[redacted]

Statistical Analysis Plan

Protocol Title	Phase II randomized study of pembrolizumab with or without epigenetic modulation with CC-486 in patients with platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer
Protocol Number	TRIO026 (Part A) / NCT02900560
[redacted]	[redacted]
Revision	01
Product Name	CC-486
Indication	Platinum-resistant epithelial ovarian cancer (EOC), fallopian tube carcinoma (FTC) or primary peritoneal carcinomas (PPC)
Study Phase	II
Sponsor	TRIO
Version Date	10-Apr-2018

Confidentiality Statement

Revision History

Not applicable; this is the initial version of the Statistical Analysis Plan.

List of Abbreviations

AE	Adverse Event
CI	Confidence Interval
CM	Concomitant Medications
EOC	Epithelial Ovarian Cancer
FTC	Fallopian Tube Carcinoma
GCIG	Gynecologic Cancer Intergroup
irCR	Immune-related Complete Response
irDCR	Immune-related Disease Control Rate
irNE	Immune-related Unevaluable
irORR	Immune-related Overall Response Rate
irPD	Immune-related Progressive Disease
irPR	Immune-related Partial Response
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
irSD	Immune-related Stable Disease
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PEM	Pembrolizumab
PPC	Primary Peritoneal Carcinomas
PT	Preferred Term
RDI	Relative Dose Intensity
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SSC	Study Steering Committee
TRIO	Translational Research in Oncology
WHODD	World Health Organization Drug Dictionary
ULN	Upper Limit of Normal

[redacted]

1. Introduction

This Statistical Analysis Plan (SAP) describes the detailed statistical methodology for executing the statistical analyses to assess the safety profile of CC-486, futility evaluation as well as CA-125 response according to TRIO026 protocol version 2.0 for patients enrolled in Part A of the trial. Separate document(s) will be prepared to describe statistical analysis perform on Part B of this trial.

Statistical analysis will be performed by TRIO using SAS® software Version 9.4 or higher.

2. Study Design and Objectives

2.1. Study Design

The protocol synopsis is provided in Appendix 6.1. Refer to protocol for additional details.

2.2. Study Objectives

2.2.1. Primary Objectives

The primary objective for Part A of this study is to establish an optimal schedule of CC-486 combined with pembrolizumab (PEM) in patients with platinum-resistant/refractory EOC. This will be determined based on safety profile, futility evaluation as well as immune-related Overall Response Rate (irORR)/ immune-related Disease Control Rate (irDCR) per irRECIST criteria.

2.2.2. Secondary Objectives

To assess the CA-125 response based on the Gynecologic Cancer Intergroup (GCIG) criteria.

2.2.3. Exploratory Objectives

- Tumor samples will be used to assess potential prognostic or predictive biomarkers, improve understanding of ovarian cancer biology and identify candidate biomarkers that may correlate with treatment benefit and/or safety signals
- Whole blood samples will be used to analyze changes in DNA methylation during treatment with CC-486

Details of methodologies used to assess exploratory objectives will be described in a separate SAP.

2.3. Sample Size

At least 20 patients will be enrolled to TRIO026 Part A. Patients are assigned to one of the following four treatment schedule cohorts in the order they are enrolled in the study (minimum of five patients per cohort):

- Cohort 1: CC-486 100 mg/d, 21 d on, 7 d off + PEM 200 mg iv q3 weeks
- Cohort 2: CC-486 100 mg BID, 21 d on, 7 d off + PEM 200 mg iv q3 weeks

- Cohort 3: CC-486 300 mg/d, 14 d on, 14 d off + PEM 200mg iv q3 weeks
- Cohort 4: CC-486 300 mg/d, 21 d on, 7 d off + PEM 200 mg iv q3 weeks

2.4. Timing of Analyses

The analysis for TRIO026 Part A is conducted when five patients in each cohort are considered evaluable. The criteria for evaluability is described under Section 3.1.3.

3. Statistical Methods

3.1. Analysis Population

3.1.1. Intent-to-Treat Population

The **Intent-to-Treat (ITT) Population** includes all patients who were enrolled in the study, regardless of whether they actually received study medication. All efficacy analyses will be evaluated based on data from this population according to the cohort they were assigned to at enrollment.

3.1.2. Safety Population

The **Safety Population** consists of all patients who receive any study treatment, and will be used for the analysis of safety data of the study. This population will assign patients to the cohort based on the treatment schedule observed in Cycle 1. If this differs from that to which the patient was enrolled, the actual observed treatment schedule will be used for the analysis of safety data.

3.1.3. Evaluable Population

As per protocol version 2.0, the **Evaluable Population** consists of patients in ITT population who also meet the following criteria:

- Completed at least two CC-486 cycles
- Undergone 1st post-baseline tumor burden assessment
- Undergone 2nd tumor biopsy with adequate paired tissue obtained

3.2. Data Handling

3.2.1. Baseline Assessment/Measurement

The last available assessment/measurement of a particular data point on or prior to the latter of the date of enrollment and the date of first dose of study treatment. If patients have no value as defined above, the baseline value will be missing.

3.2.2. Date of First Dose

The date of first dose (of study drug) is derived as the first date when a non-zero and non-missing dose of study drug is administered. This is also referred as the start of the study treatment.

3.2.3. Date of Last Dose

The date of last dose (of study drug) is derived as the last date when a non-zero and non-missing dose of study drug is administered.

3.2.4. Duration

Duration, except for duration of treatment, is calculated as:

- Duration (days): (End Date – Start Date + 1).
- Duration (weeks): (End Date – Start Date + 1) / 7
- Duration (months): (End Date – Start Date + 1) / 30.4375
- Duration (years): (End Date – Start Date + 1) / 365.25

3.2.5. Missing Data

All analyses and descriptive summaries will be based on the observed data. Unless otherwise specified, missing data will not be imputed or “carried forward.”

3.2.6. Partial Dates

Only partial or missing date for Adverse Events (AE) and Concomitant Medications (CM) (including prior and on study systemic anti-cancer therapies) will be imputed according to the following:

3.2.6.1. Imputation Rules for Partial or Missing Stop Dates:

If the month and year are present, impute the last day of that month.

If only the year is present, impute December 31 of that year.

If the stop date is entirely missing, assume the event or medication is ongoing.

If a partial or complete stop date is present and the ‘ongoing’ box is checked, then it will be assumed that the AE or CM stopped and the stop date will be imputed if partial.

3.2.6.2. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		Missing
		< 1st dose	≥ 1st dose	< 1st dose *yyyymm*	≥ 1st dose *yyyymm*	< 1st dose *yyyy*	≥ 1st dose *yyyy*	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	2	1	n/a	1	1
	≠ 1st dose *yyyymm*		2		2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

- 1 = Impute the date of first dose
- 2 = Impute the first of the month
- 3 = Impute January 1 of the year
- 4 = Impute January 1 of the stop year

3.3. Statistical Analysis

Categorical variables will be summarized in frequency tables, with the counts and percentage of patients in each category. Percentages given in the summary tables will be rounded and thus may not always add up to exactly 100 percent. For continuous variables, summary statistics will include number of patients, mean, standard deviation, first quartile (Q1), median, third quartile (Q3), and minimum and maximum values (range).

3.3.1. Patient Disposition

The patient disposition will be tabulated using the ITT. Frequency count and respective percentages of patients who were in each population (i.e. ITT, Safety, and Evaluable), and discontinued from treatment and/or study will be summarized by cohort. The reason for discontinuation (from treatment and/or from study participation where applicable) will be summarized considering the categories specified in the case report forms. Listings of disposition information and analysis population will be provided as well.

Protocol Deviations including eligibility deviations of the inclusion/exclusion criteria will be summarized and listed for ITT, by cohort.

3.3.2. Demographics and Disease Characteristics

The following patient demographics and disease characteristics will be summarized and listed for the ITT and Safety Population (where applicable) by cohort:

Patient Demographics:

- Age, INT (Date of enrollment – Date of birth) / 365.25)
  - INT = integer part
  - Since only the year of birth is collected (YYYY), we assume the full date to be 31-Dec-YYYY
- Race
- Ethnicity
- Weight at Baseline
- ECOG Status at Baseline

Disease Characteristics:

- Time from Initial Diagnosis to Enrollment
- Primary Tumor Location
- Staging at Initial Diagnosis
- Histopathological Type at Initial Diagnosis
- Histopathological Grade at Initial Diagnosis
- Disease Status at Enrollment
- Time from First Progression/Relapse to Enrollment

Prior Surgery for Ovarian Cancer:

Number of patients who underwent prior surgeries will be summarized by type of procedures. A listing will also be done.

Prior Systemic Anti-Cancer Therapy:

Number of regimens of prior systemic anti-cancer therapies will be summarized by type and setting. A listing will be provided to show the specifics of the therapies.

Medical History:

The medical history is coded by the most current version of Medical Dictionary for Regulatory Activities (MedDRA), and will be summarized for ITT by System Organ Class (SOC) and Preferred Term (PT) by cohort.

3.4. Efficacy Analyses

Efficacy data for the primary objective and the secondary objectives will be analyzed for the ITT. Summaries and figures of the efficacy endpoints will be generated by cohort as per enrollment.

3.4.1. Primary Efficacy Objective

Immune-related Overall Response Rate (irORR):

irORR is defined as the proportion of patients achieving a best overall response of immune-related Complete Response (irCR) or immune-related Partial Response (irPR) assessed as per investigator assessment.

$$\text{irORR} = \frac{\#\text{ of patients with best overall response as irCR or irPR}}{\text{Total number of patients}}$$

The best overall response outcome (irCR/irPR/irSD/irPD/irNE) will be summarized and tabulated for ITT by cohort.

Immune-related Disease Control Rate (irDCR):

irDCR is estimated based on the proportion of patients in each cohort whose best overall response during the course of study treatment is irCR, irPR or irSD as per investigator assessment.

$$\text{irDCR} = \frac{\#\text{ of patients with best confirmed overall response as irCR/irPR/irSD}}{\text{Total number of patients}}$$

3.4.2. Secondary Efficacy Endpoints

CA-125 Response Rate:

The CA-125 response rate is defined as the proportion of patients having a CA-125 response according to the GCIG criteria:

- A response according to CA-125 is observed when there is at least a 50% reduction in CA-125 level from baseline. The response must be confirmed and maintained for at least 28 days.
- Patients can be evaluated according to CA-125 if they have a pre-treatment sample that is at least twice the upper limit of normal (ULN) and within 2 weeks prior to starting treatment

3.5. Safety Analyses

Safety analyses will be performed on the **Safety Population.**

3.5.1. Extent of Exposure

Number of Cycles, Duration of Treatment, Cumulative Dose and Relative Dose Intensity (RDI) will be summarized by treatment for the safety population.

CC-486:

Number of Cycles: number of cycles having total dose > 0 mg reported
Duration of Exposure (day) = sum of [(Date of last dose - Date of first dose + 1) of cycle]
Duration of Treatment (day) of each administration sequence = (Date of last dose – Date of first dose + 1)
Cumulative Dose (mg) = sum of (Duration of Treatment of each administration sequence × daily dose)
Dose Intensity (mg/day) = (Cumulative Dose) ÷ (Duration of Exposure)

Planned Dose Intensity (mg/day) = Planned Daily Dose as per cohort
RDI (%) = (Dose Intensity ÷ Planned Dose Intensity) × 100

The compliance of CC-486 will be summarized by cycle using the following calculation:

$$\text{Compliance (\%)} = \frac{\text{Number of Tabs taken} + \text{Number of Tabs Returned}}{\text{Number of Tabs Dispensed}} \times 100$$

Pembrolizumab:

Number of Cycles: number of cycles having total dose > 0 mg reported
Duration of Treatment (weeks) = [(Date of last dose - date of first dose) + 21] ÷ 7
Cumulative Dose (mg) = sum of total dose administered as reported
Weekly Dose Intensity (mg/week) = (Cumulative Dose) ÷ (Duration of Treatment)
Planned Weekly Dose Intensity (mg/week) = 200mg ÷ 3 weeks
RDI (%) = (Weekly Dose Intensity ÷ Planned Weekly Dose Intensity) × 100

The RDI will be additionally presented categorized (i.e., number and percentage of patients with RDI of < 60%, 60 - < 80%, 80 - < 90%, 90 - < 110%, ≥ 110%).

The number and percentage of patients with dose modifications will be summarized. The respective reasons of dose modification will be listed.

3.5.2. Adverse Events (AEs)

AE information will be collected from treatment initiation and continues throughout the study until end of participation (refer to Section 7.1.1 of the protocol).

The reported AE term will be coded using the current version of the MedDRA. The severity of AE will be presented as reported by the investigator based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grades version 4.03.

Incidence of AEs will be tabulated by SOC and PT for:

- All AEs
- AEs by relationship to study treatment and maximum severity grade
- AEs with action taken drug interrupted
- AEs with action taken dose reduced
- AEs with action taken drug withdrawn
- Serious Adverse Events (SAE)
- AEs leading to deaths – An AE is considered as leading to death if CTCAE Grade 5 is reported.

In the event a patient experiences repeated episodes of the same AE according to PT, the event with the highest severity grade to study treatment will be used for purposes of incidence tabulations.

Detailed listings for all AEs will be provided.

3.5.3. Laboratory Values

Lab values will be converted to standard units and categorized according to NCI CTCAE version 4.03. Laboratory results not corresponding to NCI CTCAE terms will not be graded.

Hematology and serum blood chemistry will be summarized in descriptive statistics by calculating the mean, standard deviation, median, and range for the following:

- Baseline value
- Minimum post baseline value
- Maximum post baseline value

Shift tables in laboratory toxicity grades (comparing baseline grade with worst post-baseline grade) will be analyzed using standard shift tables, presenting number and proportion of patients and their maximum grade shift.

For laboratory tests without a toxicity grading scale, the shift table will present directional shifts from baseline to above or below the laboratory standard normal range using the maximum increase and/or decrease observed throughout the course of treatment/observation.

3.5.4. ECOG Performance Status

Descriptive statistics of ECOG Performance Status results will be done for the following:

- Baseline value
- Minimum post baseline value
- Maximum post baseline value

A shift table will be provided as well from baseline status to the worst status of post-baseline time points.

3.5.5. Concomitant Medications

CM and on study systemic anti-cancer therapies are coded to the current version of World Health Organization Drug Dictionary (WHODD). The preferred name will be tabulated and listed by patient.

3.5.6. Death

All deaths will be reported in a patient listing, which will include date of death, date of last dose, the primary cause of death, and the number of days between the date of last dose to study drug and death.

4. Study Steering Committee (SSC)

The result of statistical analysis will be reviewed by SSC who is responsible for the scientific conduct and integrity of the trial. SSC will review the results and act in correspondence to the SSC Charter.

5. List of Planned Statistical Outputs

5.1. Planned Tables

Title	Population	Description
Patient Disposition	ITT	Tabulates the disposition of all patients by cohort, including the number of patients in each population set, discontinued from study treatment, and discontinued from study. The reason for drug discontinuation and study discontinuation will also be summarized.
Protocol Deviations	ITT	Tabulate the number of patients who reported protocol deviations by deviation category for each cohort.
Eligibility Deviations	ITT	Tabulates the number of patients who violates inclusion/exclusion criteria by criterion for each cohort
Patient Demographics	ITT Safety	Tabulates summary statistics of patient demographics (age, race, ethnicity, weight and ECOG status at baseline) for each cohort.
Disease Characteristics	ITT	Tabulates summary statistics for time from initial diagnosis to enrollment, primary tumor location, staging at initial diagnosis, histopathological type at initial diagnosis, histopathological grade at initial diagnosis, disease status at enrollment, time from first progression/relapse to enrollment for each cohort.
Prior Surgery for Ovarian Cancer	ITT	Tabulates the number of patients with type of procedures for each cohort.
Prior Systemic Anti-Cancer Therapy	ITT	Tabulates the number of regimens received by patient according to type and indication of the systemic cancer therapy for each cohort.
Medical History	ITT	Summarizes medical history by SOC and PT for each cohort.
Study Drug Exposure	Safety	Summarizes the number of cycles, the duration of treatment, cumulative dose, and RDI by cohort. The number of dose modification will also be summarized by study drug.

Title	Population	Description
Compliance	Safety	CC-486 Compliance assessment will be summarized by each cycle.
Best Overall Response/irORR and irDCR	ITT	Summary of Best Overall Response as per irRECIST will be tabulated by cohort irORR and irDCR will also be reported
CA-125	ITT	Summary of CA-125 Response Rate will be tabulated by cohort.
AEs Overview	Safety	Tabulates the number of patients with AEs, Related AEs, Grade 3 / 4 AEs, AEs with action taken dose reduced, AEs with action taken drug interrupted, AEs leading to drug withdrawn, SAEs, Fatal AEs.
AEs	Safety	Summary by SOC and PT of number of patients and events for each cohort.
Related AEs – CC-486	Safety	Summary by SOC and PT of number of patients and events for each cohort.
Related AEs – Pembrolizumab	Safety	Summary by SOC and PT of number of patients and events for each cohort.
SAE	Safety	Summary by SOC and PT of number of patients and events for each cohort.
Grade 3 / 4 AEs	Safety	Summary by SOC and PT of number of patients and events for each cohort.
Grade 5 AE	Safety	Summary by SOC and PT of number of patients and events for each cohort.
AEs with Action Taken as Dose Reduced – CC-486	Safety	Summary by SOC and PT of number of patients and events for each cohort.
AEs with Action Taken as Drug interrupted – CC-486	Safety	Summary by SOC and PT of number of patients and events for each cohort.
AEs with Action Taken as Drug interrupted – Pembrolizumab	Safety	Summary by SOC and PT of number of patients and events for each cohort.
AEs Leading to Drug Withdrawn – CC-486	Safety	Summary by SOC and PT of number of patients and events for each cohort.

Title	Population	Description
AEs Leading to Drug Withdrawn – Pembrolizumab	Safety	Summary by SOC and PT of number of patients and events for each cohort.
Laboratory Values	Safety	Summary of each laboratory parameter at baseline, minimum post baseline value, and maximum post baseline value for each cohort. In addition, shift tables will be presented.
ECOG Performance Status	Safety	Summary of ECOG performance status at baseline, minimum post baseline value, and maximum post baseline value for each cohort. In addition, a shift table will be presented.
Concomitant Medications	Safety	Tabulate the frequency and percentage of patients according to preferred name. Summary will be presented separately for concomitant medications and on study systemic anti-cancer therapies.

5.2. Planned Listings

Title	Population	Description
Patient Accountability	ITT	Listing of all patients and with population indicators. For patients who discontinued from treatment and/or study, include the reason of respective discontinuations.
Deaths	ITT	Listing of patients who died, including primary cause of death, date of death, date of last dose, and the number of days from date of last dose to death.
Patient Demographics	ITT	Listing of patient demographics.
Disease Characteristics	ITT	Listing of disease characteristics.
Prior Surgery for Ovarian Cancer	ITT	Listing of prior surgery for ovarian cancer.
Prior Systemic Anti-Cancer Therapy	ITT	Listing of prior systemic anti-cancer therapy.
Study Drug Exposure	Safety	Listing of patients for extent of exposure by cycle.

Title	Population	Description
Study Drug Exposure Summary	Safety	Listing of patients for summary of exposure (e.g. number of cycles, duration of treatment, cumulative dose, dose intensity, RDI).
Efficacy Parameters	ITT	Listing of best overall response for each patient
Tumor Assessment	ITT	Listing of tumor assessment including lesion number, date of assessment, lesion measurement/response, and time-point overall response.
CA-125	ITT	Listing of CA-125 reported for each patient.
AEs	Safety	Listing of all AEs for each patient; the listing includes the verbatim term, PT, SOC, seriousness, worst grade, start date, outcome, stop date, relationship to study drug, and action taken for study drug.
Related AE – CC-486	Safety	Listing of AEs in this category using the same structure as the AEs listing.
Related AE – Pembrolizumab	Safety	Listing of AEs in this category using the same structure as the AEs listing.
SAEs	Safety	Listing of AEs in this category using the same structure as the AEs listing.
Grade 3 / 4 AE	Safety	Listing of AEs in this category using the same structure as the AEs listing.
AEs Leading to Death	Safety	Listing of AEs in this category using the same structure as the AEs listing.
AEs with Action Taken for Dose Reduced – CC-486	Safety	Listing of AEs in this category using the same structure as the AEs listing.
AEs with Action Taken for Drug Interrupted – CC-486	Safety	Listing of AEs in this category using the same structure as the AEs listing.
AEs with Action Taken for Drug Interrupted – Pembrolizumab	Safety	Listing of AEs in this category using the same structure as the AEs listing.
AEs Leading to Drug Withdrwan – CC-486	Safety	Listing of AEs in this category using the same structure as the AEs listing

Title	Population	Description
AEs Leading to Drug Withdrwan – Pembrolizumab	Safety	Listing of AEs in this category using the same structure as the AEs listing
Laboratory Values	Safety	Listing of all laboratory values and their assigned toxicity grade (where applicable).
ECOG Performance Status	Safety	Listing of ECOG at each assessment.
Concomitant Medications	Safety	Listing of verbatim product name, preferred name, start date, end date (or ongoing) and indication.
On Study Systemic Anti-Cancer Therapies	Safety	Listing of regiment number, verbatim product name, preferred name, type of therapy, start date, end date (or ongoing)

5.3. Planned Graphs

Not Applicable.

6. Appendix

6.1. Protocol Synopsis

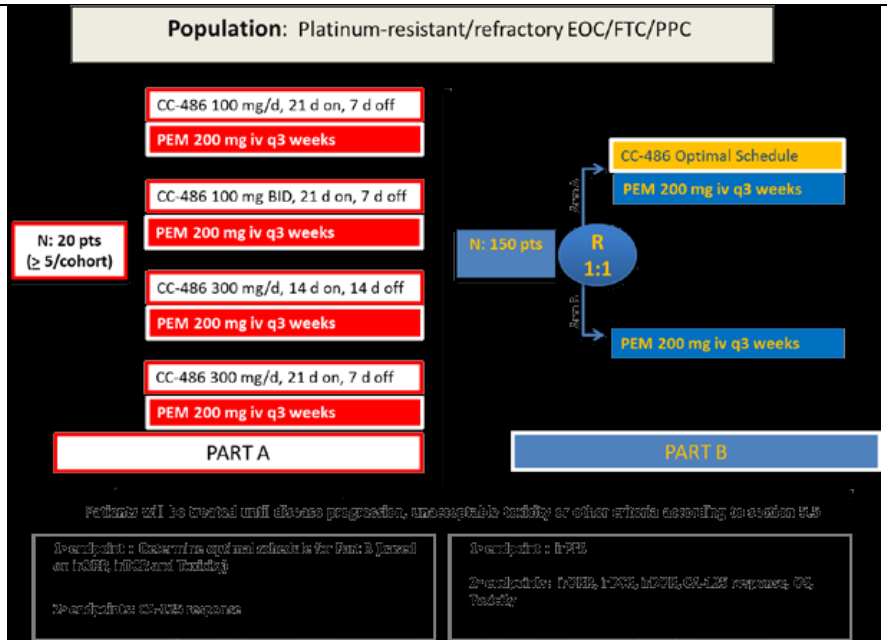
Protocol Title	Phase II randomized study of pembrolizumab with or without epigenetic modulation with CC-486 in patients with platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer
Protocol #	TRIO026
Indication	Platinum-resistant epithelial ovarian cancer (EOC), fallopian tube carcinoma (FTC) or primary peritoneal carcinomas (PPC)
Study Duration	**Part A:** ▪ Accrual: 24 months ▪ Treatment phase: 6 months ▪ Follow-up: According to subject´s status at End of Treatment **Part B:** ▪ Accrual: 24 months ▪ Treatment phase: 6 months ▪ Follow-up: 12 months

Sponsor / Participating Investigator	This is a TRIO-sponsored study, led by Dr. John Glaspy (Professor of Medicine, Jonsson Comprehensive Cancer Center, UCLA, USA) as Study Chair. The study is financially supported by Celgene Corporation.
Participating Investigator Sites	Part A: 4 sites in 1 country (USA) Part B: approximately 25 sites in 2 countries (USA and Germany; includes sites participating in Part A)
Target Population	The target study population consists of adult patients with platinum-resistant/refractory EOC/FTC/PPC who have received a maximum of 2 prior treatment regimens for the platinum-resistant/refractory relapse (definition of platinum resistant/refractory disease will be based on the platinum-free interval following frontline chemotherapy). Subjects must have previously received platinum-based chemotherapy (intravenous and/or intraperitoneal) following and/or preceding debulking surgery. They will be required to have measurable disease according to irRECIST (Immune-related Response Evaluation Criteria in Solid Tumors) for Part A. For Part B, subjects will be required to have either measurable and/or non-measurable disease. They will also be required to have a life expectancy of at least 6 months, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-1, adequate liver, renal and bone marrow functions; absence of known autoimmune diseases, of certain bone marrow conditions and of serious diseases which could affect protocol compliance or the interpretation of study results.
Background and Rationale	There are approximately 200,000 new cases of EOC diagnosed each year in the world and this is the leading cause of death from gynecologic cancer in the United States and in many other countries. More than 75% of patients present with advanced disease at primary diagnosis. The current standard initial therapy is debulking surgery followed by platinum-based doublet chemotherapy administered either intravenously and/or intraperitoneally. Neoadjuvant chemotherapy is being increasingly used. Despite aggressive surgery and frontline chemotherapy, most patients with advanced disease experience a relapse. Patients with a platinum-free interval of less than 6 months are considered to have platinum-resistant disease and those that recur/progress while receiving frontline chemotherapy are considered to have platinum-refractory disease. At first relapse, approximately 25% of patients

	have platinum-resistant/refractory ovarian cancer and their prognosis is poor, with a median overall survival of approximately 12 months. All current treatment options have a response rate of < 15-20%. There is a clear, unmet medical need for effective treatments for patients with platinum-resistant/refractory relapsed EOC. Recent advances in immunotherapy have led to the development and rapid introduction into clinical practice of monoclonal antibodies directed against two immune checkpoints, CTLA-4 (Cytotoxic T-lymphocyte-associated antigen-4) and PD-1 (Programmed death protein 1) (or PD-L1, Programmed death-ligand 1). All of these agents, and in particular the anti-PD-1 antibodies, have shown clear benefit in the treatment of metastatic melanoma and non-small cell lung cancer (NSCLC). Moreover, responses have been of long duration, suggesting that the immune system may be adaptive and to some extent being able to counteract the development of treatment resistance. Immune checkpoint inhibitors have recently demonstrated encouraging signs of antitumor activity for patients with pretreated advanced ovarian cancer. It is known that epigenetic modifications in gene expression associated with methylation and de-acetylation of DNA and histones occurs in human malignancies and can be associated with disease progression and resistance to treatment. Epigenetic therapies with either hypomethylating agents, such as azacitidine, or histone deacetylase (HDAC) inhibitors have been shown to be of benefit in the treatment of some malignancies. More recently, exciting data have emerged indicating that treatment with azacitidine may increase the response to anti-PD-1 therapy in patients with NSCLC, suggesting that hypermethylation may in part explain failure to respond to immune checkpoint inhibition. Pre-clinical research investigating the effects of epigenetic therapy (azacitidine and/or HDAC inhibitors) on gene expression in human cancer cell lines has identified a group of relevant genes whose expression increases in response to epigenetic therapy. In general, these genes are involved in immune response, supporting a hypothesis that anti-PD-1 therapy may be more effective when combined with epigenetic therapy. This “immune signature” that is seen following epigenetic therapy may also be a useful biomarker to predict a benefit from epigenetic priming during immune checkpoint therapy. In a broad screen across cell lines of multiple tumor types, the strongest “immune signature” that is seen following epigenetic therapy was observed in ovarian cancer cell lines. However, the optimal clinical dosing and scheduling of epigenetic therapy aimed at enhancing response to anti-PD-1 has and the efficacy of combined epigenetic therapy and immune checkpoint inhibition has not been studied yet in EOC.

	CC-486 is a new, oral formulation of azacitidine. This drug is well tolerated and produces evidence of induced hypomethylation at doses of 100 to 300 mg daily. The primary toxicity of this agent is hematologic; however doses of 300 mg per day are well tolerated in patients with myelodysplastic syndromes, a setting where marrow tolerance is known to be reduced. We expect doses of 300 mg daily to be well tolerated in patients with EOC, who do not have intrinsic bone marrow disease. This study will enroll subjects with platinum-resistant/refractory EOC/FTC/PPC into a phase II clinical trial to be conducted in two sequential parts. Part A aims to explore the optimal combination of the monoclonal anti-PD-1 antibody pembrolizumab (given at a dose of 200 mg every 3 weeks) with CC-486 (given at four different dosing schedules). Part B will then further evaluate the efficacy and safety of the optimal schedule of CC-486 and pembrolizumab selected in Part A, and compare the combination therapy with pembrolizumab as a single agent in a randomized controlled trial setting. Part B will test whether adding epigenetic therapy to pembrolizumab can improve the progression free survival to pembrolizumab monotherapy in relapsed EOC.
Part A Objectives / Endpoints	**Primary Objectives:** ▪ To establish an optimal schedule of CC-486 combined with pembrolizumab in subjects with platinum-resistant/refractory EOC. The primary endpoint will be based on the safety profile, futility evaluation as well as on the irORR/irDCR per irRECIST criteria (also, data from the correlative analyses to be done in the biologic samples may be taken into consideration for determining the optimal schedule). **Secondary Objective:** ▪ To assess the CA-125 response based on the Gynecologic Cancer Intergroup (GCIG) criteria. **Exploratory objectives:** ▪ Tumor samples will be used to assess potential prognostic or predictive biomarkers, improve understanding of ovarian cancer biology and identify candidate biomarkers that may correlate with treatment benefit and/or safety signals. ▪ Whole blood samples will be used to analyze changes in DNA methylation during treatment with CC-486.
Part B Objectives/Endpoints	**Primary Objective:**

	▪ To evaluate whether the addition of CC-486 to pembrolizumab (optimal schedule selected in Part A) improves the Investigator-assessed immune-related Progression free survival (irPFS) compared to pembrolizumab alone, in subjects with platinum-resistant/refractory EOC. The primary endpoint will be assessed according to the Immune-Related Response Evaluation Criteria in Solid Tumors (irRECIST). **Secondary Objective:** ▪ To assess secondary measures of efficacy for CC-486 combined with pembrolizumab (optimal schedule selected in Part A) relative to pembrolizumab alone. Efficacy endpoints: o Immune-related Overall Response Rate (irORR) o Immune-related Disease Control Rate (irDCR) o Immune-related Duration of Response (irDoR) o CA-125 response based on GCIG criteria o Overall Survival (OS) ▪ To assess the safety and tolerability of CC-486 combined with pembrolizumab **Exploratory objectives:** ▪ Tumor samples will be used to assess potential prognostic or predictive markers, improve understanding of ovarian cancer biology and identify candidate biomarkers that may correlate with treatment benefit and/or safety signals.
Study Design	This is an open-label, multicenter, multinational trial that will be carried out in two sequential parts.



Part A: Part A is an open-label, non-randomized, four-cohort, lead-in selection phase in which intravenous pembrolizumab will be combined with 4 different schedules of administration of oral CC-486, for the treatment of platinum-resistant/refractory EOC. Part A is also a futility trial for the strategy to combine pembrolizumab and CC-486 in EOC.

Eligible subjects will be treated in one of four cohorts of combined oral CC-486 and intravenous pembrolizumab (200 mg IV q 3 weeks in all cohorts) to evaluate the safety of each combination schedule and to have preliminary data on their efficacy. The primary objective of Part A is to establish the optimal dosing schedule for comparison with pembrolizumab alone in Part B of the study.

Subjects will be assigned to a treatment cohort in the order they are enrolled in the study. In all subjects, tumor tissue will be obtained via image-guided core biopsy at study entry and 6 weeks after commencing treatment with CC-486 (provided that the tumor lesion is amenable to a second biopsy). A cohort will remain open to accrual until five subjects treated on that cohort have completed two CC-486 cycles and have had the first post-baseline tumor burden assessment and both tumor biopsies performed and adequate paired tissue obtained. At least 5 evaluable subjects per cohort will be accrued to Part A over an estimated period of approximately 24 months.

Subjects will be treated in the assigned cohort until progressive disease based on irRECIST, unacceptable toxicity, consent withdrawal or the Investigator concludes that it is in the subject´s best interest to discontinue. Once 5 subjects

	in each cohort are considered evaluable for response, toxicity and treatment responses will be analyzed for each of the four cohorts and an optimal schedule to be taken forward into Part B will be selected. Part A includes mandatory tumor core biopsies for biomarkers research and mandatory whole blood sampling for DNA methylation analyses. **Part B:** This will be an open-label, randomized phase II study that will compare the safety and efficacy of CC-486 and pembrolizumab (using the schedule that was established as optimal in Part A) with pembrolizumab alone, for the treatment of platinum-resistant/refractory EOC. Eligible subjects will be randomly assigned in a 1:1 ratio to either: ▪ Arm A: Pembrolizumab (200 mg IV every 21 days) in combination with CC-486 (dosing schedule established in Part A) or ▪ Arm B: Pembrolizumab (200 mg IV every 21 days) as a single agent A total of 150 subjects, 75 per arm, will be randomized over an estimated period of 24 months. To ensure equal distribution of prognostic factors in the two study arms, subjects will be stratified according to the following parameters: ▪ Platinum-refractory vs. platinum-resistant ▪ Number of prior treatment regimens for the platinum-refractory/resistant EOC: none vs. 1 or 2. Subjects with tumor lesions amenable to core biopsy will be proposed (although not mandated) to undergo an image-guided core biopsy at study entry and 6 weeks (± 1 week) after first dose of study treatment, provided that the tumor lesion is amenable to a second biopsy. Subjects will be treated until progressive disease based on irRECIST, unacceptable toxicity, consent withdrawal or the Investigator concludes that it is in the subject´s best interest to discontinue. Once the subject has discontinued from study treatment and has undergone the End of Treatment visit, she will enter into the follow-up phase. Part B includes an optional exploratory research component.
Population	**Inclusion Criteria** 1. Signed and dated informed consent document obtained prior to initiation of any study-specific procedure and treatment (by the subject or a legally acceptable representative as per the local regulations).

	2. Women ≥ 18 years old. 3. Histologically confirmed EOC, FTC or PPC. 4. Received debulking surgery and preoperative and/or postoperative platinum-based frontline chemotherapy (intravenous and/or intraperitoneal) for the treatment of EOC/FTC/PPC. 5. Documented platinum-resistant or platinum-refractory disease. Platinum-resistant disease is defined as progression within < 6 months from completion of a minimum of 4 platinum frontline therapy cycles in the pre or postoperative setting (the date should be calculated from the last administered dose of platinum agent). Platinum-refractory is defined as disease that has recurred/progressed while receiving platinum-based frontline therapy. 6. Measurable disease according to irRECIST for Part A. For Part B, subjects must have either measurable and/or non-measurable disease according to irRECIST (Appendix 2). 7. Indication of systemic treatment for the relapsed EOC, FTC or PPC. 8. For Part A, subjects must have a tumor lesion that is amenable to an image-guided core biopsy and willingness to undergo two biopsies (baseline and 6 weeks after first dose of study treatment). For Part B, subjects will be eligible even if their disease is not amenable to biopsy and/or the subject does not consent to the optional biopsies. 9. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1. 10. Expected survival of more than 6 months. 11. Adequate organ function within 7 days prior to enrollment in Part A or randomization in Part B, as defined by the following criteria: • Absolute neutrophils count (ANC) ≥ 1.5 x 109/L, platelets ≥ 100 x 109/L, hemoglobin > 9 g/dL (without transfusion or erythropoiesis stimulating agents' dependency). • Serum creatinine ≤ 1.5 x upper limit of normal (ULN). • Total serum bilirubin ≤ 1.5 x ULN regardless of liver involvement secondary to tumor. Higher levels are acceptable if these can be attributed to active hemolysis or ineffective erythropoiesis.

- Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) < 2.0 x ULN or ≤ 5 x ULN for subjects with liver metastases.
- International Normalized Ratio (INR) or Prothrombin Time (PT) ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
- Partial Thromboplastin Time (PTT) or Activated Partial Thromboplastin Time (aPTT) ≤ 40 seconds unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants.

12. For women of childbearing potential, negative serum pregnancy test within 7 days of enrollment in Part A or randomization in Part B.
13. Women of childbearing potential must agree to use acceptable methods of birth control starting with the screening visit and up to 120 days after the last dose of study treatment. Recommendation is for 2 effective contraceptive methods during the study. Adequate forms of contraception are double-barrier methods (condoms with spermicidal jelly or foam and diaphragm with spermicidal jelly or foam), oral depo provera, or injectable contraceptives, intrauterine devices, and tubal ligation.
14. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.

Exclusion Criteria

1. Non-epithelial ovarian cancers, including malignant mixed Müllerian tumors.
2. Ovarian tumors with low malignant potential (i.e. borderline tumors).
3. Relapse/progression based solely on elevation of CA-125, in absence of measurable disease (for Part A) or in the absence of measurable/non-measurable disease (for Part B), according to irRECIST criteria.
4. More than 2 prior treatment regimens for the platinum-resistant/refractory relapsed EOC, FTC, or PTC, defined as investigational, chemotherapy, hormonal, biologic, or targeted therapy.
5. Any concurrent or previous malignancy within 5 years prior to enrollment in Part A or randomization in Part B, except for adequately and radically treated basal or squamous skin cancer, or carcinoma in situ of the cervix, or other non-invasive/in-situ neoplasm. A subject with

previous history of invasive malignancy (other than adequately and radically treated basal or squamous skin cancer or carcinomas in situ) is eligible provided that she has been disease free for more than 5 years.

6. Brain metastases (even if treated and/or stable), spinal cord compression, carcinomatous meningitis, or leptomeningeal disease.
7. Prior systemic anticancer therapy within 4 weeks prior to enrollment in Part A or randomization in Part B; or who has not recovered (i.e. ≤ Grade 1 or baseline grade) from adverse events due to a previously administered agent

   Notes: subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study. If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy. Subjects with toxicity that has not recovered to ≤ Grade 1 or baseline grade are allowed if meeting all inclusion criteria.
8. Prior treatment with a monoclonal antibody within 4 weeks prior to enrollment in Part A or randomization in Part B; or who has not recovered (i.e. ≤ Grade 1 or baseline grade) from adverse events due to agents administered more than 4 weeks earlier.

   Notes: subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
9. Diagnosis of immunosuppression or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to enrollment in Part A or randomization in Part B. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.
10. Active autoimmune disease or history of autoimmune disease or syndrome that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Subjects with vitiligo or resolved childhood asthma/atopy will not be excluded.
11. Received live vaccines within 30 days prior to enrollment in Part A or randomization in Part B.
12. Current or prior history of myelodysplastic syndrome, leukemia or clinically significant (as per Investigator judgment) bone marrow failure.

	13. Uncontrolled systemic fungal, bacterial or viral infection at time of enrollment in Part A or randomization in Part B (defined as ongoing signs/symptoms related the infection without improvement despite appropriate antibiotics, antiviral therapy and/or other treatment). 14. Known history of active TB (Bacillus Tuberculosis). 15. Known HIV infection or known history of Hepatitis B or known positivity for active Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA [qualitative] is detected). 16. Known history of non-infectious pneumonitis that required steroids or has current pneumonitis (infectious or non-infectious). 17. Significant active cardiac disease within 6 months prior to enrollment in Part A or randomization in Part B , including but not limited to New York Heart Association class 4 cardiac heart failure, unstable angina, myocardial infarction 18. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator. Is or has an immediate family member (e.g. spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject. 19. Any contraindication to oral agents or significant nausea and vomiting, malabsorption, or significant small bowel resection that, in the opinion of the Investigator, would preclude adequate absorption. 20. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 21. Prior treatment with any anti-PD-1, or PD-L1 or PD-L2 agent; or with azacitidine (any formulation) or any other hypomethylating agent; or with anti-CD137, or anti-CTLA-4 antibody (including ipilimumab) or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. 22. Known or suspected hypersensitivity to azacitidine, pembrolizumab or the excipients of any of the study drugs (including mannitol). Known or suspected hypersensitivity to monoclonal antibodies.

	23. Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks prior to enrollment in Part A or randomization in Part B. 24. Pregnant or lactating women or is expecting to conceive children or breastfeed within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
Study Treatment	In this study, CC-486 and pembrolizumab are both considered Investigational Medicinal Products (IMP) given their intended use and the objectives of the study. Collectively they are referred as "study treatments". **Part A:** Pembrolizumab 200 mg IV every 21 days combined with one of the below four schedules of CC-486: • Cohort 1: CC-486 100 mg q.d. 21 days on, 7 days off. • Cohort 2: CC-486 100 mg BID, 21 days on, 7 days off. • Cohort 3: CC-486 300 mg q.d. 14 days on and 14 days off. • Cohort 4: CC-486 300 mg q.d. 21 days on, 7 days off. **Part B:** Subjects will be randomized (1:1) to receive: • Arm A: pembrolizumab 200 mg IV every 21 days combined with CC-486 (optimal schedule selected in Part A) or • Arm B: pembrolizumab 200 mg IV every 21 days
Efficacy Assessments	Assessment of irORR, irPFS, irDoR, irDCR will be based on tumor assessments (according to irRECIST criteria) using CT/MRI of chest, abdomen and pelvis. Contrast-enhanced CT scan is the preferred method. The same assessment technique must be used throughout the study to evaluate a particular lesion. Tumor burden assessments will be performed: • At baseline: within 28 days prior to enrollment in Part A or randomization in Part B. Lesions must be clearly identified and documented as Target or Non-Target lesions per irRECIST. • After baseline:

	• In Part A: ○ 6 weeks (± 1 week) after first CC-486 intake (first post-baseline tumor assessment). ○ Thereafter, every 12 weeks (± 1 week), always taking as a reference the date of the first post-baseline tumor assessment (not the date of the immediately previous tumor assessment). ○ Whenever disease progression is suspected based on signs, symptoms, performance status deterioration, CA-125, etc. ○ Confirmation of progression (irPD) is recommended minimum 4 weeks after the first irPD assessment and is required during the flare time-window of the first 12 weeks of treatment. • In Part B: ○ Every 12 weeks (± 1 week), always taking as a reference the date of randomization in the study (not the date of the previous tumor assessment). ○ Whenever disease progression is suspected based on signs, symptoms, performance status deterioration, CA-125, etc. ○ Confirmation of progression (irPD) is recommended minimum 4 weeks after the first irPD assessment and is required during the flare time-window of the first 12 weeks of treatment. Assessment of response will also be based on GCIG CA-125 criteria in subjects with CA-125 evaluable disease at baseline. However, progression cannot be declared on the basis of CA-125 alone. Disease assessments with imaging and CA-125 will be performed until progressive disease based on irRECIST, regardless of the end of study treatment and start of a subsequent anticancer therapy. After progressive disease, subjects in Part B will be followed every 6 months (visit or phone contact) until death or for at least 1 year after the End of Treatment visit, to assess the survival status.
Safety Assessments	Safety assessments will be done at baseline, at each visit during the study treatment phase and at the End of treatment visit. Additionally, hematology testing will be done weekly. All assessments will be scheduled as indicated in the Schedule of Visits and Assessments and include:

	• Physical examination and vital signs • Hematology: hemoglobin, absolute neutrophils count (ANC), platelets • Blood chemistries: creatinine, AST, ALT, alkaline phosphatase, bilirubin, glucose, TSH • Coagulation tests (at baseline and then only if clinically indicated) Recording of adverse events will be done according to NCI-CTC AE version 4.03.
Biomarker Studies	**Tumor core biopsies: Fresh-frozen tissue (FFT) and Formalin-fixed paraffin-embedded (FFPE) samples (and ascites samples if feasible):** will be collected on a mandatory basis at baseline and 6 weeks after study treatment start in all subjects participating in Part A. In Part B, tumor will be collected in subjects consenting to participate in the optional tissue acquisition study, provided they have lesion(s) amenable to biopsy. These samples will be transported to the Translational Oncology Research Laboratory at the University of California Los Angeles (TORL-UCLA). **Formalin-Fixed Paraffin-Embedded (FFPE) block/partial block from the debulking surgery:** for subjects consenting to the optional tissue acquisition part of the study, a FFPE block/partial block from the ovarian cancer debulking surgery (or a minimum of 15 unstained slides if FFPE tissue block cannot be provided) will be obtained and submitted to the TORL-UCLA. **Whole-blood samples for DNA methylation analysis:** these samples are mandatory in Part A and will be used to analyze changes in DNA methylation during treatment with CC-486. Peripheral whole blood samples will be obtained on Day 1 of the 1st CC-486 cycle (prior to the first CC-486 intake) and on the pre-treatment visit prior to the 2nd CC-486 cycle. Procedures for sample collection, labeling, storage and shipment will be described in the study lab manual.
Statistical Methods	**Analysis populations:** For each of the 2 parts of the study, there will be 2 analysis sets : • Intent-to-Treat Population (ITT): defined as all enrolled subjects • Safety Population: defined as all subjects who received at least one dose of study treatment (CC-486 and/or pembrolizumab) **Sample size justification:** **Part A**

	Part A is an exploratory pilot study of various possible schedules for the combination of CC-486 and pembrolizumab. Part A is also a futility trial for the strategy to combine pembrolizumab and CC-486 in EOC. Criteria for Part B Go/No-Go decision and the determination of an optimal dosing schedule can be found in section 3.3 of the protocol. There is no formal sample size calculation for lead-in safety and efficacy selection phase of the trial. **Part B** Part B is designed to test the hypothesis that combined epigenetic/immune checkpoint inhibition is superior to checkpoint inhibition alone in the treatment of EOC. The study will be powered to detect a difference in the log rank tests of the irPFS curves reflecting a hazard ratio of 0.625 favoring the combination. Assumptions are based on (a) an anticipated median irPFS in the pembrolizumab monotherapy arm to be 4 months and 6.4 months in the combination arm, (b) that the accrual time will be 24 months and the total study time will be 46 months and (c) a power of 80% and an alpha error at 0.05 for a two-sided test. Based on these assumptions 75 evaluable subjects need to be enrolled in each arm (n=73 subjects exactly) resulting in a total planned enrollment of 150 subjects. **Statistical Methods:** **Part A** The immune-related Overall response rate (irORR) is defined as the proportion of subjects who achieve a best overall response of immune-related Complete response (irCR) or an immune-related Partial response (irPR) based on irRECIST criteria, as per Investigator assessment. The immune-related Disease Control Rate (irDCR) is defined as the proportion of subjects who achieve a best overall response of irCR, irPR or irSD, as per Investigator assessment. The CA-125 response rate is defined as the proportion of subjects having a CA-125 response according to the GCIG criteria. **Part B** The immune-related Progression-Free Survival (irPFS) is defined as the time from the date of randomization until the date of progression (assessed by irRECIST) or death due to any cause, whichever occurs first, as per Investigator assessment. Progression will be based on tumor assessment made by the Investigators according to the irRECIST criteria. Progression will not be declared on the basis of CA-125 alone. The immune-related Duration of Response (irDoR) is defined as the time (in months) from the date when irPR or irCR is first met (whichever status comes

	first) and the date of irPD or death, whichever occurs first (as per Investigator assessment). irORR, irDCR and CA-125 response rate as described above. Overall Survival (OS) defined as the time (in months) from randomization to death from any cause.