, refer to the current version of the Investigator's Brochure)

Preferred Term	Study ID APX005M-	Grade					
		1	2	3	4	5	All
		Number of subjects (%), N=430					
Cytokine Release Syndrome	001	—	2	3	1	—	12
	002	—	—	2	—	—	
	005	—	1	—	—	—	
	006	—	—	1	—	—	
	009	—	2	—	—	—	
Blood Bilirubin Increased	002	—	—	1c	—	—	3
	005	—	1	—	—	—	
	008	—	—	1	—	—	
AST Increased	005	—	1	—	—	—	3
	008	—	—	1[a]	1	—	
Pyrexia	002	1[c]	—	—	—	—	2
	008	1	—	—	—	—	
ALT Increased	005	—	1	—	—	—	2
	008	—	—	—	1	—	
Colitis	002	—	—	2[c]	—	—	2
Infusion-related Reaction	005	—	—	2	—	—	2
Acute Hepatic Failure	004	—	—	—	—	1[b]	1
Acute Kidney Injury	002	—	—	1[a]	—	—	1
Acute Respiratory Distress Syndrome	008	—	—	—	1	—	1
Diabetic Ketoacidosis	002	—	—	1[a]	—	—	1
Dysphagia	006	—	—	1	—	—	1
Dyspnea	008	—	1	—	—	—	1
Facial Pain	002	—	1[c]	—	—	—	1
Fatigue	005	—	1	—	—	—	1
Gastritis	002	—	—	1c	—	—	1
Hemorrhage Intracranial	004	—	—	—	—	1[a]	1
Headache	009	—	1	—	—	—	1
Hyperglycemia	002	—	—	1[a]	—	—	1
Immune-mediated Encephalitis	002	—	—	1[c]	—	—	1
Immune-mediated Myositis	002	—	1[c]	—	—	—	1
Optic Ischemic Neuropathy	002	—	—	1[a]	—	—	1
Pancreatitis acute	002	—	—	1	—	—	1
Pancreatitis	004	—	—	1	—	—	1
Platelet Count Decreased	008	—	—	1	—	—	1
Pleural Effusion	002	—	1[a]	—	—	—	1
Pulmonary Hemorrhage	004	—	—	1[a]	—	—	1
Respiratory Distress	004	—	—	1	—	—	1
Thrombocytopenia	001	—	—	—	1	—	1
Transaminases Increased	010	—	—	1	—	—	1
Seizure	005	—	—	1	—	—	1

[a] Assessed as not related to APX005M by Apexigen (s. below)
[b] Assessed as related to gemcitabine, nab-paclitaxel and APX005M
[c] Assessed as related to nivolumab and APX005M

Table 4 from APX005M IB edition 8

Fifty (50) SAEs in 40 subjects were considered related to APX005M by the investigator (Table 4). Upon review of the case files, given the timing of the event relative to APX005M administration, the subjects' medical history and concomitant medications, Apexigen assessed the following 7 events as not related to APX005M: pulmonary hemorrhage, acute kidney injury, optic ischemic neuropathy, hemorrhage intracranial, pleural effusion, hyperglycemia and elevated aspartate aminotransferase. For information on all identified and potential risks with APX0005M please always refer to the current version of the APX005M IB.

2.3.6 Reference Safety Information

Expected Serious Adverse Reactions in the RSI (refer to Apexigen's, current version of the Investigator's Brochure for APX005M) represent treatment-emergent non-life-threatening and non-fatal serious adverse events that were reported as related to APX005M in more than one participant across the APX005M clinical program. All suspected fatal or life-threatening SARs will be considered unexpected and reported as suspected unexpected severe adverse reactions (SUSARs). Events (including fatal) of disease progression or lack of efficacy are not reported as SUSARs.

2.3.7 Summary of the Known and Potential Risks and Benefits

Symptoms associated with cytokine release syndrome (including but not limited to flushing, itchiness, chills, fever, rash, tachycardia, hypotension, hypertension, rigor, and myalgia) after administration of APX005M are possible and have been observed in some subjects receiving APX005M. Guidance for monitoring and management of cytokine release syndrome are included in this protocol and in the APX005M Investigator's Brochure.

Asymptomatic transient transaminase elevations, with or without transient bilirubin increase, have been observed in subjects receiving APX005M and these elevations seem to correlate with the presence of liver metastases. Liver function test abnormalities tend to resolve to baseline within 7 days from APX005M administration.

Transient decreases in peripheral blood lymphocyte count in general, and B-cell count in particular, have been observed for APX005M as well as for other CD40-agonistic mAbs and are believed to be a pharmacodynamic (PDn) effect. Transient decreases in platelet counts were observed for some subjects receiving higher doses of APX005M but were not associated with bleeding or other clinical manifestations.

Other symptoms might also occur, including allergic reactions (which could be severe), pulmonary edema, and rarely thromboembolic events, myocardial infarction and/or death.

In the first in human Phase 1 study APX005M-001, APX005M demonstrated a dose-dependent activation of APCs, T-cell activation and increases in circulating levels of cytokines.

The biological effects and the overall tolerability of APX005M up to 1mg/kg body weight suggest a best in class profile for APX005M and the possibility of a safe and efficacious treatment for patients with immunotherapy naïve melanoma.

2.4 Low Dose Ionizing Radiation

For the past century, radiotherapy (RT) has been at the cutting edge of cancer treatment. Thanks to its efficacy, RT is presently given as frontline therapy to approximately 60% of all patients with newly diagnosed cancer [20], and often in combination with chemotherapy. Furthermore, RT is routinely used in the palliative setting to address symptoms and enhance quality of life in patients with advanced tumors. Over the years there have been (a few) reports of abscopal effects in patients (i.e., the disappearance of metastases that are outside of the irradiated area), but only recently has this been attributed to radiation-induced local and systemic immunity. It was demonstrated, that the abscopal effect does not occur in athymic mice [21]. In immune-competent mice RT was shown to trigger several biological mechanisms that promote tumor immunity [22]. For example, RT induces ‘immunogenic cell death’ as evidenced by the translocation of calreticulin to the plasma membrane, which provides ‘eat me’ signals to promote the uptake of dying tumor cells by dendritic cells (DCs) and macrophages [23]. More recently, RT was shown to activate the complement pathway with the release of the anaphylotoxin effectors C3a and C5a, which promote DC activation and ultimately increase the infiltration of T cells into the tumor [24]. In addition, RT affects the cGAS- and STING-dependent cytosolic nucleic acid-sensing pathway to trigger type I interferon (IFN) signaling in DCs, which (i), enhances antigen cross-presentation [25,26,27], (ii) promotes the maturation of tumor associated dendritic cells (DC) [28], and (iii), increases the expression of major

histocompatibility class I glycoproteins (MHCI) and tumor associated antigens (TAAs) [29]. Radiation-damaged tumor cells can also activate DCs through the release of damage-associated molecular pattern molecules (DAMPs) including adenosine triphosphate [30] and high mobility group box 1 (HMGB1) protein [31,32,33]. Remarkably, a recent pre-clinical study demonstrated, that a single fraction of low dose irradiation (LDI; 0.5-2 Gy) can reprogram the tumor microenvironment [34]. Due to potent immunosuppressive mechanisms in the tumor microenvironment and the draining lymph nodes [35], the immunomodulatory effects of RT are insufficient for triggering effective antitumor immune responses, which explains why abscopal tumor regression is seldom observed in clinical practice with RT alone.[22] The purpose of this study is to test low dose irradiation in combination with immunotherapy.

2.4.1 Preclinical/Clinical Evidence

2.4.1.1 Radiation Therapy

Radiation therapy (RT) is a local treatment, which primarily affects the part of the body defined as target (by delineation), that is being treated. The goal of radiation treatment is to damage cancer cells, with as little harm as possible to nearby healthy cells [21]. Studies have estimated that a 1 Gy dose of x-ray radiation can result in 105 ionization events per cell, producing 1000-2000 single-stranded breaks (SSB) and 40 double-stranded breaks (DSB) in DNA [36]. In clinical practice RT is used at a conventional/high dose and fractionation schemes ranging between 1.8 and 2 Gy per fraction daily for several weeks, to reach total doses 50-60 Gy [37]. These high doses cannot be applied to large areas of the body, like the whole peritoneal cavity, due to risk of severe side effects. For this reason, radiation was abandoned in the treatment of ovarian cancer [38].

Recent breakthroughs with checkpoint blockade therapy, as well as adoptive transfer of genetically modified T cells expressing new T-cell receptors (TCRs) or chimeric antigen receptors (CARs), have demonstrated the clinical potential of cancer immunotherapy. However, not all patients benefit from such therapies, in part because the tumor microenvironment is not conducive to T cell engraftment. Vascular barriers, lack of appropriate chemokines, and other stroma immunosuppressive factors may play an important role in preventing proper T cell homing and function [35,39,40]. Ionizing irradiation may render these tumors immunogenic, thereby restoring inflammatory mechanisms that allow T cell infiltration [41,42,43].

Recent evidence in mouse models suggest, that a single fraction of low-dose irradiation (LDI) i.e. 0.5-2 Gy, can reprogram the tumor microenvironment and induce macrophage M1 polarization. In turn the iNOS M1 macrophages produced the appropriate chemokines to recruit effector T cells, and induced tumor vasculature normalization and inflammation, allowing T cell infiltration [34]. The potential clinical applicability of LDI-mediated reprogramming of macrophages is supported by a retrospective analysis of human pancreatic adenocarcinomas previously treated by LDI in the neo-adjuvant setting. In these tumors, LDI significantly increased the proportion of iNOS+ macrophages and CD8+ T cells and decreased the average size of the tumor blood vessels, possibly reflecting vascular normalization [34]. The laboratory of Prof George Coukos recently confirmed this evidence in an ovarian cancer mouse model, where low dose irradiation in combination with agonistic CD40, PD-1 and CTLA-4 blockade were able to trigger complete tumor responses. We confirmed this evidence in ovarian cancer patients (paper in revision Herrera et al., Cancer Discovery). The purpose of this study is to directly compare the effect of low dose RT on the tumor microenvironment, to confirm the mouse/human findings described above, and establish an optimal treatment-schedule to reprogram human tumor macrophages and other antigen presenting cells and enhance T cell infiltration.

LDI may be effective as a preparatory step to induce T-cell homing in tumors lacking T cells, when used in combination with checkpoint inhibitors and drugs that boost antigen presenting cells (like CD40 agonist), with minimal side effects compared to high-dose irradiation. Therefore, this trial focuses on LDI in combination with CD40 agonist and chemotherapy.

We hypothesize, that by manipulating the tumor microenvironment with LDI we can induce endogenous T cell responses, that when combined with CD40 agonistic antibody and chemotherapy administration, will favor T cell vasculature infiltration into the tumor nest. The T cells that were primed by CD40 agonist, chemotherapy and low dose irradiation will be able to recognize and kill cancer cells.

2.4.1.2 Evidence for Combining Radiation with CD40 Agonist

Radiotherapy alone will not be able to induce abscopal effects. To increase the incidence of abscopal effects, the “in situ vaccination properties” of radiation should be enhanced with additional pharmacological activation of antigen presenting cells. Drugs currently under clinical development include agonists to the stimulator receptor CD40. CD40 is a member of the tumor necrosis factor

(TNF) receptor superfamily, expressed on B cells, DCs, monocytes, hematopoietic precursors, endothelial cells, smooth muscle cells, epithelial cells, platelets, as well as many human tumor cells.[44] CD40 activates antigen processing and presentation pathways in DCs and enhances their migration to lymph nodes. CD40 agonists have shown activity in different cancer types in preclinical models and early phase clinical trials [45-47]. In a B cell lymphoma mouse model, anti-CD40 and 5 Gy total body irradiation (TBI) in combination, resulted in increased survival with long-term T cell-mediated protection in more than 80% of animals [48].
Concomitant activation of CD40 and CD137 (a costimulatory receptor expressed on activated T cells) enhanced the antitumor effects of local hypo-fractionated RT (single fraction of 12 Gy), and promoted the rejection of established subcutaneous syngeneic 4T1.2 breast tumors in a CD8+ T and NK cell dependent manner, inducing immunologic memory capable of controlling a secondary tumor challenge [49].

In a preclinical model of pancreatic cancer, inherently resistant to immune checkpoint blockade and an example of a cold (immune desert) tumor; the combination of radiation (>10 Gy), agonist CD40 antibody, and dual checkpoint blockade (anti-CTLA4 and anti-PD1), eradicated irradiated and non-irradiated tumors (i.e. abscopal), generating long-term immunity. The mechanisms underlying this response were due to i) radiation triggered an early inflammatory response and upregulation of MHCI and CD86 on antigen presenting cells, ii) this inflammation was sufficient for the CD40 agonist to induce APC recognition of the tumor, iii) the immune checkpoint blockade increased the immune infiltration and the killing capacity of T cells. [50]

2.4.1.3 Evidence for Combining Low Dose Irradiation (LDI) with Chemotherapy

The current clinical experience with low dose irradiation is very limited. A few trials have reported the use of single fraction 0.5 Gy irradiation in combination with chemotherapy with unexpectedly high rates of disease control [51-55]. This was in part explained by the ability of LDI to sensitize tumor cells to cytotoxic chemotherapy [56,57]. All clinical studies have reported excellent tolerability of LDI, with no additional toxicity observed, compared to conventional chemotherapy alone. Even in the setting of low-dose whole abdominal RT (0.6 Gy per fraction, twice daily, two days weekly, for 6 weeks) for large radiation fields [52, 58].

2.4.2 Side Effects of Radiation Therapy

Side effects of radiotherapy depend largely on the irradiated area and the exposure of normal tissue to high doses of radiation. Typically >45 Gy given in fractions of 2 Gy/day 5 days a week, can provoke inflammation of the irradiated site (esophagitis, mucositis, erythema, proctitis, urethritis, cystitis), which can be mild to moderate, but in < 3-4 % of the patients may be grade 3 or more.

Low to intermediate doses (approximately 3-10 Gy in fractions as low as 0.5 Gy) can provide effective control of a number of benign conditions, ranging from inflammatory/proliferative disorders (e.g. Dupuytren's disease, heterotopic ossification, keloid scarring, pigmented villonodular synovitis) to benign tumors (e.g. glomus tumors or juvenile nasopharyngeal angiofibromas). In our experience with low dose irradiation (NCT03728179 and NCT03992326) we have not observed major side effects. In case of persistent moderate-to-severe inflammatory symptoms, the management of local symptoms should follow the recommendations of the American Society of Radiation Oncologists [59]. Importantly, it is considered, that low-dose radiation will not significantly enhance backbone treatment toxicity.

LDI will be delivered with intensity modulated radiation therapy, thereby taking all measures to minimize the exposure of healthy tissue to ionizing radiation.

2.5. Standard of Care

Until the early 2000s, monotherapy with platinum was the standard treatment for patients with platinum-sensitive relapsed ovarian cancer.

More recent clinical trials have demonstrated the superiority of platinum-based combination therapy versus monotherapy, making this strategy the standard treatment in these patients (the superiority of platinum doublets of carbo plus paclitaxel, carbo plus gemcitabine, and carbo plus PLD to single-agent platinum). Moreover, carboplatin plus PLD was superior to carboplatin plus paclitaxel with a favorable toxicity profile [65]. In the CALYPSO study PLD plus carbo was associated with a decreased risk of alopecia (RR, 0.09; 95% CI, 0.07–0.12; I2 = 0%; $p < 0.01$) and neuropathy (RR, 0.19; 95% CI, 0.14–0.27; I2 = 19%; $p < 0.01$) compared with paclitaxel plus carbo. PLD plus carbo, however, was associated with an increased risk of mucositis/stomatitis (RR, 2.12; 95% CI,1.54–2.93; I2 = 0%; $p < 0.01$) and hand–foot syndrome (RR, 6.12; 95% CI, 3.84–9.76; I2 = 0%; $p < 0.01$).

Compared with grade 3–4 severe toxicities, both hand–foot syndrome and mucositis/stomatitis primarily arose with low-grade toxicities, and the patients' adverse symptoms were mild. Both anemia and thrombocytopenia were principally associated with severe toxicities. Fortunately, the adverse incidence was not high (8.2 and 14.7%, respectively).

Addition of concomitant and maintenance bevacizumab has further improved progression-free survival [66], however most of the patients may have received bevacizumab as first-line therapy and bevacizumab retreatment is not reimbursed.

Maintenance PARP inhibitors have revolutionized the management of ovarian cancer [67], both in the platinum-Sensitive relapsed patients [68] as well as in first-line maintenance therapy [69], however the efficacy of treatment with PARP inhibitors after earlier PARPi therapy is not documented. Therefore, patients will not have any option of maintenance therapy following treatment with bevacizumab and PARP inhibitors and carboplatin doublet will be the only standard of care therapy.

2.5.1. Expected, manageable treatment related toxicity to SoC, Carboplatin and PLD

In this trial, two registered compounds will be used. The side effect profiles of these compounds given in monotherapy as well as in combination are well known and well characterized. In the present protocol, the below listed side effects are considered expected and should be managed according to clinical routine.

- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Abdominal pain
- Dysgeusia
- Fatigue
- Anemia
- Platelet count decreased
- White blood cell decreased

- Neutrophil count decreased
- Pyrexia
- Chills
- Stomatitis/Mucositis
- Skin reaction at site of injection
- Flu like symptoms
- Alopecia
- Peripheral sensory neuropathy
- PPE
- Myocardial infarction
- Allergic reaction to Carboplatin or PLD

3 RATIONALE FOR CURRENT TRIAL AND RISK-BENEFIT ANALYSIS

3.1 Study Rationale

Due to the poor prognosis of recurring ovarian cancer and the substantial symptom burden for these patients, there is an urgent need for novel therapeutic options. Introduction of PARP inhibitors (PARPi) considerably improved progression-free survival, however most of the patients will eventually relapse on PARPi therapy with not many following options in hand. Thus, novel treatment modalities are needed.

Among the promising approaches to activating therapeutic antitumor immunity is the modulation of the host immune system. Immune modulation includes inhibitory or stimulatory pathways in the immune system, that are crucial for activating the immune response, maintaining self-tolerance, and modulating the duration and amplitude of physiological immune responses. Modulation of immune checkpoints by antibodies against immune inhibitory molecules has shown clinical benefits for patients with various solid tumors such as melanoma, lung cancer, bladder cancer, renal cell carcinoma [3-5]. Currently, both antagonistic monoclonal antibodies (mAb) against immune inhibitory molecules such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed death receptor-1 (PD-1)/programmed death-ligand 1 (PD-L1), and agonistic antibodies against immune costimulatory molecules, such as CD40 and OX40, are under development for different cancer indications [6].

Addition of immunotherapy to standard of care treatment is of interest. Multiple randomized controlled trials have demonstrated a significant effect of PARPi maintenance therapy in platinum-sensitive patients, regardless of BRCA status and regardless of HRD status, however, efficacy is highest in the BRCAmut population. This early phase trial aims to identify the optimal combination therapy to produce the greatest clinical effect, in terms of overall response rate, in patients with relapsed ovarian cancer.

The rationale for integrating immunotherapy with chemotherapy is based on preclinical studies, which have shown, that chemotherapy induces immunogenic cell death leading to increased recognition of the tumor by the immune system. Carboplatin is shown to inhibit PD-L2 expression, thereby limiting immunosuppression by both dendritic cells and tumor cells. Paclitaxel decreases the percentage of CD4+ and FoxP3+ regulatory T cells (Tregs) and reduces their cytokine production without disrupting the function of its effector counterpart (CD4+ and FoxP3 effector T (Teff) cells). Several trials have shown effect of checkpoint inhibition following chemotherapy and radiotherapy, most notably in the PACIFIC trial in stage III NSCLC [63]. We therefore hypothesize, that the proposed combined therapies will yield improved clinical effect in this patient population.

The hypotheses in this study is, that the CD-40 agonist APX005M with or without radiotherapy, and in combination with platinum-doublet chemotherapy, will provide the necessary immune activation and serve as a basis for increased clinical effect of the combination.

This study will be performed within the ENGOT collaboration.

4. TRIAL OBJECTIVES AND ENDPOINTS

4.1 Scientific Study Objectives

The overall objective is to demonstrate preliminary efficacy of APX005M-carboplatin-PLD and APX005M-radiotherapy-carboplatin-PLD combinations as treatment for relapsed BRCAwt ovarian cancer patients, where platinum combination therapy is an option.

Primary objective:

• To evaluate the preliminary efficacy of APX005M-carboplatin-PLD and APX005M-radiotherapy-carboplatin-PLD combinations

Secondary objectives:

- To evaluate Patient Reported Outcomes (PROs) in treatment arms
- To evaluate safety

Exploratory translational research objectives:

- To describe genetic, molecular, and immunological mechanisms in blood and tumor
- To explore the efficacy of APX005M in combination in the molecular and immunological subgroups

Primary endpoint:

- Overall Response Rate (ORR) at 12 wks

Secondary endpoints:

- ORR at 24 wks
- Progression-free survival (PFS) at 24 months
- Safety until 30 days after last dose of study drug(s)
- PROs at baseline and every 12 wks for 24 months
- Disease Control Rate (DCR) at 12 wks and 24 wks

Exploratory translational research endpoints

- Evaluation of changes in molecular and immunological markers of response and/or resistance over time
- Correlation between changes in molecular and immunological markers and efficacy and/or resistance to treatment in defined subgroups

Table 5 Trial objectives and endpoints

	Objectives	Endpoints
Primary	To evaluate the preliminary efficacy of APX005M-carboplatin-PLD and APX005M-radiotherapy-carboplatin-PLD combinations	Overall Response Rate (ORR) at 12 wks
Secondary	To evaluate safety	Overall Response Rate (ORR) at 24 wks Progression-free survival (PFS) in each treatment arm at 24 months DCR at 12 wks and 24 wks
		Safety until 30 days after last dose of study drug(s)
	To evaluate Patient Reported Outcomes (PROs) in treatment arms	PROs: EORTC QLQ C30 and OV28 overall measures and single items at baseline and every 12 wks for 24 months
Exploratory/ translational research	To describe genetic, molecular, and immunological mechanisms in blood and tumor	Evaluation of changes in molecular and immunological markers of response and/or resistance over time
	To explore the efficacy of APX005M in combination in the molecular and immunological subgroups.	Correlation between changes in molecular and immunological markers and efficacy and/or resistance to treatment in defined subgroups

5 TRIAL DESIGN

This multicenter, prospective, open-label, randomized phase II study is evaluating the preliminary efficacy of APX005M (+/-RT) – carboplatin-PLD for BRCAwt patients with relapsed ovarian cancer

5.1 Number of Subjects

90 subjects.

5.2 Treatment Arms, Dosing and Duration

Arm A: Subjects will receive the following:

• Carboplatin (AUC = 5, day 1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², day1) IV q4 wks x 6 cycles or until progressive disease or unacceptable toxicity.

Arm B: Subjects will receive the following:

• Carboplatin (AUC = 5, day 1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², day 1) IV q4 wks x 6 cycles or until progressive disease or unacceptable toxicity.

• APX005M (0.3 mg/kg, days 1 & 15) IV q4 wks x 6 cycles concomitant with chemotherapy

Arm C: Subjects will receive the following:

• Carboplatin (AUC = 5, day 1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², day 1) IV q4 wks x 6 cycles or until progressive disease or unacceptable toxicity.

• APX005M (0.3 mg/kg, days 1 & 15) IV q4 wks x 6 cycles concomitant with chemotherapy

• External beam radiation therapy; a dose of 0.5 Gy per fraction. (administered as single fractions prior to APX005M administration) days 1 & 15 q4 wks x 6 cycles or until progressive disease or unacceptable toxicity. Maximum 24 wks of therapy; total dose 6 Gy.

Radiation therapy should be discontinued in case of CR at wk 12 (at first tumor assessment).

Re-planning of target lesions is permitted at wk 12.

If it is impossible to draw target lesions due to diffuse character of disease, radiation therapy can be omitted.

Figure 1

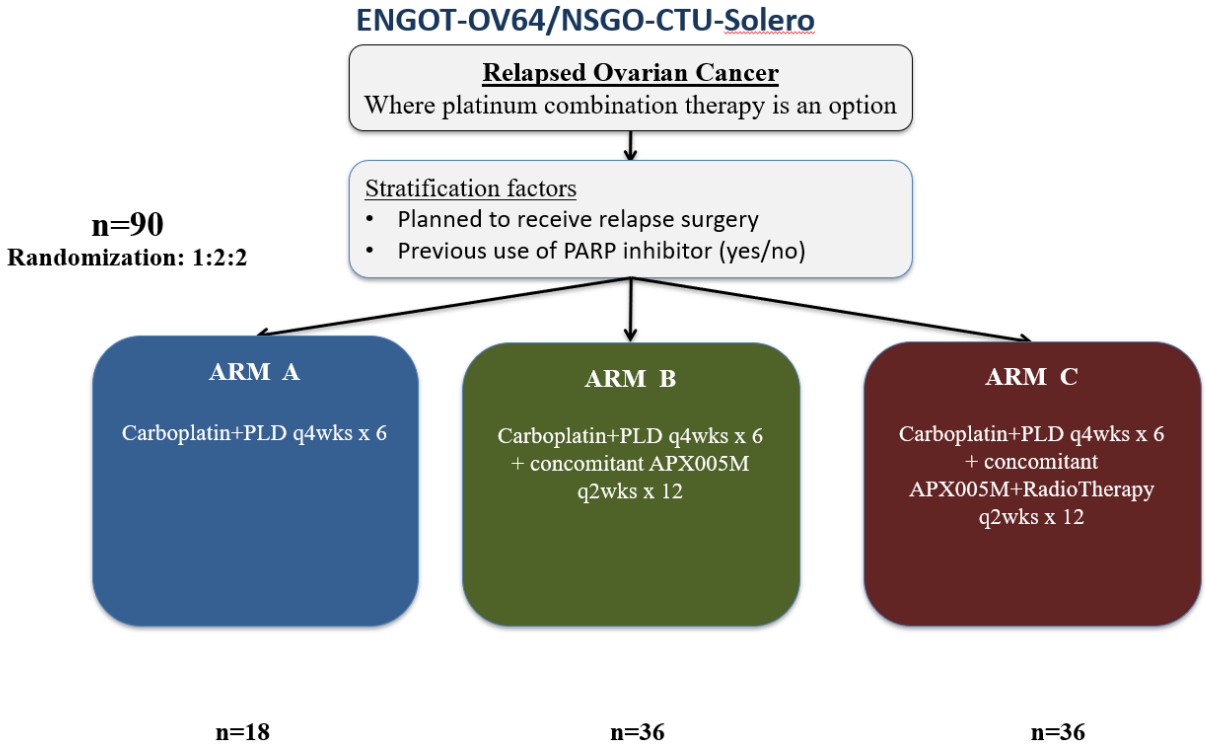
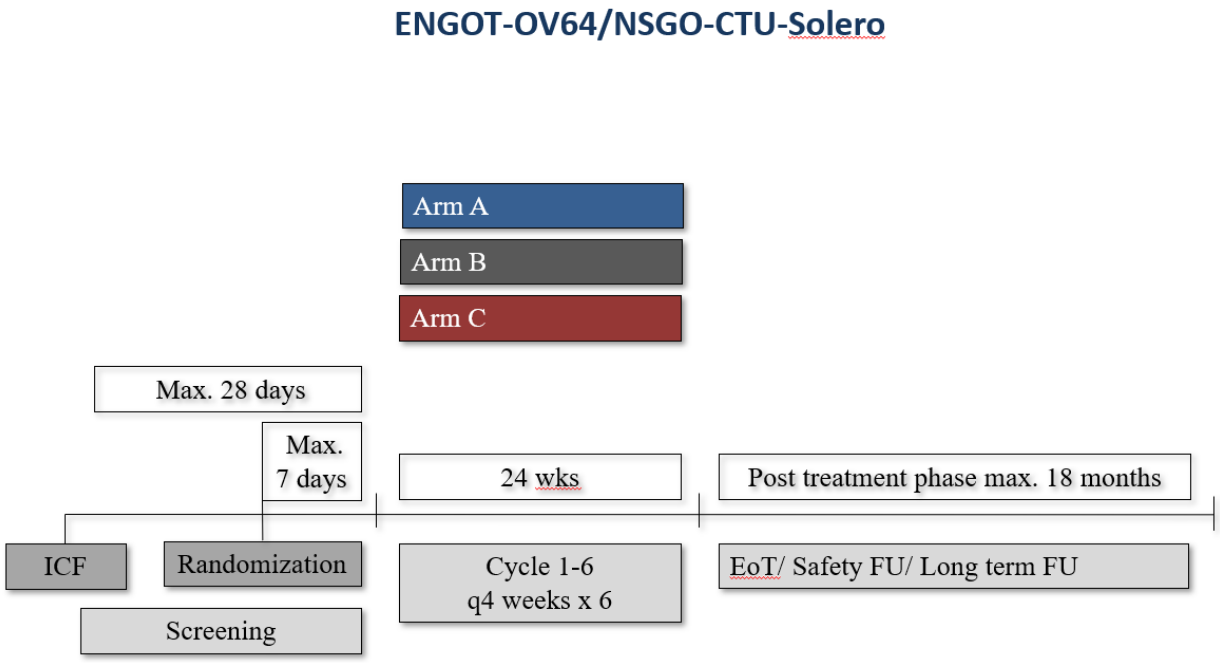


Figure 2



5.3 Randomization

1:2:2 randomization (arm A:B:C):

Arm A: 18 subjects

Arm B: 36 subjects

Arm C: 36 subjects

5.4 Stratification

Subject population will be stratified according to:

- Planned to receive relapse surgery
- Previous use of PARP inhibitor (yes/no)

5.5 IDSMC (Independent Data Safety Monitoring Committee)

An IDSMC will be established to review safety data in compliance with a prospective charter. The IDSMC will be comprised of medical oncologists with experience in treating subjects with the cancer being studied and a statistician, all of whom are not otherwise involved in the study as investigators. The IDSMC will meet after six subjects in Arm B and six subjects in Arm C have been included and received the 1st cycle of therapy (4 wks). Subjects who have stopped study participation for adverse events before completion of the 1st cycle will be included in the analysis. The IDSMC will review all so far available trial data. Subject enrollment will continue during the first IDSMC review.

After the first IDSMC review the IDSMC will meet at least semi-annually after sufficient data has been collected during the treatment period. The IDSMC responsibilities, authorities, and procedures for this study will be documented in the IDSMC charter, which will be endorsed and signed by the IDSMC members prior to the first data review meeting. The IDSMC may recommend to the sponsor whether the trial should be terminated, modified or continue unchanged based on ongoing reviews of safety data. Further details will be outlined in the IDSMC charter.

5.6 Subject Flow

Informed consent must be obtained prior to commencing any screening procedures. Following screening procedures, performed within 28 days prior to randomization, eligible subjects will be

randomized to treatment arm A, B or C. Investigational medicinal products will be administered according to description in section 8. All screening intervals must be respected. Clinic visits during active treatment in arm A are planned every 28 days (+/- 2 days) (CxD1), clinic visits during active treatment in arm B and C are planned every 14 days (+/- 2 days) (CxD1, CxD15), Assessments required during the study are described in section 8.1 and summarized in [Table 6: Schedule of Assessments].

Subjects experiencing disease progression determined by RECIST v1.1 [Appendix 1], as assessed by the investigator, will be discontinued from treatment and enter the follow-up phase. A subject will only be considered to have disease progression according to RECIST 1.1 criteria. Subjects who discontinue treatment, for other reasons than disease progression (according to RECIST 1.1) or death, will also enter the follow up phase until disease progression, or withdrawal of consent or death, though not exceeding study period. Discontinuation from treatment or from the trial is described in section 12.

Subjects will be continuously monitored for safety. Health outcome assessments, AEs and SAEs are graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.00 [Appendix 2].

5.7 Study Timelines

The total expected study duration is 36 months; 12 months of enrollment, 6 months of treatment period and max. 18 months of follow up. Once subjects have been discontinued from study treatment, they will enter follow up period until progression, or until 18 months after the last dose of investigational product, death, initiation of new anticancer therapy or withdrawal of consent, whichever occurs first.

First patient first visit: Q4 2021

Last patient first visit: Q4 2022

Last patient last visit: Q4 2024

Primary endpoint analysis (ORR at 12 wks): Q1 2023

Study closure: Q2 2025

Final Clinical Study Report: Q2 2026

ORR by RECIST v1.1 [Appendix 1] will be assessed by the investigator for the primary endpoint.

For an overview of the study design see Figure 1 and 2, Section 5.

For details on what is included in the efficacy and safety endpoints, see Section 4 Trial Objectives and Endpoints.

6 SELECTION OF SUBJECTS

6.1 Inclusion Criteria

A subject will be eligible for inclusion only if all the following criteria are fulfilled:

1. Have signed an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation.
2. Histologically diagnosed epithelial ovarian, fallopian tube or primary peritoneal cancer.
3. Radiological or histological confirmation of relapse disease ≥ 6 month after last chemotherapy
4. Known BRCAwt
5. Have completed at least one line of platinum-containing chemotherapy (maximum three previous lines of therapy are permitted). Earlier PARPi treatment permitted
6. Must have measurable or evaluable disease according to RECIST 1.1.
7. Baseline biopsy: Tissue biopsy for submission to central laboratory prior to study treatment should be from a newly obtained metastatic biopsy, if there is a lesion suitable for biopsy. If a metastatic biopsy is not feasible, or patient is unwilling to provide new biopsy, archival tissue samples should be submitted. Archival tissue sample from metastatic site is preferred; however, archival tissue sample of primary tumor is acceptable.
8. Must consent to undergo mandatory tumor biopsy of at least one metastatic site at baseline and at day 84 (±7). Biopsy at day 84 (±7) is only applicable if surgery is not performed.
9. Age ≥ 18 years
10. Body weight > 30 kg
11. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
12. Must have a life expectancy ≥ 12 weeks.
13. Must have normal Left Ventricular Ejection Fraction (LVEF > 50%) measured by MUGA scan or echocardiography.
14. Must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below (5% deviation for hematological parameters and 10% deviation for biochemistry is permitted):
    a. Haemoglobin ≥ 10.0 g/dL (≥ 6.2 mmol/L) with no blood transfusion in the past 28 days
    b. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    c. Platelet count ≥ 100 x 10^9/L
    d. Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)

e. Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) /Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case, they must be ≤ 5 x ULN

15. Must have creatinine clearance estimated ≥ 50 mL/min using the Cockcroft-Gault formula
16. A participant is eligible to participate, if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:
    - Is not a woman of childbearing potential (WOCBP)

      OR
    - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in [Appendix 5] during the intervention period and for at least 90 days after the last dose of APX005M and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (i.e., noncompliance, recently initiated) prior to the first dose of study intervention.

    - A WOCBP must have a negative urine or serum pregnancy test within 28 days of study treatment and a confirmed negative highly sensitive pregnancy test within 24 hours before the first dose of study intervention.

Additional requirements for pregnancy testing during and after study intervention are in Section 8.1: Table 6: Schedule of Assessments

6.2 Exclusion Criteria

A Subject will not be eligible for inclusion if any of the following criteria are fulfilled:

1. Previous immunotherapy (for example anti-PD-1/L1).
2. Other malignancy unless curatively treated with no evidence of disease for ≥ 3years, except adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS) and stage 1 grade 1 endometrial carcinoma.
3. Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g. unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or subjects with congenital long QT syndrome.
4. Subjects with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.
5. Subjects with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. Subjects with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.

6. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Subjects who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) or physiologic replacement doses (i.e. prednisone 5 - 7.5 mg/day) for adrenal insufficiency may be enrolled in the study. Inhaled or topical steroids, and adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
7. Prior radiation therapy.
8. Planned concomitant therapy with any other anticancer therapy
9. Conditions requiring ongoing therapy with antibiotics
10. History of any arterial thromboembolic event within 3 months prior to first dose of APX005M
11. Active coagulopathy
12. Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation
13. History of organ transplant
14. Major surgery or significant traumatic injury within 4 weeks prior to first dose of study drugs
15. Pregnant or breastfeeding women.

16. Subjects with a known hypersensitivity to any of the excipients of the product.
17. Any unresolved toxicity NCI CTCAE Grade ≥ 2 from previous anticancer therapy, except alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
    a. Subjects with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the **Lead Principal Investigator (PI) of the respective collaborative group**
    b. Subjects with irreversible toxicity not reasonably expected to be exacerbated by treatment with study drugs may be included only after consultation with the **Lead PI of the respective collaborative group**.
18. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    a. Subjects with vitiligo or alopecia
    b. Subjects with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement
    c. Any chronic skin condition that does not require systemic therapy
    d. Subjects without active disease in the last 5 years may be included, but only after consultation with the **Lead PI of the respective collaborative group.**
    e. Subjects with celiac disease controlled by diet alone

19. Subjects considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, recent (within 3 months), uncontrolled major seizure disorder, serious chronic gastrointestinal conditions associated with diarrhea, interstitial lung disease or any psychiatric disorder/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the Subject to give written informed consent.
20. Immunocompromised subjects, e.g. subjects who are known to be serologically positive for human immunodeficiency virus (HIV).
21. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg)), **hepatitis C.** Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
22. Receipt of live attenuated vaccine within 30 days prior to the first dose of Investigational Product (IP). Note: Subjects, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP. COVID-19 vaccination must be performed minimum 7 days prior to first dose of APX005M.

7 RECRUITMENT PLAN AND SUBJECT ENROLLMENT

7.1 Screening

Potential subjects for the trial may be identified by the treating physician or by referrals from another department/hospital/GP. Furthermore, the investigator may screen subjects' medical records for suitable study candidates and discuss the study with the subject incl. their potential for enrolling in the research study.

This must be done in strict confidentiality and no information jeopardizing the subjects' identity may leave the site. Enrollment will only occur after the subject has given written informed consent, all screening assessments have been completed and the subject meets all eligibility criteria.

All subjects must commence treatment within 28 days after first screening assessments have been performed. A subject who fails to commence treatment within 28 days after screening, and is otherwise considered eligible to enter the study, will have to repeat all screening procedures.

7.2 Screen Failures

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently randomly assigned to study treatments. Minimal information including demography, screen failure details, eligibility criteria, and any serious adverse event (SAE), must be recorded in the eCRF.

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened.

7.3 Randomization

Subjects cannot be registered or randomized to the study until the site has been activated to begin recruitment for the study.

All subjects must be registered in the OpenClinica eCRF (electronic case report form) system as soon as the informed consent formed (ICF) has been signed. Subjects meeting all inclusion criteria, and none of the exclusion criteria, will be eligible to proceed to randomization. OpenClinica will be used for randomization of subjects to the treatment arms. All subjects will be given a subject ID number. This number will allow the identification of the subject in the eCRF.

Subjects not proceeding to randomization, must be registered as screen failures on the Screening and Enrollment Log and in the eCRF.

Treatment must start no later than 7 days after the subject is randomized.

8 CLINICAL EVALUATION, LABORATORY TESTS AND FOLLOW-UP

8.1 Schedule of Assessments

Table 6

Visit	Screening/Baseline		Every Cycle			End of treatment visit	Long Term Treatment Follow up (PFS)[v]
Base Date	Day -28 to -1	Day -7 to -1	Day 1	Day 15 Arm B and C (only)	Day 84	Date of last Dose +30 days	Every 12 weeks
Visit window	N/A	N/A	±2	±2	±7	+7	±7
Administrative Procedures							
Informed Consent[a]	x						
Inclusion/Exclusion Criteria	X						
BRCA Status[b]	X						
Subject Alert Card	x						
Demographics and Medical History[c]	x						
Concomitant Medication		x	x	x	x	x	
Arm A, B & C: PDL Administration – 28 Day Cycle[h]			x				
Arm A, B & C: Carboplatin Administration – 28 Day Cycle[g]			x				
Arm B, C: APX005M Administration – 28 Day Cycle[f]			x	x			
Arm C: Radiation Therapy Treatment – 28 Day Cycle			x	x			
PFS status							x
Clinical Procedures/Assessments							
Review Adverse Events[i]			x	x		x	x
12-Lead Electrocardiogram		x					
Echocardiogram/MUGA scan	x						
Chrom-EDTA clearance	x						
Physical Examination[d]		x	x	x		x	
Vital Signs Weight and Height[e]		x	x	x	x	x	
ECOG Performance Status		x	x			x	

Visit	Screening/Baseline Every cycle		Every cycle			End of Treatment Visit [t]	Long term treatment Follow up (PFS)[v]
Base Date	Day -28 to -1	Day -7 to -1	Day 1	Day 15 Arm B and C (only)	Day 84	Date of last Dose +30 days	Every 12 weeks
Treatment compliance			x	x			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory							
Pregnancy Test – Urine or Serum β-HCG[j]		x	x			x	x[j]
INR, aPTT and D-dimer test[o]		x	x				
CBC with Differential[m]		x	x	x		x	
Chemistry Panel[l]		x	x	x		x	
Urinalysis[n]		x					
CA-125		x	x			x	
HIV Testing[o]		x					
Hepatitis B and C Testing[o]		x					
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory							
Blood sample for biomarker analysis (plasma and whole blood)[s]	x				x		
Efficacy Measurements							
Tumor assessment (CT scan or MRI) and evaluation of measurable disease (RECIST1.1)[k]	x				x	x[u]	
Tumor Tissue Collection							
Archival Tissue Collection for biomarker analysis[p]	x						
Fresh tumor core biopsies for biomarker analysis[q]	x				x		
Patient Reported Outcomes							
EORTC QLQ-C30[r]			x			x	x
QLQ-OV28[r]			x			x	x

a. Informed consent must be obtained before any screening procedures begin.
b. Analysis is performed on archival tumor tissue (from primary or metastatic site) according to the institutional guidelines
c. Collect relevant medical history, medical conditions or symptoms experienced during the previous 30 days, as well as those ongoing at the time of screening. Collect all prior cancer therapies. Please identify the start date of all current medical conditions by at least the month/year.
d. Full Physical examination (Section 9.2.2) will be performed at screening. For subsequent and end of treatment (EOT) visits, physical examinations maybe more directed but should include examination of lungs, abdomen, skin, and cardiovascular system. Physical examination is only repeated on Cycle 1 Day 1 if clinically significant changes from Screening (in the opinion of the investigator) are observed. Vital signs and weight will be completed on day 1 of each cycle for Arm A and days 1 and 15 of each cycle for Arm B and C, and at EOT visit. Vital signs will also be performed at follow up visit.
e. Vital signs and weight will be completed on day 1 of each cycle for Arm A and days 1 and 15 of each cycle for Arm B and C, and at EOT visit. Vital signs will also be performed at follow up visit.
f. APX005M will be administered on Days 1 and 15 of every 28-day cycle. Weight-based dosing is calculated using the subject's actual body weight on Day 1 of each cycle. The dose does not need to be recalculated based on actual weight on Day 15 of each cycle for Arm B and C. Subjects receiving APX005M should be observed during APX005M administration and for at least 4 hours following the first 2 infusions. After discharge, all subjects will receive a phone call by a healthcare professional within 24 hours of the first two infusions of APX005M (C1D1 and C1D15) and as clinically indicated thereafter.
g. Carboplatin will be administered on Day 1 of every 28-day cycle. Subjects receiving carboplatin should be observed during study drug administration according to the institutional guidelines.
h. PLD will be administered on Day 1 of every 28-day cycle. Subjects receiving PLD should be observed during study drug administration according to the institutional guidelines.
i. AEs must be registered using CTCAE 5.0 [Appendix 2]. AEs must continue to be followed for 30 days after the last dose of the treatment drugs. AEs with potential immunologic etiology will be recorded up to 90 days after the last dose of investigational product, death, or initiation of new anticancer therapy, whichever occurs first.
j. For all female subjects of childbearing potential only. A urine or serum pregnancy test will be performed at baseline. A urine or serum pregnancy test will then be repeated on Day 1 of each cycle prior to study drug administration, at EOT and 1. Follow-up visits (90 days after last dose of study drug). If a serum β-HCG laboratory test is performed within 7 days prior to the first day of dosing, it does not need to be repeated on Cycle 1 Day 1. For subsequent cycles the serum β-HCG laboratory test may be performed ≤ 3 days of CxD1.
k. At baseline CT of chest, abdomen & pelvis. CT scans of abdomen and pelvis will be performed at day 84. The scans must be obtained and reviewed prior to start of the next cycle. Overall response will be scored by the Investigator according to RECIST 1.1. MR scan or PET/CT scan are allowed if same method and technique is used throughout the study.
l. Biochemistry: See Section 9.2.7 Laboratory Assessments. All biochemistry laboratory tests should be collected at the start of the following timepoints: Screening and CxD1 and CxD15 (Arm B and C only) of each subsequent cycle. If all biochemistry laboratory tests were performed within 7 days prior to the first day of dosing, they do not need to be repeated on Cycle 1 Day 1. For subsequent cycles biochemistry laboratory test may be performed ≤ 3 days of CxD1/15
m. Hematology: See Section 9.2.7 Laboratory Assessments. Hematology tests should be collected at the following timepoints: Screening and CxD1 and CxD15 (Arm B and C only) of each subsequent cycle. If all biochemistry laboratory tests were performed within 7 days prior to the first day of dosing, they do not need to be repeated on Cycle 1 Day 1. For subsequent cycles hematology laboratory test may be performed ≤ 3 days of CxD1/15

n. Routine urinalysis will be performed at screening and whenever clinically indicated.
o. INR, aPTT and D-dimer test; required only at screening and as clinically indicated thereafter. HIV and Hepatitis B and C testing is acceptable to be based on history unless testing is required by local regulation.
p. Tissue for submission to central laboratory prior to study treatment should be from a newly obtained metastatic biopsy, if there is a lesion suitable for biopsy. If a metastatic biopsy is not feasible, archival tissue samples should be submitted. Archival tissue sample from metastatic site is preferred; however, archival tissue sample of primary tumor is acceptable. It is desirable to collect paraffin block. If paraffin block cannot be sent out, then 15 blank unstained serial sections (4-5 micron thickness) from a block containing viable tumor tissue, should be prepared by pathologists. Refer to local guidelines for pausing of anticoagulant treatment (prophylactic/therapeutic) prior to invasive procedures.
q. Fresh tumor core biopsies at baseline and post-combinatorial therapy will be performed at day 84 (±7) for multiplexed immunohistochemistry in formalin-fixed, paraffin embedded tumour biopsy samples. It is desirable to collect paraffin block. If paraffin block cannot be sent out, 15 blank unstained serial sections (4-5 micron thickness) from a block containing viable tumor tissue should be prepared by pathologists. Tissue can be biopsy or surgical tissue.
r. QOL questionnaires (EORTC-QLQ-C30 and QLQ-OV28) will be completed at Baseline (Day -7 to -1), C1D1 and on CxD1 for the first 24 weeks and then every 12 weeks afterward, EOT visit and at the follow-up visit. Post progression QOL questionnaires will be collected at week 12 and week 24.
s. Blood sample for biomarker analysis is drawn at baseline (pre-dose) and at time of fresh tumor core biopsies, at day 84 (±7) as indicated in Schedule of Assessments.
t. In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (±7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.
u. Tumor Assessment at EOT is only to be performed if the most recent scan is ≥ 4 wks old.
v. End of study must be recorded, when the subject ends the study 18 months after the last dose of investigational product, death, initiation of new anticancer therapy or withdraw of consent, whichever occurs first. At end of study, the following information should be collected: Date for end of study and reason for end of study. Information can be collected from medical records or other source documents.

8.1.1 Screening Phase

All subjects must commence treatment within 28 days after first screening assessments have been performed.

Screening includes:

• Informed Consent

• Inclusion/Exclusion Criteria

• Subject Alert Card

• BRCA status

• Demographics and Medical History

• Concomitant Medication

• 12-Lead Electrocardiogram

• Echocardiogram/MUGA scan

• Chrom-EDTA clearance

• Physical Examination

• Vital Signs (blood pressure, pulse and temperature), Weight and Height

• ECOG Performance Status [Appendix 3]

• Pregnancy Test – Urine or Serum β-HCG

• INR, aPTT and D-dimer test

• CBC incl. differential analysis

• Chemistry Panel

• HIV Testing (Acceptable to be based on history unless testing is required by local regulation).

• Hepatitis B and C Testing (Acceptable to be based on history unless testing is required by local regulation).

• CA-125

• Urinalysis

• Tumor Assessment (CT scan or MRI of chest, abdomen and pelvis) and evaluation of measurable disease (RECIST 1.1)

• Fresh Tumor Core Biopsy for biomarker analysis or archival tissue for analysis

• Blood sample for biomarker analysis (plasma and whole blood)

For submission of tissue biopsy at baseline, please refer to section 5.1., Inclusion Criteria 8 & 9

8.1.2 Treatment Period

8.1.2.1 Cycle 1 Day 1

Visit one in cycle 1 must be performed within 28 days after signed informed content and within 7 days from randomization and includes:

• Physical examination* **

• Vital Signs (blood pressure, pulse and temperature)

• Weight*

• ECOG Performance Status [Appendix 3]*

• Review Adverse Events

• Concomitant Medication

• INR, aPTT and D-dimer test*

• CBC incl. differential analysis*

• Chemistry Panel*

• CA-125*

• Pregnancy Test – Urine or Serum β-HCG

• Study Drug Administration

• Treatment Compliance

• Phone call from health care professional within 24 hours of study drug administration

• PROs using EORTC QLQ-C30 and EORTC QLQ-OV28 [Appendix 4]

*Only to be performed if screening test is more than 7 days old.

** Full physical examination must be performed at screening. For subsequent visits physical examinations may be more directed [Table 6: Schedule of Assessments and Section. 9.2.2]

8.1.2.2 Cycle 1 Day 15 (Arm B and C only)

Must be performed in a window of 15 +/- 2 days from day 1 and includes:

• Physical Examination

• Vital Signs (blood pressure, pulse and temperature)

• Review Adverse Events

• Concomitant Medication

• CBC incl. differential analysis

• Chemistry Panel

• Study Drug Administration

• Treatment Compliance

• Phone call from health care professional within 24 hours of study drug administration

8.1.2.3 Cycle 2+ Day 1

Must be performed in a window of 28 +/- 2 days from previous CxD1 (subsequent cycles should not be adjusted for conceivable variations) and includes:

• Physical examination

• Vital signs (blood pressure, pulse and temperature)

• Weight

• ECOG Performance Status [Appendix 3]

• Review Adverse Events

• Concomitant medication

• INR, aPTT and D-dimer test*

• CBC incl. differential analysis

• Chemistry Panel

• CA125

• Pregnancy test – urine or serum β-HCG

• Study Drug Administration

• Treatment Compliance

• PROs using EORTC QLQ-C30 and EORTC QLQ-OV28 [Appendix 4]

8.1.2.4 Cycle 2+ Day 15 (Arm B and C only)

Must be performed in a window of 15 +/- 2 days from CxD1 (subsequent cycles should not be adjusted for conceivable variations) and includes:

• Physical Examination

• Vital Signs (blood pressure, pulse and temperature)

• Review Adverse Events

• Concomitant Medication

• CBC incl. differential analysis

• Chemistry Panel

• Study Drug Administration

• Treatment Compliance

8.1.3 Day 84

• CT scan and Tumor assessment. Must be performed during the whole study period

• Blood sample for biomarker analysis

• Fresh tumor core biopsies for biomarker analysis

• Concomitant Medication

• Vital Signs

• Weight

8.1.4 Unscheduled Visits

If the subject comes in for an unscheduled visit the following can be performed:

• Physical Examination

• Vital Signs (blood pressure, pulse and temperature)

• Weight

• ECOG Performance Status [Appendix 3]

• Review Adverse Events

• Concomitant Medication

• CBC incl. differential analysis

• Chemistry Panel

• CA125

• Pregnancy Test – Urine or Serum β-HCG

• Other analysis can be performed at the discretion of the investigator

8.1.5 Post Treatment Phase

8.1.5.1 End of Treatment Visit

End of Treatment visit must be performed 30 days after last dose of study drug and includes:

• Physical examination

• Vital signs

• ECOG Performance Status [Appendix 3]

• PROs using EORTC QLQ-C30 and EORTC QLQ-OV28 [Appendix 4]

• Review Adverse Events

• Concomitant Medication

• CBC incl. differential analysis

• Chemistry Panel

• CA125

• Pregnancy Test – Urine or Serum β-HCG

• Tumor assessment (CT scan or MRI of chest, abdomen and pelvis) and evaluation of measurable disease (RECIST 1.1)

8.1.5.3 Long Term Study Follow Up

Long term study follow-up must be performed every 12 weeks (counted from EOT date) until progression (PFS), or until 18 months after the last dose of investigational product, death, initiation of new anticancer therapy or withdraw of consent, whichever occurs first.

At all follow up time points the following information should be collected:

• PROs using EORTC QLQ-C30 and EORTC QLQ-OV28 [Appendix 4]. Post progression subject should complete EORTC QLQ-C30 & QLQ-OV28 [Appendix 4] at week 12 and 24 after EOT.

• PFS status

• Review Adverse Events with potential immunologic etiology *

• Pregnancy Test – Urine or Serum β-HCG**

* Only at the 1. follow-up visit (90 days after end of treatment): Only SAEs, pregnancies and AEs with potential immunologic etiology will be recorded up to 90 days after the last dose of investigational product, death, or initiation of new anticancer therapy, whichever occurs first.

**Pregnancy test will only be performed at the 1. Follow-up visit (90 days after end of treatment)

8.1.5.4 End of Study

End of study must be recorded when the subject ends the study ,18 months after the last dose of investigational product, death, initiation of new anticancer therapy or withdrawal of consent, whichever occurs first. At end of study the following information should be collected:

• Date for end of study

• Reason for end of study

8.2 Data Collection

8.2.1 Clinical Laboratory Investigations

Laboratory testing will be performed in accordance with the subject's Schedule of Assessments. The institutional laboratory will analyze all hematology, blood biochemistry, and pregnancy test assays described in 8.1: Schedule of Assessments. Samples will be analyzed at a facility meeting Good Laboratory Practice requirements and using methods documented in a methods validation report. Hematology results must be reviewed by the investigator prior to the start of treatments.

8.2.2 Translational Samples

Translational studies will be exploratory in nature. In-depth immune profile and immune responses of blood and tumor tissue will be conducted to assess T cell infiltration, persistence and function in all subjects enrolled in the study. Deep molecular and cellular interrogation of the subjects at the level of blood and tumor tissue is crucial for our understanding how therapy increases TILs and reprograms the tumor microenvironment. Blood and tissue samples will be collected according to Section 8.1, table 6: Schedule of Assessments, and Section 15.1, table 13 and table 14.

As the research field is continuously improving now, new translational research objectives may become relevant to be explored at the study completion. If Sponsor decides to explore such new translational research objectives, subjects will be reconsented. If sponsor decides that no further translational research will be carried out, the samples collected may be requested destroyed. In case the collected samples are already analyzed, data will be used and cannot be withdrawn.

8.2.3 Laboratory Evaluations

Laboratory reports will be reviewed by the investigator or delegated physician who must comment on out-of-range parameters and assess clinical significance. Clinically significant abnormalities and associated panel results, as well as results of any additional tests performed as follow-up to the abnormalities, will be documented on the eCRF as an AE per the criteria specified in section 13.

8.2.4 Safety Assessments

The following safety endpoints will be assessed: AEs, vital signs, physical examinations, 12-lead ECGs and laboratory evaluations. Time points is illustrated in Table 6.

9 EFFICACY AND SAFETY ASSESSMENTS

A Schedule of Assessments is provided in Section 8.1.

9.1 Efficacy Assessment

Response and progression will be evaluated using RECIST v1.1 [Appendix 1]. Imaging for all treatment arms will be performed at screening/baseline and at day 84 (± 7 days) from the first dose of study treatment. Baseline imaging performed prior to informed consent as standard of care, may be used, so long as it is performed within 28 days prior to randomization. If a subject discontinues study drug prior to radiological disease progression, the subject should continue to undergo imaging assessment day 84 (± 7 days) until disease progression is documented, or the subject starts another anticancer treatment, whichever occurs earlier. A CT scan with contrast (chest, abdomen and pelvis) is the preferred modality for tumor assessment. At baseline CT of chest, abdomen & pelvis will be performed. Chest CT should only be repeated, if there is metastatic disease in baseline scan or if clinically indicated. Magnetic resonance imaging is acceptable if local standard practice, or if CT scans are contraindicated in a subject (e.g. subject is allergic to contrast media). All other RECIST approved scanning methods such as x-ray are optional. Additional instructions for imaging assessments can be found in the study procedures manual. The assessment will include tumor measurements for target lesions, non-target lesions and any new lesions. An overall assessment will be characterized for a given time point evaluation. At the end of the study for that subject, the best overall response to the study regimen will be characterized. To ensure comparability, the screening and subsequent assessment of response should be performed using identical techniques. The same

individual should assess images for any 1 subject for the duration of the study, if possible. The location of disease progression including target, non-target and/or new lesions should be documented in the eCRF. Additional imaging may be performed at any time to confirm suspected progression of disease. This study will be analyzed based on the results of local (investigator site) radiologic assessments, including dates of progression and death.

9.1.2. Evaluation of Target Lesions

9.1.2.1 Complete Response

CR is defined as disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm from baseline measurement.

9.1.2.2. Partial Response

PR is defined as at least a 30 % decrease in the sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) of target lesions, taking as reference the baseline sum of diameters.

9.1.2.3 Stable Disease

SD is defined as neither sufficient decrease to qualify for PR, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of diameters while on study drug.

9.1.2.4 Progressive Disease

PD is defined as at least a 20 % increase in the sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) of the target lesions, taking as reference the smallest sum on study (this includes the baseline sum, if that is the smallest on study). In addition to the relative increase of 20 %, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

9.1.3 Evaluation of Nontarget Lesions

To acknowledge unequivocal progression on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease, such that even in presence of SD or PR

of target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression.

9.1.3.1 Complete Response
For CR of non-target lesions, subjects must have disappearance of all non-target lesions and all lymph nodes must be non-pathological in size (< 10 mm short axis).

9.1.3.2 NonCR/NonPD
Non-CR/Non-PD of non-target lesions is defined as persistence of 1 or more non-target lesions.

9.1.3.3 Progressive Disease
PD of non-target lesions is defined as unequivocal progression of existing non-target lesions or the appearance of 1 or more new lesions.

9.1.4 Evaluation of Time Point Response
The overall response status at each time point for subjects with measurable disease at baseline will be reported according to [Appendix 1: table 1, table 2 and table 3].

9.2 Safety Assessments
9.2.1 Medical History
At screening a medical history will be obtained to determine relevant underlying conditions.

9.2.2 Physical Examinations
Standard, full physical examinations will be performed at screening to assess general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status and lymphatic systems. For subsequent and end of treatment (EOT) visits, physical examinations may be more directed but should include examination of lungs, abdomen, skin, and cardiovascular system. Physical examinations will be conducted at visits as

outlined in section 8.1: Schedule of Assessments. Each physical examination will include weight. Height is only required at Screening. If clinically significant worsening of findings from baseline is noted at any study visit, the changes will be documented as AEs on the AE eCRF. Clinical significance is defined as any variation in physical findings, that has medical relevance which could result in alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to Grade ≤ 1, or to the baseline level, or until the investigator determines that follow up is no longer medically necessary.

9.2.3. ECG

A standard 12-lead ECG will be performed and assessed using local standard procedures according to the Schedule of Assessments [Section 8.1]. Clinically significant abnormal findings at screening should be recorded as medical history.

9.2.4 Echocardiogram/MUGA-scan

A standard Echocardiogram or MUGA-scan will be performed and assessed using local standard procedures according to the Schedule of Assessments [Section 8.1]. Clinically significant abnormal findings at screening should be recorded as medical history.

9.2.5 Vital Signs

Vital signs, including systolic and diastolic blood pressures (mmHg), radial pulse rate (beats/minute) and temperature will be obtained according to table 6 8.1: Schedule of Assessments and recorded. All vital sign measures will be obtained with the subject in the

sitting or supine position.

If clinically significant vital sign changes from baseline (pre-treatment) are noted, the changes will be documented as AEs on the AE page of the eCRF. Clinical significance will be defined as a variation in vital signs, that has medical relevance as deemed by the investigator, that could result in alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to Grade ≤ 1, or to the Baseline (pre-treatment) level, or until the investigator determines that follow up is no longer medically necessary.

9.2.6 ECOG Performance Status

ECOG performance status should be assessed a time points indicated in [Appendix 3].

Table 7: ECOG Performance Criteria

Grade	Description
0	Normal activity, fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but fully ambulatory, restricted in physically strenuous, but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work)
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50 % of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

It is recommended, where possible, that a subject's performance status be assessed by the same person throughout the study.

9.2.7 Laboratory Assessments

Below is a table of the laboratory tests that will be performed during the conduct of the study.

See [Table 6: Schedule of Assessments] for study visit collection dates.

Table 8: Laboratory Tests

Biochemistry	Albumin, Alkaline phosphatase, Bicarbonate, BUN, Calcium, Chloride, Creatinine, Creatinine clearance (calculated or measured), Glucose, Lactate dehydrogenase, Magnesium, Phosphorous, Potassium, SGOT/AST, SGPT/ALT, Sodium, Total bilirubin, Total protein, Uric acid

Hematology	Hemoglobin, Hematocrit, White blood cell count with complete manual or automated differential (reported as absolute counts): Total neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils), Red blood cell count, Platelet count.
Coagulation	aPTT, INR, D-dimer
β-HCGm	Pregnancy
Ca-125	
Urinalysis	

All clinical laboratory tests will be performed at local laboratories. Assessments performed within 3 days (with results available) prior to the administration of study treatment, could be used for Day 1 of any cycle. Additional laboratory tests should be performed according to institutional standard of care. Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician.

INR; required only at screening and as clinically indicated thereafter

D-dimer test; D-dimer test should be performed if available at local lab at baseline and on Day 15 in Cycles 1 and 2 and as clinically indicated thereafter.

9.2.8 Pregnancy Testing

For WOCBP a pregnancy test is required for eligibility determination and should be performed at the local laboratory. A WOCBP is a sexually mature woman who:

• Has not undergone a hysterectomy or bilateral oophorectomy, or

• Has not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months)

At a minimum, serum pregnancy test will be done within 7 days followed by a urine pregnancy test within 3 days of first dose of APX005M, or a serum pregnancy test should be done within 3 days prior to first dose of APX005M. Pregnancy testing should be conducted every other cycle and at the End of Treatment Visit. More frequent pregnancy tests may be conducted if required per local regulations.

9.2.9 Plasma and Whole Blood

Plasma and whole blood samples for translational research are to be collected before study drug administration and at day 84 (±7 days).

10 RESTRICTIONS DURING THE STUDY

10.1 Pregnancy

Women of childbearing potential and their partners, who are sexually active, must agree to the use two highly effective forms of contraception in combination as described in [Appendix 5: Acceptable Birth Control Methods]. This should be started from the signing of the informed consent and continue throughout the period of taking study treatment and for at least 90 days after last dose of study drug(s), or they must totally/truly abstain from any form of sexual intercourse.

A woman is considered of childbearing potential unless one of the following applies:

• Subject is considered permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

• Subject is postmenopausal, defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level consistently in the postmenopausal range (30 mIU/mL or higher) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a postmenopausal state.

A man is considered of reproductive potential unless the following applies:

• The man is considered permanently sterile. Permanent sterilization methods include bilateral orchiectomy or vasectomized with appropriate post-vasectomy documentation of absence of sperm in ejaculate.

10.2 COVID-19

The conduct of this clinical trial may be affected by COVID-19 due to the impact on function of the health care systems which may become overwhelmed by patients affected by COVID-19, and the free circulation of patients due to the local government's extraordinary laws oriented to the isolation

of the population at home. [Appendix 8] is aiming to secure the impact of COVID-19 on this trial, to secure the trial subjects and to minimize risks on the quality of data.

10.3 Concomitant Therapy

The Investigator must be informed as soon as possible about all concomitant medication taken from the time of screening and up to 30 days after the last dose of study drug. All concomitant medication including all prescription, over-the-counter, herbal supplements and IV medications and fluids will be recorded on the electronic case report form (eCRF) along with:

• Reason for use

• Dates of administration including start and end dates

• Dosage information including dose and frequency

10.4 Prohibited, Restricted, and Permitted Concomitant Medications

Restricted, prohibited, and permitted concomitant medications for the investigational study medication (APX005M) are described in the Sections 10.4.1 and 10.4.2. For non-investigational agents, please refer to the local prescribing information with regards to warnings, precautions, and contraindications. All concomitant medication received from the time of first dose of APX005M and up to 30 days after the last dose will be recorded on the electronic case report form (eCRF) including all prescription, over-the-counter, herbal supplements and IV medications and fluids.

10.4.1 Permitted Concomitant Medications

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.

10.4.2 Prohibited and/or Restricted Therapies

Subjects are prohibited from receiving the following therapies during the screening period and treatment period of this trial:

• Antineoplastic systemic chemotherapy or biological therapy

• Treatment with bevacizumab

• Investigational agents other than study drugs

• Live attenuated vaccines within 30 days prior to the first dose of trial treatment and up to 30 days after the last dose of IP. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection and COVID-19 vaccines (though not live attenuated vaccines) are allowed as long as they can be administered 6-7 days before/after any dose of APX005M.

• Systemic corticosteroids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor, Medical Monitor (or designee). A maximum dose of prednisone ≤10 mg or equivalent is permitted. Inhaled corticosteroids are allowed for management of asthma (regarding general caution of the use of steroids see also Section 11.7.4.6).

• Medications described in the Exclusion Criteria.

Subjects, who in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management will be discontinued from study treatment. Herbal medicine for anticancer treatment (such as botanical formulation 'Xiao Chai Hu Tang') should be stopped 1 week prior to first dose of APX005M. Subjects taking narrow therapeutic index medications (such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin) should be monitored proactively.

For non-investigational agents, please refer to the local prescribing information with regards to warnings, precautions, and contraindications.

There are no prohibited therapies during the follow-up period.

11 TRIAL MEDICATION, DOSE MODIFICATION AND OTHER TREATMENTS

11.1 Treatment. Identification of Investigational Product

11.1.1 APX005M

The investigational product, APX005M is supplied in 20 mL Type 1 clear glass vials for IV injection. Each vial contains 10 mg APX005M/mL in a sterile, clear to slightly opalescent, colorless to slightly yellow, preservative-free solution (pH 5.5) containing 25 mM sodium acetate, 248 mM trehalose, and 0.02% polysorbate 20 in water for injection (WFI). The 20 mL vials are intended for single use. Details of investigational product receipt, labeling, storage and preparation are provided in a supplemental pharmacy guide.

11.1.2 Chemotherapies

Carboplatin and PLD will be supplied by the responsible site pharmacy of each investigational site. Sites are permitted to utilize generic carboplatin that is approved by the respective regulatory authority. Refer to product labels for carboplatin and PLD for storage & handling conditions and caution statements.

Please refer to Section 11.6: Dosing and Administration of Study Drug(s) and Other Medication(s) for specific dosing instructions.

11.2 Packaging and Labeling

APX005M used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at Catalent Pharma Solution in accordance with Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Each carton and vial will bear a label conforming to regulatory guidelines, GMP, and local laws and regulations that identifies the contents as investigational drug.

11.3 Drug Accountability

Catalent Pharma Solution will be responsible QP-release and distribution to all study sites.

A drug dispensing log will be available and must be kept up to date. The log must record:

- Drug shipments received from pharmacy (date received and quantity).
- Subject ID number.
- Amount of medication dispensed and dispensing date.
- LOT No.
- Disposition of unused treatment drugs not dispensed to subjects must also be recorded.

A drug accountability log will be available and must be kept up to date (to be used for a single subject). The log must record:

- Subject ID
- Date and visit no.
- Bottle No.
- Lot No.
- Drug expiry date
- Dispenser and collector initials
- Drug destruction

The treatment drug inventory must be available for inspection by the Monitor.

The site is responsible for the destruction of study drug as required. Any study drug accidentally or deliberately destroyed must be accounted for. All study drug containers must be accounted for prior to their destruction at the study center, according to institutional procedures for disposal of cytotoxic drugs. Unused study drug containers should be destroyed on-site if possible. Destruction of damaged or expired study drug at the site requires prior approval by the sponsor. If destruction on site is not possible, supply should be returned to the drug depot.

11.4 Treatment Compliance

The dose and schedule of RT, carboplatin, PLD and APX005M administered to each subject will be recorded on the appropriate electronic case report form (eCRF) at every cycle. Reasons for dose delay, reduction or omission will also be recorded. If toxicities or adverse events occur on day 1 of any cycle and APX005M, carboplatin or PLD cannot be administered, then the start of the cycle may be delayed (see section 11.7.3). If toxicities occur on Day 15 of any cycle and require the APX005M dose to be held >7 days, then the dose should be eliminated, rather than delayed.

11.5 Drug Destruction

Where appropriate facilities and procedures for drug destruction exist and prior approval from the site monitor has been received site personnel will account for appropriate destruction.

11.6 Dosing and Administration

11.6.1 APX005M

The Pharmacy Manual contains specific instructions for the preparation of the APX005M infusion and administration of infusion solution.

APX005M must be administered as an intravenous infusion over 60 minutes on Days 1 and 15 of every 28-day cycle. Sites should make every effort to target infusion timing as close to 60 minutes as possible. A window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 55 minutes to 70 minutes). The APX005M infusion should be interrupted in the case of infusion reaction/cytokine release syndrome (see Section 11.7.4.6). Once symptoms resolve, infusion should be restarted at 50 % of the initial infusion rate (e.g., from 100 mL/hr to 50 mL/hr). APX005M must not be administered as an intravenous push or bolus. APX005M should not be mixed with other medications. Weight-based dosing is calculated using the subject's actual body weight on Day 1 of each cycle. The dose does not need to be re-calculated based on actual weight on Day 15 of each cycle unless it is required by institutional standards or weight changes by more than 10 % from last measurement. Subject weight must be measured during all relevant assessment timepoints as described in [Table 6: Schedule of Assessments].

The subject should be observed during administration and for at least 4 hours following the first 2 infusions of APX005M.

All subjects will be discharged from clinic after a clinical evaluation. Subjects must have stable vital signs including: lack of orthostatic hypotension (systolic blood pressure >100 mmHg, or no lower than 10 mm from baseline) without IV hydration (no hydration for at least 2 hours prior to discharge), lack of hypoxia (oxygen saturation >90% without oxygen), temperature < 38°C, and heart rate <110 beats/min. After discharge, all subjects will receive a phone call by a healthcare professional within 24 hours after the first two infusions of APX005M (C1D1, C1D15) and as clinically indicated thereafter. Radiation therapy will be administered prior to administration of APX005M. The infusion of APX005M will be started within a time window of 24 ± 2 hours after completion of radiation therapy this will allow delays due to drug related reactions, administrative reasons etc. Treatment delays related to study therapy are discussed in Section 11.7.3 Treatment interruption of APX005M and re-treatment criteria.

Subjects should have good pre-treatment hydration (good oral intake and/or IV fluids) prior to infusion. Subjects should be encouraged to drink volume-increasing fluids (e.g., Gatorade®, broth) for the reminder of the infusion day and maintain an adequate oral fluid intake for the first 24-48 hours after APX005M administration. Subjects must be premedicated prior to all APX005M infusions, unless otherwise specified in the protocol.

Approximately 30 minutes before any administration of APX005M, premedicate subjects with a regimen containing:

- Oral H1 antagonist (e.g., loratadine 10 mg)
- Optional oral H2 antagonist (e.g., ranitidine 150−300 mg, cimetidine 300−800 mg, nizatidine 150−300 mg, and famotidine 20−40 mg)
- Oral nonsteroidal anti-inflammatory drug (may comprise ibuprofen 400 mg or equivalent)
- Acetaminophen 650 mg

Intravenous formulations of these medications could be administered approximately 10 min prior to infusion. When the time between premedication and scheduled APX005M administration exceeds 4 hours, subjects may receive an additional course of premedication prior to APX005M administration.

Additional premedication or treatment delays should be considered when a subject experiences a Grade 2 infusion-related reaction to any drugs administered prior to APX005M.

Administration of APX005M must not immediately follow any other drug administration that results in a Grade ≥3 IRR/CRS.

Given the potential of APX005M-associated hypotension during or after infusion, the investigator may consider withholding antihypertensive medications on the day of APX005M administration if in the opinion of the investigator such action poses no risk to the subject.

It is recommended that subjects continue antipyretics (e.g., ibuprofen every 8 hours, alternating with acetaminophen every 6 hours) for 24 hours following each APX005M administration.

11.6.2 Chemotherapy

Local product labels or summary of product characteristics (SmPC) and institutional guidelines must be followed for the administration of chemotherapy agents and precautions taken to prevent

extravasation per institutional standards and as described in “Chemotherapy and Biotherapy Guidelines and Recommendations for Practice” [Polovich et al, 2014] and “Management of Chemotherapy Extravasation: ESMO-EONS Clinical Practice Guidelines” [Fidalgo et al, 2012]. Chemotherapy will be administered according to local practice before the infusion of APX005M Arms B and C, with a minimum of 30 minutes between completion of the administration of chemotherapy and start of the infusion of APX005M.

Anti-emetic prophylaxis/therapy will be administrated according to the local guidelines. However, corticosteroids are **NOT PERMITTED** as antiemetic prophylaxis or antiemetic treatment on days of APX0005M infusion. Throughout the entire treatment phase (except on days of APX0005M infusion) it is recommended, that the dose of corticosteroids is minimized to the extent that is clinically feasible during the study, i.e. corticosteroids ≤10 mg of prednisone or equivalent (see also Section 11.7.4.6).

11.6.3 Radiation Therapy

External beam radiation therapy is administered as single fractions on Days 1 and 15 of each cycle, to metastatic deposits visible by PET/CT or CT scan, at a dose of 0.5 Gy per fraction. Radiation therapy will be administered prior to administration of APX005M. The infusion of APX005M will be started within a time window of 24 ± 2 hours after completion of radiation therapy.Irradiation of isolated tumor metastases:

Any number of metastatic deposits can be irradiated.

A highly conformal dose distribution to the tumor with 0.5 cm safety margin will be delivered using a 6-15 MV linear acceleration (LINAC). Technics are left to the discretion of the investigator as soon as intensity modulated radiation therapy is implemented (i.e. step and shoot IMRT, volumetric intensity-modulated radiotherapy -VMAT/Rapid Arc/Tomotherapy, sliding window IMRT).

A planning CT scan with or without contrast (at the discretion of the investigator) will be used to plan the delivered dose. The scan should be performed with subject in supine position, with a knee and arm support, the latter will allow the subject to position the arms outside the RT field. The scan should include all the tumors to be irradiated with a 10 cm superior/inferior margin, to allow proper dose reports to organs-at-risk (OARs).

Due to the low dose of radiation, no specific recommendations for dose constraints to OARs are established by this protocol, but we recommend to delineate OARs including kidneys, liver, lungs, bones, heart, and spinal cord and whenever possible active bone marrow. [64]

The investigators are encouraged to plan the radiation dose delivery by co-registering all images available (diagnostic PET/CT, MRI, CT scans) which will allow the clear identification of the gross tumor volume (GTV).

The GTV should encompass all visible tumor deposits with a 5 mm tumor margin for clinical target volume (CTV). The CTV will be encompassed by the planning target volume by adding 5 mm (PTV).

A total dose of 6 Gy will be delivered to the PTV.

Whole abdominal irradiation is not permitted. Reirradiation is not allowed.

If it is impossible to draw target lesions due to diffuse character of disease, radiation therapy can be omitted.

11.6.3.1 Arms A, B, and C Study Treatment Administration

Arm A: Chemotherapy administrated according to local guidelines

Arm B: Chemotherapy administrated according to local guidelines followed by APX005M with a minimum of 30 minutes between the last chemotherapy drug and APX005M

Arm C: Radiation Therapy followed by Chemotherapy administrated according to local guidelines followed by APX005M with a minimum of 30 minutes between the last chemotherapy drug and APX005M

11.7 Dose Adjustment of Study Treatment

11.7.1 Trial Dose

- APX005M (0.3 mg/kg, CxD1 & D15) q4 wks (28-day cycle) x 6 or until disease progression or unacceptable toxicity. Maximum 6 cycles of therapy.
- Carboplatin (AUC = 5, CxD1) q4 wks (28-day cycle) x 6 or until progressive disease or unacceptable toxicity. Maximum 6 cycles of therapy.

- Pegylated liposomal doxorubicin (PLD) (30 mg/m², CxD1) q4 wks (28-day cycle) x 6 or until progressive disease or unacceptable toxicity. Maximum 6 cycles of therapy.
- External beam radiation therapy, at a dose of 0.5 Gy per fraction. (administered as single fractions, CxD1 & D15) q4 wks x 6 or until progressive disease or unacceptable toxicity. Radiation therapy should be discontinued in case of CR at wk 12 (first tumor assessment). Replanning is permitted at wk 12 in case there is residual disease.

11.7.2 Dose Modifications

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of 1 or more components of study treatment, as shown in [Table 9: Dose Levels (DL)]. Toxicity will be described and graded according to the NCI-CTCAE version 5.00. If a subject experience several toxicities, the recommended dose adjustment should be based on the highest-grade toxicity. Up to 2 dose reductions for APX005M and carboplatin and 1 dose reduction for PLD is permissible; beyond this, the subject will be discontinued from treatment. The discontinuation/interruption for toxicity of one of the 3 drugs of the combination therapy, during the chemotherapy period, does not prevent to pursue the other(s) drug(s) according to the protocol schedule. Dose modifications will be applied for all subsequent doses. All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded in the eCRF.

Table 9: Dose Levels

	Starting dose (DL 0)	Dose Level -1 (DL -1)	Dose Level -2 (DL -2)
APX005M	0.3 mg/kg	0.2 mg/kg	0.1 mg/kg
Carboplatin	AUC 5	AUC 4	AUC 3
PLD	30 mg/m^2	20 mg/m^2	NA

11.7.3 Dose Modification, Treatment Interruption, Treatment Reduction and Re-treatment

During concurrent chemotherapy, given the known potential for cytopenia associated with carboplatin and PLD, the chemotherapy agents will first be modified with any episode of clinically relevant hematologic toxicity. During concurrent chemotherapy any scheduled dose of APX005M ± RT should be held, while chemotherapy is being held.

Treatment with chemotherapy (carboplatin and PLD) should be withheld for drug-related toxicity ≥ Grade 3, and subsequent doses modified as per Table 10. Dose modifications will be applied for all subsequent doses. Dose modifications should also be considered according to local product labels or SmPC and institutional guidelines. For carboplatin and PLD associated hematologic toxicities ≥ 3, transfusions or growth factors may be used as indicated per institutional guidelines. If either carboplatin or PLD is discontinued because of toxicity, it is permitted to continue with the other drug. The chemotherapy discontinued should be registered as Dose 0.

Dose interruptions for APX005M associated toxicity is permitted at the discretion of the site investigator. Dose interruption may last up to 15 days. If treatment is paused more than 15 days, PI must consult with Sponsor if the treatment can be resumed. Dose interruptions for subjects, who are deriving clinical benefit from treatment, may be extended beyond 8 weeks, if the subject's toxicity does not otherwise require permanent discontinuation. During the treatment period the schedule for response assessments will be adjusted for chemotherapy dose interruptions only (response evaluation at 12 wks ≈ 3 cycles of chemotherapy).

For treatment interruption of radiation therapy see Table 10. No dose modifications are permitted. No dose reductions are permitted.

Subjects that do not meet the criteria for treatment discontinuation may start CxD1 of investigational products as scheduled if WBC ≥3,000/mm3, ANC ≥1,500/mm3, platelets ≥100,000/mm3. (WBC ≥2,000/mm3, ANC ≥1,000/mm3, platelets ≥75,000/mm3 for CxD15), and disease or treatment-related AE has resolved to baseline or Grade ≤1 (excluding Grade 2 alopecia and Grade 2 fatigue). Subjects who have experienced a Grade ≤2 skin suspected adverse reaction may resume treatment in the presence of Grade 2 skin toxicity.

If a subject fails to meet the criteria to resume treatment, then the treatment cycle can be delayed a maximum of 15 days. The subject should be evaluated within these 15 days whether treatment can

be resumed or discontinued. If treatment is paused more than 15 days, PI must consult with Sponsor if the treatment can be resumed.

Dose modification recommendations are presented in Table 10 below.

Table 10: Dose Modification Guidelines for Drug-Related Adverse Events

	Action taken with Carboplatin/PLD			**Action taken with APX005M**			**Radiation Therapy ******
	1st Occurrence	**2nd Occurrence**	**3rd Occurrence**	**1st Occurrence**	**2nd Occurrence**	**3rd Occurrence**	
Hematologic Toxicity							
Neutropenia Grade 4 (lasting >15 days)	Hold treatment until neutrophils recover to ≥1500/µl Restart treatment at: Carboplatin: AUC 4 PLD: Maintain DL	Hold treatment until neutrophils recover to ≥1500/µl Restart treatment at: Carboplatin: AUC 3 PLD: Maintain DL	Hold treatment until neutrophils recover to ≥1500/µl **Restart treatment at: Carboplatin: AUC 3 PLD: DL -1	Hold until chemotherapy is resumed. Maintain DL*	Hold until chemotherapy is resumed. Maintain DL*	Hold until chemotherapy is resumed. Maintain DL*	Hold until APX005M is resumed
Thrombo-cytopenia Grade 3 (Platelets <50,000/mm^3 with significant bleeding or requiring blood transfusion) and Grade 4 (Platelets <25,000/mm^3)	Hold treatment until platelets recover to ≥100000/mm3 Restart treatment at: Carboplatin: AUC 4 PLD: Maintain DL	Hold treatment until platelets recover to ≥100000/mm3 Restart treatment at: Carboplatin: AUC 3 PLD: Maintain DL	Hold treatment until platelets recover to ≥100000/mm3 **Restart treatment at: Carboplatin: AUC 3 PLD: DL -1	Hold until chemotherapy is resumed. Reduce to DL -1	Hold until chemotherapy is resumed. Reduce to DL -2	Hold until chemotherapy is resumed. Evaluated by PI and Sponsor	Hold until APX005M is resumed
Anemia	Hold treatment until anemia resolves to Grade 1 or baseline Restart treatment at: Carboplatin: AUC 4 PLD: Maintain DL	Hold treatment until anemia resolves to Grade 1 or baseline Restart treatment at: Carboplatin: AUC 4 PLD: Maintain DL	Hold treatment until anemia resolves to Grade 1 or baseline Restart treatment at: Carboplatin: AUC 4 PLD:DL -1	Hold until chemotherapy is resumed. Maintain DL	Hold until chemotherapy is resumed. Maintain DL	Hold until chemotherapy is resumed. Maintain DL	Hold until APX005M is resumed
Non-hematologic toxicities							

	Action taken with Carboplatin/PLD			Action taken with APX005M			Radiation Therapy ****
	1st Occurrence	2nd Occurrence	3rd Occurrence	1st Occurrence	2nd Occurrence	3rd Occurrence	
Nausea/ vomiting Grade 3 (despite optimal medical treatment)	Hold treatment until grade improves to Grade ≤2, then resume treatment. Maintain dose level	Hold treatment until grade improves to Grade ≤2, then resume treatment. Restart treatment at: Carboplatin: AUC 4 PLD: Maintain DL	Hold treatment until grade improves to Grade ≤2, then resume treatment. Restart treatment at: Carboplatin: AUC 3 PLD: DL -1	Hold until chemotherapy is resumed. Maintain dose level	Hold until chemotherapy is resumed. Maintain dose level	Hold until chemotherapy is resumed. Reduce to DL -1	Hold until APX005M is resumed
Nausea/ vomiting Grade 4	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor
Diarrhea Grade 3 (despite optimal medical treatment)	Hold treatment until grade improves to Grade ≤2, then resume treatment. Maintain DL	Hold treatment until grade improves to Grade ≤2, then resume treatment. Restart treatment at: Carboplatin: AUC 4 PLD: Maintain DL	Hold treatment until grade improves to Grade ≤2, then resume treatment. Restart treatment at: Carboplatin: AUC 3 PLD: DL -1	Hold until chemotherapy is resumed. Maintain DL	Hold until chemotherapy is resumed. Maintain DL	Hold until chemotherapy is resumed. Reduce to DL -1	Hold until APX005M is resumed
Diarrhea Grade 4	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor
IRR/CRS to APX005M Grade 3 (≤15 days)	Maintain DL	Maintain DL	Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Reduce to DL -1	Hold treatment until symptoms improve to Grade ≤1 Reduce to DL -2	Evaluated by PI and Sponsor	Hold until APX005M is resumed
IRR/CRS to APX0005M Grade 3 (>15 days) and Grade 4	Maintain DL	Maintain DL	Maintain DL	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor

	Action taken with Carboplatin/PLD			Action taken with APX005M			Radiation Therapy ****
	1st Occurrence	2nd Occurrence	3rd Occurrence	1st Occurrence	2nd Occurrence	3rd Occurrence	
Renal toxicity to carboplatin Grade ≥3 *****	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Restart treatment at: Carboplatin: AUC 4 PLD: Maintain DL	Discontinue carboplatin Continue with PLD for remaining doses.	Maintain DL	Maintain DL	Maintain DL	Hold until APX005M is resumed
PPE to PLD Grade ≥2	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Maintain DL	Maintain DL	Maintain DL	Hold until APX005M is resumed
Pneumonitis grade 2	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Reduce to DL -1	Hold treatment until symptoms improve to Grade ≤1 Reduce to DL -2	Evaluated by PI and Sponsor	Hold until APX005M is resumed
Pneumonitis grade ≥ 3	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor
Esophagitis grade 2	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Reduce to DL -1	Hold treatment until symptoms improve to Grade ≤1 Reduce to DL -2	Evaluated by PI and Sponsor	Hold until APX005M is resumed
Esophagitis Grade ≥ 3	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor
Gastric or small bowel ulcer Grade ≥2	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Reduce to DL -1	Hold treatment until symptoms improve to Grade ≤1 Reduce to DL -2	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor

	Action taken with Carboplatin/PLD			Action taken with APX005M			Radiation Therapy ****
	1st Occurrence	2nd Occurrence	3rd Occurrence	1st Occurrence	2nd Occurrence	3rd Occurrence	
Colitis or proctitis Grade ≥3	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Hold treatment until symptoms improve to Grade ≤1 Maintain DL	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor	Evaluated by PI and Sponsor
Other Grade ≥3 toxicities (except alopecia)***	Adjusted as medically indicated at the discretion of the site investigator.						Hold until APX005M is resumed

Abbreviations: CRS = cytokine release syndrome

For all toxicity Grade <2, the current dose should be maintained

* For neutropenic fever (body temperature >38.3ºC (oral) and ANC <1000/mm3) consider reducing the APX005M dose following discussion with the Sponsor

** Treatment discontinuation should be considered

***In the event of the "other" Grade 3 or 4 non-hematologic toxicities that, in the opinion of the Investigator, are unrelated to the investigational product, subject may continue on therapy with or without dose reduction.

****In case of suspected synergistic toxicity between APX0005M and Low dose Irradiation, first discontinue RT to allow continuation of APX005M.

***** Carboplatin is omitted if the toxicity is not resolved within 28 days (applies for all occurrences)

11.7.4 Rescue Medications & Supportive Care Guidelines (AEs related to APX005M)

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events (AEs) with potential immunologic etiology are outlined below. These treatment guidelines are intended to be applied when the investigator determines the events to be related to APX005M and should not substitute for dose delays and/or modifications. Additional guidance for management of AEs with potential immunologic etiology is provided in the Investigator's Brochures.

If an adverse event is determined by the investigator not to be related, the investigator does not need to follow the treatment guidance outlined in this section. For each disorder, attempts should be made to rule out other causes (such as metastatic disease or bacterial/viral infection) which might require additional supportive care.

11.7.4.1 Diarrhea/Colitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes

should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- Grade 1-2: 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), or Grade 2 colitis, the use of oral corticosteroids is recommended. Other antidiarrheal agents (e.g. octreotide) may be used if necessary.
- Grade 3-4: treat with IV corticosteroids followed by oral corticosteroids until symptoms improve to Grade 1 or less. Add prophylactic antibiotics for opportunistic infections and consider lower endoscopy.

11.7.4.2 Creatinine Elevation Due to Inflammatory Causes

- Grade 2-3: treat with IV or oral corticosteroids until symptoms improve to Grade 1 or less. Consider renal biopsy and nephrology consult.
- Grade 4: treat with IV corticosteroids followed by oral corticosteroids until symptoms improve to Grade 1 or less. Consider renal biopsy and consult nephrologist.

11.7.4.3 Pneumonitis

- Grade 2: request pulmonary and infectious disease consults. Treat with IV or oral corticosteroids until symptoms improve to Grade 1 or less. Consider bronchoscopy, lung biopsy and hospitalization.
- Grade 3-4: request pulmonary and infectious disease consults. Hospitalize and treat immediately with IV corticosteroids. Administer additional anti-inflammatory measures, as needed. Consider adding prophylactic antibiotics for opportunistic infections. Consider bronchoscopy and lung biopsy.

11.7.4.4 Liver Function Tests

- Grade 2 and Grade 3 elevated transaminases (≤ 72 hours): monitor liver function tests more frequently until returned to Grade 1 or less.
- All other Grade 3 and any Grade 4: treat with IV corticosteroids for 24-48 hours followed by oral corticosteroids until symptoms improve to Grade 1 or less. If no improvement in 3-5 days administer additional immunosuppressive measures (e.g. mycophenolate mofetil), as needed. Consider adding prophylactic antibiotics for opportunistic infections. Consult gastroenterologist.

11.7.4.5 Skin Adverse Events

- Grade 1-2: symptomatic treatment (e.g. antihistamines, topical steroids). For persistent (> 1-2 weeks) or recurrent symptoms consider skin biopsy and treatment delay.
- Grade 3-4: consider skin biopsy and consult dermatologist. Treat with IV corticosteroids followed by oral corticosteroids until symptoms improve to Grade 1 or less.

11.7.4.6 Infusion Reaction/Cytokine Release Syndrome

AEs associated with APX005M infusion or cytokine release (fever, tachypnea, headache, tachycardia, hypotension, rash, hypoxia and headache) are possible and have been observed in subjects receiving APX005M. At the RP2D of 0.3 mg/kg of APX005M, the majority of these AEs were mild to moderate in severity. Some Grade 3/4 events have been reported.

All study subjects receiving APX005M should be carefully monitored during and after infusion and as mandated per study protocol. Precautions for IRR/CRS should be observed before and during and after administration of APX005M. These measures include maintaining adequate hydration and the administration of premedication as defined in the study protocol. Additional administration of antipyretics, nonsteroidal anti-inflammatory drugs, antihistamines, anti-emetics, analgesics and narcotics may be necessary for medical management. Emergency agents including oxygen, oral and endotracheal airways intubation equipment, epinephrine, antihistamines, and corticosteroids should be available and should be used at the investigator's discretion and if medically indicated (Table 11).

Steroids should not be used routinely to prevent or treat IRR/CRS, as steroidal therapy may significantly impair the therapeutic benefit of APX005M; **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. Administration of tocilizumab should be considered if CD40-mediated IL-6 cytokine release is suspected.

- Grade 2: stop infusion and treat symptoms following guidance above and in Table 11. If symptoms resolve within two hours, the infusion may be restarted at 50 % of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr).
- Grade 3-4: stop infusion and treat symptoms following guidance in Table 11.

Table 11: Guidance for Management of Cytokine Release/Infusion Reaction Symptoms

<table>
<tr><th colspan="2">Suspected Cytokine Release/Infusion-related Toxicity</th><th>Recommended Treatment</th></tr>
<tr><td colspan="2">• Mild toxicity requiring symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise)</td><td>• Vigilant supportive care
• Maintain adequate hydration
• Antipyretics, non-steroidal anti-inflammatory drugs, antihistamines, anti-emetics, analgesics as needed
• In case of mild symptoms persisting for > 24 hours assess for infections; empiric treatment of concurrent bacterial infections</td></tr>
<tr><td>• Symptoms or clinical findings requiring and responding to moderate intervention, such as:
○ O_2 requirement < 40%
○ Hypotension responsive to fluids ± low dose of one vasopressor (e.g., < 50 mg/min phenylephrine)
○ CTCAE Grade 2 organ toxicity</td><td>• No extensive co-morbidities</td><td>• All of the above
• Monitor cardiac and other organ functions closely</td></tr>
<tr><td rowspan="2">• Symptoms or clinical findings requiring aggressive intervention, such as:
○ O_2 requirement ≥ 40%
○ Hypotension requiring high dose or multiple vasopressors
○ Ventilator support required
○ CTCAE Grade ≥ 3 organ toxicity</td><td>• Extensive co-morbidities
• Age ≥ 70 years</td><td rowspan="2">• All of the above
• Tocilizumab
• Corticosteroids if symptoms do not improve within 4 hours after tocilizumab of if tocilizumab is not available</td></tr>
</table>

Subjects should be instructed, that symptoms associated with cytokine release syndrome/infusion reaction can occur within 48 hours following the administration of the APX005M. If such symptoms develop while at home, they should contact the Investigator and/or seek emergency medical care if appropriate.

TEAEs that are suspected to be drug related and occur during the study drug infusion or in the 48-hour post study drug infusion period are to be recorded individually. If multiple AEs occur at the same time, Investigators may choose to record (in addition to the individual events) the parent event of:

- IRR if several (≥2) AEs occur during infusion of APX005M

- CRS
    - if the combination of at least one event of both groups occurs

Group 1	Group 2
hypotension	fever
hypoxia	headache
shortness of breath	nausea
	rash
	tachycardia
	tachypnea

    - or any of the above AEs if concomitant with a laboratory result showing increased cytokines in the blood.

11.7.4.7 Any Other Possibly Immune Mediated Toxicity

• Grade 2: symptomatic treatment per local guidelines

• Grade 3-4: Consult Sponsor. Administer IV corticosteroids followed by oral corticosteroids until symptoms improve to Grade 2 or less. Consider adding prophylactic antibiotics for opportunistic infections. If symptoms worsen or for atypical presentation, consider an additional immunosuppressive measures per local guidelines.

11.8 Toxicity Management Guidelines

It is recommended to use institutional toxicity managing guidelines for symptomatic treatment according to local guidelines.

12 TREATMENT AND STUDY DISCONTINUATION

12.1 Treatment Discontinuation of Individual Subject(s)

A discontinuation from treatment is defined as a subject who is enrolled in the study and for whom study treatment is permanently discontinued for any reason.

The subject is free to discontinue from study treatment and/or withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The

investigator is also free to discontinue the subject from study treatment or to terminate a subject's involvement in the study at any time, if the subject's clinical condition warrants it.

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol specific follow up procedures as outlined in [Table 6: Schedule of Assessments], until the subject specifically withdraws consent for any further contact with her or persons previously authorized by the participant to provide this information.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result significantly outside of the reference range, the investigator will attempt to provide follow-up, until the condition stabilizes or no longer is clinically significant. All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication, must be reported (and 90 days for SAEs, pregnancies and AEs with potential immunologic etiology. If SAEs, they must be reported within 24 hours) and followed to resolution as above.

The following are discontinuation criteria from treatment for individual subjects:

- Subject develops radiological disease progression.
- Subject is required to receive another systemic anti-cancer treatment for underlying or new cancer.
- Subject develops unacceptable toxicity.
    - Failure to recover from a disease or treatment-related AE to baseline or ≤ Grade 1 within 8 weeks of last dose of investigational products (except Grade 2 alopecia, Grade 2 fatigue or Grade 2 skin toxicity), unless the subject is benefiting from therapy and after discussion with and approval by Sponsor
    - Failure to recover from an AE related to infusion reaction/cytokine release within 4 weeks of last dose of APX005M
    - Inability to reduce corticosteroid to ≤ 10 mg of prednisone or equivalent per day within 8 weeks of last dose of APX005M
- Subject becomes pregnant.
- Investigator decides it is in the subject's best interest to discontinue.
- Subject declines further treatment.

- Subject is noncompliant with the protocol based on the investigator or medical monitor assessment.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Death.

Subjects who discontinue study drug prior to progression, and enter the post treatment follow-up period, will be discontinued from the post treatment period if any of the following occur:

- Subject develops radiological progressive disease (i.e. PD) based on investigator assessment
- Subject initiates a new systemic anticancer treatment (first line of anticancer therapy after discontinuation of study drug)
- Death
- Subject declines further study participation (i.e. withdraws consent)
- Subject is lost to follow up despite reasonable efforts by the investigator to locate the subject

Sponsor (or designee) must be notified within 24 hours, if a subject is withdrawn from treatment. The primary reason for treatment discontinuation will be documented in the eCRF.

12.2 Study Discontinuation of Individual Subject(s)

Subjects who are withdrawn from study treatment will enter the follow-up period, unless study treatment discontinuation is due to any of the following:

- Subject death
- Withdrawal of consent for all study procedures
- Initiation of any anticancer therapy
- Subject is lost to follow-up
- Study termination by Sponsor

12.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for any cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required, if the study is stopped due to safety concerns. If sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

13 MANAGEMENT OF ADVERSE EVENTS/ASSESSMENT OF SAFETY

The Investigator's Brochure will be used as reference document for APX005M and will be provided to the investigators in the Investigator's File.

13.1 Adverse Events and Laboratory Abnormalities Reporting

13.1.1 Adverse Event

An adverse event (AE) is defined in the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice as "any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment" (ICH E6[R2]). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory findings), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Table 12: Classification of adverse events by causality

Not Related	The lack of a temporal relationship of the event to study treatment makes a causal relationship not reasonably possible, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation.
Related	The temporal relationship of the event to study treatment makes a causal relationship reasonably probable, and the event is more likely explained by exposure to the study treatment than by other drugs, therapeutic interventions, or underlying conditions.

13.1.2 Adverse Drug Reaction

An adverse drug reaction (ADR) is any noxious and unintended response to a medicinal product related to any dose administered. A causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

A serious ADR (SADR) is an ADR that meets the definition of serious (provided below)

13.1.3 Definition of a Serious Adverse Event and Serious Adverse Drug Reaction

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

• Results in death.

• Is life-threatening (this means the subject is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death, if it was more severe.)

• Requires in-patient hospitalization or causes prolongation of existing hospitalization.

• Results in persistent or significant disability/incapacity.

Or

• Is a congenital anomaly or birth defect.

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission, that includes a minimum of an overnight stay in a healthcare facility. Any adverse event that does not meet one of the definitions of serious (e.g. visit to A&E, out-patient surgery, or requires urgent investigation) may be considered by the investigator to meet the "other significant medical hazard" criterion for classification as a serious adverse event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization or disability, but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above. Medical judgement should be exercised in deciding whether such an AE should also be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

13.1.4 Events NOT to be Reported as Serious Adverse Events

For this study, the following are **not** considered SAEs and therefore do not need to be reported as such:

- Progression or deterioration of the malignancy under study (including new metastatic lesions) or death due to progression.
- Hospitalization for the performance of protocol-required procedures or administration of study treatment. However, hospitalization or a prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Hospitalization or procedures planned prior to study start. A pre-planned procedure must be documented in the source documents. However, hospitalization or prolonged hospitalization for a complication remains to be reported as an SAE.
- An elective hospitalization for a pre-existing condition unrelated to the studied indication.
- Hospital admission that is not associated with an adverse event (e.g. social hospitalization for purpose of respite care).
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusions remains to be reported as an SAE.
- Emergency out-patient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

• Overdose of study drug or concomitant medication unless the event meets SAE criteria (e.g. hospitalization). However, the event should still be captured as a non-serious AE.

13.1.5 SUSAR/Unexpected Serious ADR

A SUSAR/ Unexpected Serious ADR is a suspected unexpected serious adverse reaction. A suspected adverse reaction is an adverse event for which there is a reasonable possibility, that the drug caused the event. An unexpected adverse reaction is any adverse drug reaction, the specificity or severity of which is not consistent with the current investigator's brochure for APX005M. Also, reports that provide significant information on the specificity or severity of a known, already-documented adverse event constitute unexpected adverse events. An event more specific or more severe than described in the investigator's brochure would be considered "unexpected". All suspected adverse reactions related to APX005M which occur in the trial and that are both unexpected and serious (SUSARs/ Unexpected Serious ADR) are subject to expedited reporting.

13.2 Reporting of SAEs

Any clinical adverse event or abnormal laboratory test value that is serious and occurring during the course of the study (from the date of signing the informed consent), irrespective of the treatment received by the subject, must be reported to the sponsor within 24 hours following knowledge of the SAE (expedited reporting). For each subject, all serious adverse events must be reported up to 30 days after the last dose of investigational product, SAEs, pregnancies and AEs with potential immunologic etiology will be recorded up to 90 days after the last dose of investigational product, death, or initiation of new anticancer therapy, whichever occurs first. Serious adverse events occurring more than 90 days after a subject is discontinued from the study treatment, may be reported at the discretion of the investigator.

The completed SAE form must be sent to: pharmacovigilance@oncodrugconsult.com

The method of recording, evaluating, and assessing causality of AE and SAE, and the procedures for completing and transmitting SAE reports are provided in [Appendix 6: Adverse event definitions and additional safety information].

The sponsor will medically review all SAEs.

The following detailed information must be recorded for each serious adverse event in the SAE report form:

- The severity grade as assessed by the investigator according to the definitions in NCI-CTCAE Version 5.0
- The date of the SAE becoming serious and the date of acknowledgement (if different)
- The reason for seriousness
- The outcome of the SAE at the time of the report
- Information on administration of the study drug and chemotherapy and any action taken
- Information on any treatment procedures necessary for the SAE, concomitant medications, relevant lab tests, and relevant medical history

If the same SAE occurs on several occasions in the same subject, then the SAE in question must be documented and assessed anew each time.

The investigator is required to submit SAE follow-up reports, until the SAE has resolved or stabilized and all queries have been answered.

13.3 Reporting of SUSARs/Expedited Reporting of Unexpected Serious ADRs

The sponsor will ensure the notification of the appropriate ethics committees, competent authorities and participating investigators of all SUSARs occurring at the sites in accordance with local legal requirements, statutes and the European Clinical Trial Directive as follows:

- Reporting of the SUSAR to the competent authorities and ethics committees within 15 days (or within 7 days for fatal and life-threatening events)
- Information to all participating investigators of the SUSAR (with confirmation of receipt).

All events that require a new assessment of the risk-benefit ratio will be reported to the Ethics Committee and the Competent Authority of each concerned Member State within 15 days. This includes:

- Single reports of expected serious adverse reactions with unexpected outcome.
- An increase in the rate of occurrence of expected serious adverse reactions, which is judged to be clinically relevant
- Post-study SUSARs that occur after the subject has completed a clinical trial
- New events related to the conduct of the trial or the development of the investigational medicinal products which are likely to affect the safety of the subjects.

The sponsor is responsible for ensuring, that the latest investigator's brochure is used as the source document for determining the expectedness of an SAE.

13.4 Recording of Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by subjects are properly recorded in the subjects' medical records and the electronic case report form.

The investigator must assign the following adverse event attributes:

- AE Term
- Severity grade according to the NCI CTCAE criteria Version 5.00
- Start date and stop date (or date of last assessment)
- Outcome
- Causality to study drug and chemotherapy (to be assessed as either related or unrelated)
- Any action taken

Adverse events will be followed until they have resolved to baseline or are considered stable. It will be left to the investigator's clinical judgment to determine, whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arise, the subject should be strongly encouraged to undergo end-of-study assessment and be under medical supervision, until symptoms cease or the condition becomes stable.

Pre-existing diseases that become worse during study therapy, must be considered as adverse events. They can progress to serious adverse events, if they meet the criteria described in Section 13.1.3.

13.4.1 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

13.4.2 Adverse Events after the 30 day Follow Up Period

At any time after a subject has completed the study, if an Investigator learns of any SAE (including sudden death of unknown cause), and he/she considers there is a reasonable possibility, that the event is causally related to the investigational product(s), then the investigator should notify sponsor.

After study treatment completion (i.e. after any scheduled post treatment follow-up period has ended), there is no obligation to actively report information on new AEs or SAEs occurring in former study subjects. This includes new AEs/SAEs in subjects still being followed up for survival, but who have completed the post treatment follow up period (30 days or 90 days for SAEs, pregnancies and AEs with potential immunologic etiology).

13.4.3 Causality Collection

The Investigator will assess causal relationship between each Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational products?

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in [Appendix 6: Adverse event definitions and additional safety information to the Clinical Study Protocol].

13.4.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms, that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

13.4.5 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results pages of the eCRF. In the event of unexplained abnormal laboratory test values, the tests should be repeated and followed up, until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

Laboratory test value abnormalities should not be reported on the AE page of the eCRF as adverse events, unless they are treatment-emergent, and they satisfy one or more of the following conditions for clinical significance:

1. Accompanied by clinical symptoms
2. Leading to a change in study medication (e.g., dose modification, interruption, or permanent discontinuation)
3. Require a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)

Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value).

Please note: Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an adverse event in the eCRF.

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination, as compared with the baseline assessment, will be reported as an AE unless unequivocally related to the disease under study.

13.4.6 Adverse Events of Possible Hepatic Origin

See [Appendix 18.9: Liver Safety Monitoring and Assessment] for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in Liver Function Tests value ([LFT], e.g., AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction. Subjects with AEs of hepatic origin accompanied by LFT abnormalities should be carefully monitored.

13.4.7 Disease Progression

Disease progression can be considered as a worsening of a subject's condition, which is attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study, and/or increase in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer, should be

considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

13.4.8 New Cancers

The development of a new primary cancer should be reported as an AE and would in most cases meet seriousness criteria (except for some non-melanoma skin cancers). New primary malignancies are new cancers, that are not the primary reason for the administration of the study treatment, which have developed after the inclusion of the subject into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are disease progression.

13.4.9 Lack of Efficacy

Events that are clearly consistent with the expected pattern of progression of the underlying disease, should not be recorded as AEs nor as lack of effect.

13.4.10 Deaths

All deaths that occur during the study (i.e. from the time of signing the informed consent), or within the protocol defined 30 days post study follow up period (after the administration of the last dose of study treatment), must be reported as follows:

• Death which is clearly the result of disease progression should be reported to the sponsor at the next monitoring visit and should be documented in the eCRF but should not be reported as an SAE.

• Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death, must be reported to the sponsor as a SAE within 24 hours.

The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the eCRF. Deaths with an unknown cause should always be reported as a SAE. A post-mortem autopsy may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to sponsor within the usual timeframes.

13.4.11 Pregnancy

Female subjects must be instructed to immediately inform the investigator, if they become pregnant during the study. The study treatment must immediately be discontinued, and the subject must be withdrawn from the study. Pregnancies occurring up to 90 days after the completion of the last treatment cycle must also be reported to the investigator. The investigator must report all pregnancies within 24 hours of acknowledgement to Sponsor. The investigator should counsel the subject; discuss the risks of continuing the pregnancy and the possible effects on the fetus. The subject should be monitored until the conclusion of the pregnancy.

13.4.12 Adverse Drug Reactions with Concomitant Medication

The investigators must be aware, that for all concomitant medications the regulations of post-marketing reporting for suspected adverse drug reactions apply, i.e. reporting to the marketing authorization holder or the local regulatory bodies.

13.5 APX005M Adverse Events of Clinical Interest

Adverse Events of Clinical Interest should be reported, in the same format and timeframe as SAEs, even if the events do not meet the definition of SAEs. The events should be reported as described in section 13.2.

13.5.1 Infusion-Related Reaction/Cytokine Release Syndrome

Acute reactions following administration of APX005M have been observed. Such reactions may occur at any treatment cycle, predominantly within 48 hours following the APX005M administration, and the underlying mechanism may involve CD40-mediated cytokine release. Associated symptoms may resemble infusion-related reaction (IRR) or cytokine release syndrome (CRS).

13.5.2 Hepatic Impairment

Transaminases and Bilirubin Increase

Treatment-emergent elevations in liver transaminase levels have been observed in some subjects receiving APX005M either as monotherapy or in combination with other agents. These events were

mostly mild to moderate in severity (≤ Grade 2), generally transient in duration (≤ 48 hours), observed 2–7 days after APX005M infusion and had resolved to baseline by the time of the next cycle. Many of the subjects had known liver metastases, suggesting that the presence of liver metastasis may potentially increase the risk of transaminitis following APX005M administration.

13.5.3 Treatment-Emergent Hematologic Abnormalities

Treatment-emergent reductions in white blood cells or platelets was observed following infusion of APX005M and are considered to be a pharmacodynamic effect of CD40 activation due to a redistribution of these cells between different compartments. These changes were transient, predominantly mild or moderate in severity, and blood counts generally recovered to baseline by the beginning of the subsequent cycle.

14 STATISTICAL METHODS

A summary of the general statistical analysis methods is provided below; full details will be provided in a separate Statistical Analysis Plan (SAP). A change to the data analysis methods described in the protocol, will require a protocol amendment, only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock.

14.1 Analysis Populations

The full analysis set (FAS) will consist of all subjects initiating trial treatment (safety population). Exclusions from the FAS may be made, if deemed reasonable based on ICH-E9 guidance criteria (cf. Section 5.2.1 in ICH E9 guidance) In order to avoid bias in the assessment of the primary efficacy endpoint, subjects without evaluable disease at screening, will be excluded from the FAS. The safety analysis set (SAF) will consist of all subjects initiating trial treatment with no exclusions.

14.2 Demographics and Baseline Characteristic

Descriptive statistics will be used to summarize demographics and baseline characteristics. Medical history, medications used prior to treatment, and concomitant medications will be summarized by treatment group. The number of subjects in each of the analyzed study populations will be described. Subjects who discontinue study drug, or are removed from the study prematurely, will

also be reported. Reasons for study drug discontinuation, and time of withdrawal from the study, will be described.

Subject characteristics at entry into the study, will be summarized in frequency tables, and descriptive statistics will be provided for quantitative variables.

14.3 Efficacy Analysis

Analyses of efficacy endpoints are described below. ORR, PFS, and DCR will be summarized by treatment arm and by treatment arm and stratification factors. Supportive analyses, including any sensitivity analyses that may be performed will be detailed in the SAP.

14.3.1 Primary Endpoint Analysis

14.3.1.1 ORR at 12 Weeks

The primary endpoint is ORR at 12 weeks according to investigator. The overall response rate (ORR) is defined, as the proportion of subjects with measurable disease at baseline, which achieve a complete or partial objective response as best response through 12 weeks based on the RECIST V1.1[Appendix 1]. ORR will be calculated together with an exact binomial two-sided 60 % confidence interval.

In case complete pathological remission is documented by surgery, the subject will be considered in complete remission (CR).

14.3.2 Secondary Endpoints Analysis

14.3.2.1 ORR at 24 Weeks

Analyzed similarly as ORR at 12 weeks.

14.3.2.2 Progression-Free Survival

PFS will be estimated with Kaplan-Meier methods based on the time from start of treatment to progression or death by any cause. PFS will be censored at the date of last disease evaluation before new anti-cancer treatment.

14.3.2.3 Assessment of Subject Reported Outcomes

Quality of Life scores, assessed by EORTC's general EORTC QLQ-C30 and EORTC QLQ-OV28 questionnaires, will be calculated using EORTC's Scoring Manuals. Scores will be calculated for each individual subject at selected visits.

At each evaluation the number of subjects completing the questionnaire, and the main reason for not completing the questionnaire, will be presented.

Each individual scale at baseline, and the percentage change from baseline, will be presented per treatment group using descriptive statistics. Graphical summaries of subject values (e.g. median) across the trial period, will be presented per treatment arm for each scale.

All subject scores will be listed by visit. In addition to the global health status, subscales describing level of functioning and symptoms will be listed per subject and visit.

The EORTC QLQ-C30 and EORTC QLQ-OV28 Scoring Manuals describe an elementary method of calculating scale-scores, when there are a few missing values for some items, where subjects may have failed to complete all items on a form, possibly accidentally. If at least half of the items from the scale have been answered, it will be assumed, that the missing items have values equal to the average of those items, which are present for that respondent. This is algebraically equivalent to using all items, which were completed, and applying the equations already given under EORTC's "Scoring procedures" for calculating the scale scores. Quality of life at each measurement will be summarized by treatment arm, and changes in Quality of life over time will be compared between treatment arms using a repeated measures approach. More specifically, the analysis will assess the adjusted treatment group mean differences in change from baseline on the respective PRO domains from a longitudinal mixed-effects model repeated measures (MMRM) in both adjusted and unadjusted models. Assessment visit will be treated as categorical variable in each model.

The MMRM model for assessment of the treatment effect will be in accordance with the analysis of the PRO endpoints i.e.:

• An adjusted model including treatment arm, visit, baseline PRO domain score, and randomization stratification variable.

• An unadjusted mixed model including only treatment arm, visit, and baseline PRO domain score.

All mixed models will include a fixed-effect interaction term between visit and treatment arm and a random effect for subject. Restricted Maximum Likelihood estimation will be applied as the primary method.

To present the results, the following statistics will be cited from the mixed models: Least squares mean (LS Mean), difference in LS Mean between two treatment arms and 95% CIs for the

differences. The standard error (SE) will be also calculated for each LS Mean. A P-value will be presented testing the difference in LS Mean change from baseline between treatments. Line plots will depict the adjusted mean and SE of the predicted change from baseline for the post baseline assessments.

14.3.2.4 Disease Control Rate at Week 12 and 24

The analysis of disease control rate according to investigator assessment will be performed for each treatment arm by calculating the point estimate of the percentage of subjects in the treatment arm, who have complete response or partial response or stable disease for at least 12, 24, and 48 weeks respectively as best overall response, assessed according to RECIST 1.1 criteria. The DCR will be presented in the same way as the ORR.

14.3.2.5 Safety and Tolerability

The safety analysis population will include all subjects who received at least one dose of study treatment and had at least one valid post baseline safety assessment. The statement that a subject had no AEs (on the Adverse Event eCRF) constitutes a valid safety assessment. All safety parameters will be summarized and presented in tables. Safety will be determined by AEs, laboratory tests, vital signs, performance status and ECG. All AE data will be reported in listings. Summaries of AE by the terms from the Medical Dictionary for Regulatory Activities (MedDRA), NCI CTCAE grade, seriousness and relationship to study treatment will be presented, as well as summaries of AEs leading to death and premature withdrawal from study treatment. For laboratory data, summary tables of change from baseline over time based on Standard International (SI) units will be displayed. Shifts in toxicity grade from baseline to the worst grade observed during treatment will be presented for selected laboratory parameters. Descriptive statistics will be used to summarize ECOG performance status. Vital signs and electrocardiograms will be reported in the listings. Exposure to study medication will be summarized by total duration of study medication, number of cycles started and cumulative dose using descriptive statistics. Dose interruptions and their reasons will be presented by schedule and dose level.

14.4 Interim Analysis and Missing Data

No interim analysis is planned.

A safety analysis will be performed after six subjects in arm B and six subjects in arm C have been included and received the 1st cycle of therapy (4 wks).

No imputation of missing data will be performed. For time to event endpoints missing data will be handled by censoring.

14.5 Sample Size

To at least keep track of the ORR on Standard of Care at the descriptive summary level, randomization will be 1:2:2 to SoC, SoC+APX005M, or SoC+APX005M+RT. No direct comparison of treatment arms will be performed. Assuming a response rate of 65 % in the experimental arms, with n=36 in each of these arms corresponding to a total N=90 based on a binomial test, we will have approximately 80 % power at the one-sided 20 % significance level to rule out a response rate of 50 %.

15 EXPLORATORY/TRANSLATIONAL RESEARCH

Translational studies will be exploratory in nature. In-depth immune profile and immune responses of blood and tumor tissue will be conducted to assess T cell infiltration, persistence and function in all subjects enrolled in the study. Deep molecular and cellular interrogation of the subjects by assessment of blood and tumor tissue is crucial for our understanding of how therapy increases TILs and reprograms the tumor microenvironment.

15.1 Exploratory Translational Objectives of the Study

The exploratory translational objectives of the study are as following**:**

1. Test the ability of the combinatorial treatment to reprogram the tumor microenvironment and convert cold tumors to T-cell inflamed tumors.
2. Assess the overall effects of the combined chemo-immuno-radiotherapy on the tumor microenvironment.
3. Understand whether the combined chemo-immuno-radiotherapy induces de novo infiltration of tumor specific T cells in the tumor.

4. Assess the overall effects of the combined chemo-immune-radiotherapy on antigen specific CD8+ T cells.
5. To investigate the overall effects of the combined chemo-immuno-radiotherapy on peripheral blood.

All analyses described below have been established and will be performed at the Center for Experimental Therapeutics (CTE) at the Ludwig Institute branch of Lausanne. The CTE laboratories work in compliance with GLP/GCLP guidelines regarding handling, processing, storage and traceability of clinical trial samples, assay standardization, data management and documentation required. Most assays developed to date have been validated in the context of clinical trials. The CTE laboratories are Standard Operating Procedure (SOP)-driven and quality controlled.

Test the ability of the combined therapy to reprogram the tumor microenvironment and convert cold tumors to T-cell inflamed tumors.

Hypothesis: The combinatorial strategy will induce important changes in the tumor microenvironment, which will lead to increase the infiltration of T cells. This hypothesis will be tested by comparing matched biopsies obtained at baseline and following 3 cycles of treatment for either Arm A, B, or C.

Deep immune phenotyping can be achieved using multiple methods and collecting multidimensional data as detailed below.

a) Assessment of immune protein profiling in tumors

To delineate the profile of the immune infiltrate and have a comprehensive immune phenotype protein analysis of the tumor microenvironment, we will perform the Nanostring's GeoMx Digital spatial Profiler (DSP), which is a 90-plex protein expression assay in FFPE biopsy samples. The 90-plex protein panel allow us to investigate immune cell typing, immune activation status and signalling pathways. This analysis will reveal global tumor microenvironment signature before and after treatment and will be correlated with response to combined therapy and patient outcome.

b) Immune landscape

The assessment of the interactions between tumor cells and the immune system within the tumor microenvironment (pre- and post-treatment), will be performed using multiplexed immunohistochemistry in formalin-fixed, paraffin embedded tumor biopsy samples. Multispectral imaging and linear unmixing offers the ability to analyse tumor slides stained with multiple antibodies, in a comprehensive, spatially oriented and quantitative fashion, each. Based on the results obtained with GeoMX analysis, specific panels will be customized and optimized. Those panels will be used to stain and quantify immune cells comparing tumor biopsies collected before and after treatment. The immune landscape in the tumor microenvironment will be correlated with other translational parameters and with clinical responses.

Assess the overall effects of the combined chemo-immuno-radiotherapy on the tumor microenvironment
Hypothesis: The combinatorial strategy will induce important changes in the tumor microenvironment. This hypothesis will be tested by comparing matched biopsies obtained at baseline and following 3 cycles of treatment for either Arm A, B, or C.
Similar analyses as above will be conducted on paired tumor biopsies.

Understand whether the combined chemo-immuno-radiotherapy induces the de novo infiltration of tumor specific T cells in the tumor.
Hypothesis: The combinatorial strategy will induce de novo infiltration of tumor specific T cells in the tumor. This hypothesis will be tested by comparing matched biopsies obtained at baseline and following 3 cycles of treatment for either Arm A, B, or C.

c) TCRseq

T cell infiltration will be quantified using TCR sequencing, which allow quantification of both alpha and beta variable regions. This method provides a high-resolution view of T cell clonal distribution pre- and post- therapy in tumor.

To investigate the overall effects of the combined chemo-immuno-radiotherapy on peripheral blood.
Hypothesis: The combinatorial strategy will induce changes on the phenotype and the reactivity of circulating immune cells.
This hypothesis will be tested comparing plasma obtained at different time points.

Serum/plasma analyses

Parallel with profiling of tumor samples, serum or plasma will also be analysed. Serum or plasma samples can be informative of the host/tumor interaction and contribute to the general description of the immune status of patients. The screening will be performed using Meso Scale Discovery (MSD) for establishing circulating cytokines and chemokines markers using a 9-plex assay.

Circulating tumor DNA analysis

To measure the DNA carrying specific somatic genomic alterations, we will perform a digital polymerase-chain reaction assay in plasma at different time points. This analysis will highlight somatic genomic alterations in individual tumors and offer better understanding of the tumor dynamic underlying response or resistance to therapy. The detection of targetable mutations could also allow future treatment strategies.

CYTOF

In parallel with spatiotemporal description of the tumor microenvironment, we will also perform high-dimensional multiparametric single-cell analyses using CYTOF, a microfluidic-based cell phenotyping assay which can iteratively interrogate multiple parameters at the same time. CYTOF will be used to quantify, profile and phenotype lymphocytes.

Peripheral blood drawings will be performed during the trial in order to address multiple translational research endpoints. Fifty ml (50 ml) of heparinized blood will be drawn for the preparation of PMBCs and plasma and 10 ml of native blood will be drawn for serum preparation. Blood collection, processing and analyses will be performed by CTE lab.

Table 13: Tissue collection

Timepoint	Sample type	Sample amount	Collection material	Assays
As indicated in Table 6: Schedule of Assessments	Archival tissue / fresh tissue in FFPE	1 block or 15 blank unstained serial sections	FFPE	Immuno-landscape IHC NanoString GeoMx
	Fresh tumor tissue (either new biopsy or surgical material) in FFPE	1 block or 15 blank unstained serial sections	FFPE	Immuno landscape NanoString GeoMx

Table 14: Blood collection

Timepoint	Sample type	Sample amount	Collection material	Assays
As indicated in Table 6: Schedule of Assessments	Whole blood / serum	10 ml	Vacutainer red top tube	Cytokines, chemokines
	Whole blood /PBMC /plasma	50 ml	Heparinized tubes	Immune phenotype
	Paxgene DNA	2.5 ml		
	Paxgene RNA	2.5 ml		RNAseq/TCRseq
	Paxgene BloodccfDNA	10ml		Circulating DNA

Tissue and blood samples for exploratory biomarker analyses will be collected at the time points indicated in [Table 6: Schedule of Assessments]. Complete instructions on the collection, processing, handling, and shipment of all samples described herein, will be provided in a separate procedure manual. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last subject's last visit for the study at CTE, a facility selected by the sponsor to enable analysis of biomarkers.

16 ETHICAL, REGULATORY AND ADMINITRATIVE ASPECTS

16.1 ICH/GCP

This protocol is in accordance with the principles of the Declaration of Helsinki as set forth at the 18th World Medicines Association (Helsinki 1964) and amendments thereto. The most current amended version will be in effect.

The procedures set out in this protocol are also designed to ensure that Sponsor and investigator abide by the principles of the GCP guidelines of the ICH and in keeping with local legal requirements.

This protocol is made with consideration of protecting the subjects' and the participating staffs' personal data to ensure the rights of the registered, as laid out in the EU GDPR.

16.1.1 Regulatory Authority

The protocol plus all relevant study documents will be submitted to the concerned regulatory agencies for approval prior to the study start. No subject will be admitted to the study until appropriate regulatory approval of the study protocol has been received.

16.1.2 Independent Ethics Committee/Institutional Review Board

Before implementing the study, this protocol and any material provided to the subject (such as advertisements, subject information sheets, drug dosing diaries, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to the IEC/IRB. This also applies to protocol amendments.

A signed and dated statement that the protocol and ICF have been approved must be given to PI on site before any subject(s) can be admitted in the study.

16.2 Confidentiality

The study will be conducted in accordance with applicable regulations. All data generated in this study will remain confidential. All information will be stored securely at the relevant coordinating sites and will only be available to people directly involved with the study, the subject's personal physician or other appropriate medical personnel responsible for the subject's welfare. No personal information that reveals the subject identity will be entered into the eCRFs or the study database. The subjects will be provided a study ID (subject number) that links the subject identity to the information stored in the eCRF (pseudonymization). Data generated in this trial needs to be available for inspection on request by Sponsor, the Sponsor's representatives, by the IEC and the regulatory authorities, e.g. CA.

16.3 Participant Information

Before entering this trial, all eligible subjects will receive oral information from the investigator or a delegated physician at the institution. Afterwards the subjects will receive the written participant information describing the aim of the study, as well as information of probable and possible side effects and risks.

The subjects must have the opportunity to ask questions, and to consider participation together with her relatives. It must be emphasized that the participation is voluntary, and that it is the right of the subject to refuse further participation in the study whenever she wants, and that this will not influence her subsequent care. The participant information will be written by the sponsor of the study to be accepted by the respective ethics committee and regulatory authorities.

16.3.1 Informed Consent

Prior to trial entry the subject must give written consent after being informed as described above. A copy of the signed and dated ICF will be retained by the subject and the original will be filed at the site. The informed consent procedure must conform to the ICH guidelines for GCP and the rights of the registered, as set forth in the GDPR.

16.4 Protocol Approval and Amendment

Protocol amendments must be made only with the prior approval of Sponsor, except when necessary to eliminate an immediate hazard to subjects. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent documents. The IEC/IRB must be informed of all amendments and give approval prior to their implementation. Sponsor or it's collaborators will submit any study protocol amendments to the concerned regulatory authorities for approval and keep the investigator(s) updated as detailed in the ICH GCP guidelines.

16.4.1 Data Quality Assurance

Data will be collected using an electronic data capture system (OpenClinica) by remote data entry on eCRFs, except for the paper forms:

• SAE form

The list of staff members authorized to enter data, must be identified on the signature and delegation log and sent to Sponsor by the PI or study nurse, prior to start of the study. Staff appearing on the signature and delegation log, must also sign a document stating that they give their consent to the processing of their personal data.

To enter the electronic data system, the investigator or other staff member need to use the username and password that are issued personally to them.

It remains the responsibility of the PI that data are entered in the database as soon as possible, no later than 10 working days after patients visit, and that the electronic forms are filled out completely and correctly.

Sponsor and the monitor will perform consistency checks on the received data and will issue queries in case of inconsistent data. The queries for the electronic forms will appear in the eCRF system and must be answered there directly.

The queries for the SAE forms will be sent to the site by email from the CRO and must be printed, answered and signed by the PI (or an authorized staff member) as soon as possible. The original form must be returned to CRO and a copy must be stored at site.

SAE forms will be distributed to the sites by Sponsor.

16.4.2 Source Data

The investigator will maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

A source data list will be prepared at each participating site at the time of trial start.

The investigator will provide direct access to source data and documents for trial-related monitoring, audits, IRB/IEC review and regulatory inspection.

16.4.3 Subject Identification

A sequential identification number will be attributed to each subject registered in the trial. This number will identify the subject and must be included on all eCRF pages and forms. The investigator must keep a separate list where the identity of all treated subjects can be found at a secure location, in accordance with the rules set forth in the GDPR.

16.5 General Data Protection Regulation (GDPR)

The study will be conducted in accordance with the GDPR. As the data controller for this study NSGO-CTU is responsible for a vast amount of personal data of registered people in relation to the study. A Privacy Policy will be sent out to groups, sites and other relevant collaborators. Participating subjects will be informed about the data protection in the subject information.

16.6 Investigators Responsibilities

The site will be authorized to register or randomize subjects in this trial only when they have returned the following documents to the project manager:

• Signed Clinical Trial Agreement between Sponsor and participating site.

• Investigator agreement page signed by PI.

• Signature and delegation log have been signed by all delegated study staff and PI.

• Signed 'Consent-to-Processing-of-Personal-Data' (included in the delegation log).

• Updated, signed and dated Curriculum Vitae and certificate of latest GCP training for PI and all other staff members on the signature and delegation log.

• List of the normal ranges from the laboratory/laboratories which the site is using in this trial, dated and signed by the PI and an accreditation, certification or other validation for these laboratories.

• Signed User Request Forms for the eCRF (OpenClinica) from all study staff that need access to the eCRF system.

•Signed Financial Disclosure Form

As soon as all the documents have been received by the project manager, PI will receive an activation letter and will be allowed to register/randomize subjects in the study. Randomization from sites not (yet) activated is not possible.

16.7 Study Monitoring

This study will be monitored by an external company appointed by Sponsor. A representative will be responsible for verifying the eCRF's adherence to the protocol for completeness, accuracy, and consistency of the data and adherence to local regulations in the conduct of clinical research.

16.8 Independent Data Safety Monitoring Committee

An Independent Data Safety Monitoring Committee (IDSMC) will be established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participating subjects in the trial.

The composition of the IDSMC will consist of three independent individuals, including one biostatistician and two physicians. The IDSMC is tasked with making a recommendation to the Sponsor to continue or stop the trial, based on their assessment of safety information.

Additional information regarding IDSMC can be found in the IDSMC charter.

16.9 Trial Steering Committee

A Trial Steering Committee will be composed of Sponsor representatives, study chair, the PI of each participating country involved in the trial and of other external participants, as needed. The

Steering Committee will meet regularly, in person or by phone, to review the progress of the trial in all clinical sites including recruitment, problems with protocol compliance, unexpected toxicities and need for protocol amendments. The study chair will be the chair of the Trial Steering Committee.

16.10 Archiving of Study Documents

Essential documents including subject data must be retained by the investigator for as long as needed to comply with national and international regulations, but for a minimum of 15 years after end of the study.

16.11 Financial Disclosure

The Investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study; any significant payments of other sorts from the Sponsor or Apexigen, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria; any significant equity interest in the Sponsor. In consideration of participation in the study, the Sponsor will pay the Investigator, study site or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

16.12 Trial Budget and Financing

The trial is planned by NSGO-CTU with a grant from Apexigen. Apexigen will provide (free of cost) APX005M. NSGO-CTU has no financial affiliation to Apexigen. The trial is being conducted in the auspices of ENGOT and GCIG. Other ENGOT/GCIG groups are participating in the trial. The relevant ECs will be informed of the names of the sites provided grants and exact amounts.

Sponsor will pay the investigator, study site or nominated payee the sums set out in the payment schedule attached to the investigator agreement. The money covers the costs associated with the implementation of the study.

16.13 Trial Insurance

Subjects entered in this study will be insured according to the laws and regulations in the different countries.

16.14 Publication Policy

All results regardless of their positive or negative outcome will be published in a peer reviewed journal soon after the primary endpoint is mature. Other results on the secondary endpoints will be published as these endpoints are mature. The ENGOT authorship rules will apply to this trial [Appendix 7]

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18 APPENDICES

18.1 Appendix 1: Response Evaluation Criteria in Solid Tumors (RECIST), v.1.1

Eisenhauer EA. New Response Evaluation Criteria in Solid Tumors: Revised RECIST Guideline (Version 1.1). European Journal of Cancer 45 (2009) 228–247

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.
a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Reproduced from: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45: 228-47.

18.2 Appendix 2: Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

18.3 Appendix 3: Eastern Cooperative Oncology Group (ECOG) Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Source: Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair. Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655. Available at: http://ecog-acrin.org/resources/ecog-performance-status

18.4 Appendix 4: EORTC QLQ–C30 & QLQ-OV28 Quality of Life

QLQ-C30: https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf

QLQ-OV28: https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-OV28-English.pdf

18.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

18.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range maybe used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

18.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Progestogen-only subdermal contraceptive implant[b,c] IUS[c] Non-hormonal IUD Bilateral tubal occlusion
Azoospermic partner (vasectomized or secondary to medical cause)

This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

18.6 Appendix 6: Adverse event definitions and additional safety information

Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death

- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above.

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity rating scale:

The grading scales found in the revised National Cancer Institute CTCAE latest version (5.0) will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used.

For each episode of an adverse event, all changes to the CTCAE grade attained as well as the highest attained CTC grade should be reported.

It is important to distinguish between serious and severe AEs. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria. On the other hand, a stroke that results in only a

limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria.

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? Sponsor would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.
- In difficult cases, other factors could be considered such as:
- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

18.7 Appendix 7: Guideline for Authorship for Trials run within ENGOT

18.7.1 Guidelines for Authorship for Trials run within ENGOT

Update June 2017/Approval October 2017 at ENGOT Assembly

https://engot.esgo.org/media/2019/10/ENGOT-Guidelines-for-Authorship-update-June-2017.pdf

18.7.2 ENGOT-GOG publication guidelines 2021

Publication Policy is based on the guidelines described in the Joint ENGOT and GOG-Foundation Requirements for Trials with Industry Partners (Vergote I, Coleman RL, et al. Joint ENGOT and GOG Foundation requirements for trials with industry partners. Gynecol Oncol. 2019 Aug;154(2):255-258. doi: 10.1016/j.ygyno.2019.04.677). The publication policy will follow the Company publication policy and is in conformity with the guidelines subject to agreement with the non-GOG/ENGOT countries. Authors of the

manuscript must fully comply with the International Committee of Medical Journal Editors (ICMJE) criteria regarding authorship.

a. General.

i. Authorships and Co-authorships are not granted by individual institutions but by groups for GOG and ENGOT groups. For non-GOG/ENGOT countries, authorships and co-authorships are granted by individual institutions. A waiver (e.g. for surgical trials) must be defined prospectively before and accepted by GOG and ENGOT before an GOG and ENGOT number is given to the trial.
ii. All calculations regarding the number and position of co-authorships will be based on numbers of recruited patients by group or institution, unless a protocol defines a specific exception (i.e. numbers according to individual recruitment per centre).
iii. Each GOG and ENGOT group is free and independent to fill in individual names according to its number and position of co-authorships (the group even may appoint persons not having recruited patients by themselves). However, general guidelines as the NIH guideline should be respected during this selection process by the study groups.
iv. All specific modifications for every Intergroup trial should be specified before study start and amended to the general principles in written mode as appendix to the intergroup agreements.
v. If possible, all centres who have actively recruited in the trial should be mentioned at least as co-authors in the appendix.
vi. The following "rules" should guarantee participation and benefits with respect to scientific publications for all groups involved and share as much attractive positions among the groups as possible.

b. Fixed authorship positions for publication of the primary analysis (including the primary endpoint).

i. All co-authorship positions depend on recruitment of groups except one authorship position of the International Principal Coordinator (appointed by leading group) of GOG and ENGOT and, in phase II/III studies additionally one for the statistician of the study (usually 4th position). Both positions do not count for calculation of positions per group
ii. No further fixed positions of prominent authorship positions (e.g. 2nd, 3rd, or senior) should be granted to Co-PI etc., to avoid de-motivation for the groups and countries. ENGOT policy is not to allow co-PI-ship in any trial.
iii. International Principal Coordinator is first author or senior author depending on the occasion unless he grants this to anyone else. Usually, PI is first author of the main manuscript and can be co-author in subproject papers. In the latter cases first authorship is given to a leader of a respective subproject and PI is senior author (or co-author at another position if subproject demands both most prominent positions being provided to the subproject working group).
iv. The best recruiting group can choose between 2nd author or senior author; in the latter case 2nd author would be granted to the 2nd best recruiting group, 3rd author by the 3rd best recruiting group etc. (example see below). If the leading group is the best recruiting group, they are treated as 2nd best recruiters and the senior (or 2nd position) is given to the next best recruiting group to avoid both, 1st and senior authorship be given to one study group and motivating all groups to recruit well.
v. Co-authorship positions of a potential industrial sponsor (not a study group) could be foreseen on a case by case basis, however, this should be stated in the agreement upfront and should be rather the exception than the rule. The positions authors of the industrial sponsor should not be amongst the first 4 positions nor the senior (last) position, and restricted to a maximum of 10% of the total number of authors.

vi. If NON-GOG/ENGOT groups participate as cooperating group within a joint GOG/ENGOT trial they have the same rights as GOG/ENGOT groups (e.g. getting the senior authorship if they recruit best).

c. Number of authors per group for publication of the primary analysis (including the primary endpoint).

i. Each group receives their first guaranteed authorship position when the group has recruited 1-2% of the total number of patients. The exact cut-off (1 or 2%) must be specified in the protocol (commonly the larger the study is the lower the threshold should be).
ii. All other authorship positions granted to ENGOT will be distributed to the ENGOT groups according to the ENGOT publication rules and will reflect proportional accrual.
iii. Further positions are granted according to recruitment numbers and depend on the total number of authorships possible. The latter defines the number of recruited pts per co-authorship position (e.g. if overall 30 positions are available per definition of the journal/congress or other and 10 groups participated, 18 positions would be available for further distribution after PI, statistician and the first co-author of each study group had been settled).
iv. The first authorship per group is defined by the lowest recruitment number of the last group classifying for authorship (i.e. have recruited more than 1 or 2%) and is the same for all groups. E.g. 10 groups participate in a trial with 1.000 pts. and 9 of the groups have recruited more than 10 pts. and, therefore, qualify for authorship. Among the 9 groups the lowest recruitment was 15 pts. in group X and considerable higher numbers in the remaining 8 groups. In this case, the pts. equivalence for the first authorship position per group is 15 pts. Summing up all recruitment numbers for the first authorships (in our example 9 x 15 pts = 135 pts) and subtracting them from all 1,000 recruited pts. will give the number for calculation of the further recruitment rate necessary per authorship position; in this example 1,000 – 135 = 865 which is the number for calculation of further additional authorship positions. If, in this example, 18 more co-authorship positions are available, each authorship position is qualified by 865 : 18 = 48 pts/position.

d. Position of the authors for publication of the primary analysis (including the primary endpoint).

i. The specific place of the group's representative is defined by the overall recruitment by the group; e.g. if group A has the highest recruitment number, group B the 2nd highest recruitment number, group C the 3rd highest, etc. group A would deserve the senior authorship position, group B the 2nd authorship position and group C the 3rd authorship position etc.
ii. If the leading group is also the highest recruiting group a waiver gets active and the 2nd highest recruiting group gets the senior authorship position and the leading group is regarded as 2nd highest recruiter – to avoid that the leading group has 1st and last authorship position in an ENGOT intergroup trial.

Example: the whole trial recruited 1,000 pts. Groups A-H participated and group A was leading group. The 1% limit was 10 pts. The target Journal allows 25 authors

- *Group H had the lowest recruitment and had 2 pts.*
- *Group G had the 2nd lowest with 9 pts.*
- *Group F recruited 19 pts.,*
- *Group E recruited 39 pts.,*
- *Group D recruited 48 pts.*
- *Group C recruited 183 pts,*

- *Group B recruited 325 pts*
- *Group A recruited 375 pts.*

The calculation resulted in the following authorship distribution:

- *Group H: no authorship per first round (leftover = 2 pts.)*
- *Group G: no authorship per first round (leftover = 9 pts.)*
- *Group F received 1 authorship for 19 pts. (> 1% threshold passed; thus defining 19 as prerequisite per authorship position)*
- *Group A-E receive their first authorship with 19 pts. each. Which makes A-F x 19 = 6 x 19 = 114 pts. That leaves 1,000 – 114 = 886 for further distribution.*
- *The leading group has the 1st position (as PI), the statistician has position 4, groups A-F have 6 further positions including senior, so 17 further positions can be distributed. => 886: 17 = 52 pts/position.*
- *As group A was leading and best recruiting group, therefore senior authorship goes to group B and group A gets 2nd position. Group C gets 3rd position, group D gets 5th position, group E gets 6th position, and group F gets 7th position – leaving position 8-24 for the remaining positions:*
- *Overall, group A would receive 7 authorships (plus PI): 1 on position 2nd for pts 1-19 and 6 for patients 20-331 – 52 per position) – leftover 44 pts*
- *Group B would receive 6 authors (1 = senior author for pts 1-19 and 5 for pts 20-279) – leftover 46 pts*
- *Group C would receive 4 authors (1 for pts 1-19 and 3 for pts 20-175) – leftover 8 pts*
- *Group D would receive 1 author (1 for pts 1-19) - leftover 29 pts.*
- *Group E would receive 1 author for pts 1-19 - leftover 20 pts*
- *Group F would receive 1 author for all their 19 pts.*

This first round would result in 22 authorship positions including PI and statistician. The left three authorship positions stand in front of 153 pts. who are so far not compensated (sum of the pts. "leftover"). The ranking of leftovers is: groups B > A > D > E > G > C > H. Here the protocol should foresee which way should be chosen: either groups B, A, and D (those with the highest leftover) receive each one additional position, or the leftovers are used for groups G and H (smaller groups which did not meet the threshold for the first position) and the left for group B with the highest leftover (the latter being a model "solidarity over power by size", the first model can be called "size does matter").

e. Additional sequential publications of planned analyses of secondary endpoints

i. For additional publications on planned secondary endpoints analyses, not included in the primary endpoint publication, the first authorship should alternate amongst the groups.
ii. The steering committee of the study should define the sequence of importance of the secondary endpoints if there are more than one subsequent separate analysis.
iii. The most important secondary endpoint should be presented by the group with the highest recruitment if this is not the leading group. If so, the second best recruiting group and the leading group may change position regarding the distribution of subsequent presentations/publications. The second most important endpoint will be presented by the group with the second highest recruitment (or the leading group if best recruiter), and so on.
iv. When the Leading group is not first author of a separate publication on secondary endpoints, the International Principal Investigator of the study gets the senior (last) position.

v. Furthermore, the number of authors per group and positions per groups follow the rules as outlined for the publication of the primary endpoint at the time of the primary analysis.

f. Additional publication of subgroup data or sub-projects:

i. If possible, each participating group should receive a dataset of patients recruited by the respective study group after final analysis.
ii. Separate analyses by one participating group on their included patients should not include primary or secondary endpoints and the International Principal Coordinator and Intergroup study leading committee (Trial Steering Committee [TSC] or data committee after dissolution of TSC) should be informed on each project.
iii. Further subgroup analysis of the whole population should be prospectively discussed among the groups and agreed. For acceptance and distribution of subprojects the TSC should be in charge – later on a reduced subproject committee can take over this task
iv. First author should be of the group performing the sub-analysis.
v. Other groups should be mentioned and have co-authorship positions similar to the rules for primary and main publication but with reduced numbers according to the positions already covered by project members.
vi. International Principal Investigator is usually senior author for main subprojects (eg. OS analysis after first publication of PFS primary endpoint) but can be replaced by others in secondary subprojects (e.g. prognostic factors, subgroup analysis) either in a rotating system or as reward for study groups very active in the respective subproject.
vii. The statistician responsible for the subproject analyses gets an usually the 4th authorship position, however, this may change to an even more prominent position in case of , e.g. for methodological/statistical subprojects.
viii. All sub-publications or meta-analyses can only be published after the full manuscript of the study has been published.
ix. Full paper on general analyses of secondary endpoints (e.g. quality of life, prognostic factors etc.) should be shared among the groups with rotating first authorship position by recruitment.
x. Smaller groups (who did not recruit the necessary 1% of the total number of patients) might either have an authorship granted by calculation model “group solidarity over size” or must have co-authorships in secondary publications.

g. Presentations:

i. The study should be presented as often as possible to give as many groups as possible the opportunity to present.
ii. Local and national presentations should be done by the national group as authors and without all groups mentioned; anyhow the International Principal Investigator should be mentioned as senior author.
iii. International presentations may be scheduled according to available data and rotate among the groups (a plan should be made by the TSC).

h. In each publication/presentation it will be mentioned that the study was performed according to the ENGOT model C.

18.8 Appendix 8: COVID-19

SCHEDULE OF ASSESSMENTS AND PROCEDURES DURING COVID-19

Screening / Baseline Examination

All screening and baselines examinations must be performed at the clinical trial site.

IMP administration

All IV administration of carboplatin/PLD and APX0005M must be performed at the clinical trial site. If it is not possible for the patient to visit the clinical trial site, IV administration must be postponed for a period that should be as short as possible. The acceptable length of interruption must be agreed between the Investigator and the Sponsor. In case that the above-mentioned procedure is not possible, the patient should be considered as 'end of treatment' and starting a subsequent new treatment according to standard of care, where appropriate. The patient should still continue to be followed until objective radiological disease progression as defined by RECIST 1.1.

Radiation Therapy

If it is not possible for the patient to visit the clinical trial site, Radiation Therapy must be postponed for a period that should be as short as possible. The acceptable length of interruption must be agreed between the Investigator and the Sponsor. In case that the above-mentioned procedure is not possible, the patient should be considered as 'end of treatment' and starting a subsequent new treatment according to standard of care, where appropriate. The patient should still continue to be followed until objective radiological disease progression as defined by RECIST 1.1.

Assessments during treatment

All assessments during treatment are linked to the administration of IMPs and therefore the patient should also be present at the trial site for the assessments during treatment. Nevertheless, there could be other restrictions like limited availability of trial staff or departments of the clinical trial site. In these cases, it is acceptable to perform the assessments at a local institution authorized/certified to perform the corresponding tests. It is acceptable to evaluate concomitant medication, adverse events and ECOG performance status by phone. All necessary medical results and medical records must be reported to the investigator, evaluated by the investigator and documented at the clinical trial site prior to the administration of therapy.

Tumor and Response Evaluation

Tumor assessment by CT scan is a critical component of the primary endpoint for this clinical trial. For this reason, the CT scans must be performed according to the trial schedule. If there are travel restrictions or the patient cannot visit the clinical trial site for other reasons related to COVID-19 or due to limited availability of trial staff, it may be considered to perform the CT scans in another

facility close to the patient. The images must be provided to the clinical trial site and assessed according the protocol (RECIST 1.1) in the clinical trial site.

Outcome (PRO)

The questionnaires during this period must be maintained according to protocol. Shipping of questionnaires to patients' homes or sending questionnaire by email is allowed.

End of treatment

The assessments should be performed at trial site. Nevertheless, if there are travel restrictions, the patient cannot visit the clinical trial site or due to limited availability of trial staff to perform visits, it is allowed to perform the assessments at a local institution authorized/certified to perform the corresponding tests. In these cases, adverse events, concomitant medication and ECOG could be evaluated by phone. All necessary medical results and medical records must be reported to the investigator, evaluated by the investigator and documented at the clinical trial site.

Follow up after end of treatment

It is allowed to evaluate the patient status by phone. The assessment must be reported to the investigator, evaluated by the investigator and documented at the clinical trial site. For the Qol/PRO assessment the shipping of questionnaires to patients' homes or sent questionnaire by email is encouraged.

COVID-19 Vaccine

Patients enrolled in the study can only receive non-active COVID-19 vaccine 7 days before or after UV1 injection. Enrolled should not receive live COVID-19 vaccine whilst receiving IP and up to 30 days after the last dose of IP.

MANAGEMENT OF COVID 19 PATIENTS

For patients with fever or other symptoms of active infection (dry cough, difficulty breathing) or positive coronavirus test the following action should be taken:

- Patients must be advised to immediately contact their treating investigators or local provider by phone or as indicated in your region.
- A comprehensive evaluation should be performed as per usual medical practice and local advice for possible COVID-19 patients.
- Decisions to delay or interrupt any IMP study treatment based on the current situation and any concern for active infection should be made by the treating investigator after considering the patient's current oncologic status and treatment tolerance, as well as their general medical condition, and can be discussed with the sponsor if needed.

- If study treatment is withheld in a patient for over 12 weeks, the possibility to resume treatment must be discussed with the sponsor and determined on a case by case basis.

The following additional considerations should be taken into account:

- Please consider that some organ toxicities secondary to immune-mediated adverse events (imAEs) associated with cancer immunotherapy could overlap with COVID-19 complications (e.g. pneumonitis). Please use your clinical judgement to assess if a given organ toxicity is due to imAEs or COVID-19 complications, or a combination of the two.
- Recent evidence from literature suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome (Mehta et al 2020), and viral infections are a known trigger for hyperinflammation [secondary Hemophagocytic Lymphohistiocytosis (HLH)]. In case of suspected hyperinflammatory syndrome, the investigators should consider the potential for immune overreaction [Cytokine Release Syndrome (CRS), HLH spectrum] and should refer to the appropriate management guidelines.
- Infection of patients with Covid-19 should be reported following standard AE/SAE reporting guidelines. At a minimum, a non-serious AE of Covid-19 infection should be reported. If the AE meets serious criteria, the event would be reported and managed as an SAE.

Secondary	To evaluate safety	Adverse events until 30 days after last dose of study drug(s)
	To evaluate Patient Reported Outcomes (PROs) in treatment arms	EORTC QLQ C30 and OV28 overall measures and single items at baseline and every 12 wks for 24 mounts
Secondary	To evaluate safety	Adverse events until 30 days after last dose of study drug(s)
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REPORTING OF SAES AND AES DURING CONVID-19 PANDEMIC

Various challenges exist which result in restrictions of visits to healthcare facilities, increased demands on the health service and changes to trial staff availability. Trial subjects may also be required to self-isolate, which introduces difficulties for investigators to maintain their medical oversight. These challenges could have an impact on the reporting and of serious adverse events (SAEs) and adverse events (AEs). For all upcoming decisions, the first priority is to ensure the safety and well-being of trial subjects. In general, even in the COVID-19 pandemic, the regulations

on safety reporting must be performed in accordance with §§ 12 and 13 GCP-V, Directive 2001/20 and Guidance CT-3. This concerns both the reporting of SAEs, which the investigator must report immediately to the sponsor, and the reporting obligations of the sponsor to the competent authorities and ethics committees. During the COVID-19 pandemic the following deviations from study protocol (Section 13, Management of Adverse Events/Assessment of Safety) are possible:

- SAE reporting

  - If, in the context of a SAE notification, a trial subject cannot visit the trial site in person, the initial communication with the investigator may be by telephone or telemedical visits. It must then be decided whether the trial subject's personal appearance is necessary for safety reasons, e.g., to perform further clinical or laboratory investigations. Nevertheless, the investigator is obliged to complete and send the SAE Reporting Form within 24 hours of becoming known by e-mail to the ODC BV.

  - The regulations mentioned above also apply to a SAE Follow-up notification.

- AE reporting

  - The detection and evaluation of AEs may be done by telephone or telemedical visits. If a trial subject cannot come to a planned study visit, it is the responsibility of the investigator/trial site staff to contact the trial subject by telephone or to arrange a telemedical visit. All AEs must be followed-up and should be entered in the eCRF.

BENEFIT/RISK ASSESSMENT FOR COVID-19

With this appendix all necessary measures to reduce the impact of COVID-19 on this clinical trial are taken and safety of trial participants, compliance with ICH-GCP and minimization of risks to trial integrity and quality of data are ensured. The benefit-risk ratio for this trial is still expected to be positive in the current pandemic situation.

18.9 Appendix 9: Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN (to > 5 × ULN in subjects with liver metastases) or bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		Total Bilirubin
Moderate	> 3 x ULN (in patients without liver metastases), > 5 x ULN (in patients with liver metastases)	or	> 2 x ULN
Severe	> 3 x ULN	and	> 2 x ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metastases).
- ALT or AST > 3 × ULN and International Normalized Ratio (INR) > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up. Follow-up procedures that confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Severe hepatic liver function abnormalities as defined above, in the absence of another etiology may be considered an important medical event and may be reported as a SAE. The sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases is to be recorded as “AEs” in the (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, including dose, is to be entered in the (e)CRF. Information on alcohol, other substance use and diet should be entered on an appropriate document.

- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including: Acute viral hepatitis (A, B, C, D, E or other infectious agents), Ultrasound or other imaging to assess biliary tract disease, Other laboratory tests including INR, direct bilirubin.
- Consider gastroenterology or hepatology consultations.

Submit results for any additional testing and possible etiology

Study Discontinuation

In the absence of an explanation for increased LFTs, such as viral hepatitis, preexisting or acute liver disease, presence of liver metastases, or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks (in subjects without liver metastases).
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 5 × ULN and (TBL > 2 × ULN in patients with liver metastases).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by a higher rate than control of people with 3 × and greater transaminase elevations over the upper limit of normal (2 × elevations are too common in treated and untreated patients to be discriminating).

2. Cases of increased bilirubin (to at least 2 × ULN) in people with concomitant transaminase elevation to at least 3 × ULN (but it is almost invariably higher) and no evidence of intra-or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome. [Temple, 2006]

3. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.

4. Among trial subjects showing such AT elevations, often with ATs much greater than 3 × ULN, one or more also show elevation of serum TBL to > 2 × ULN, without initial findings of cholestasis (elevated serum ALP).

5. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury [Guidance for Industry, 2009].

References

Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006;15(S4):241-3.

Guidance for Industry. "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.