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

CLINICAL TRIAL PROTOCOL TRIO026

NCT02900560

[redacted]

Protocol version / Date	3.0 / 14 September 2018
[redacted]	[redacted]

TRIO026 Protocol v. 3.0 – Rationale for Amendment

Version 3.0 of the protocol is an amendment applicable to all sites and triggered by safety findings in patients receiving investigational CC-486 in another trial.

On February 28, 2018 the Data Monitoring Committee (DMC) for the AZA-MDS-003 study released recommendations after some CC-486 related toxicities in patients, with International Prognostic Scoring System Lower-risk Myelodysplastic Syndromes, participating in that trial.

Based on these recommendations the TRIO026 Study Steering Committee (SSC) reviewed the TRIO026 safety data available in the clinical database as of 24-Apr-2018. Due to the hematologic and gastrointestinal treatment-emergent toxicities observed in the patients analyzed, the SSC decided to amend the protocol to require more frequent hematology assessments, dose modifications in case of neutropenia, and to make recommendations on the prevention and management of gastrointestinal toxicities.

The TRIO026 protocol was amended as follows:

Document	Version Date	Summary of changes
Protocol version 3.0	14 September 2018	• PROTOCOL SYNOPSIS: new requirement for hematology on day 8, day 15 and day 22 of each cycle added. Revision of exclusion criteria #15 and #16 to exclude patients with known history of hepatitis B and active infectious pneumonitis respectively. • Section 4.2 Exclusion criteria: Revision of exclusion criteria #15 and #16 to exclude patients with known history of hepatitis B and active infectious pneumonitis respectively. • Section 5.3.1 Premedication: modification of the recommended antiemetic medication. • Section 5.7.2.3 Supportive care measures for pembrolizumab toxicity: specification that immune-mediated adverse reactions in patients receiving pembrolizumab could be severe and fatal. Also it is specified that immune-mediated adverse reactions can occur after discontinuation of treatment. • Table 4 CC-486 dose modifications for hematologic toxicity: separated updated recommendations for treatment emergent neutropenia. • Table 5: addition of recommendation for proactive management of diarrhea. • Tables 6 and 7: addition of hematology test requirement was separated from the one from blood chemistry. Additionally, hematology test requirement on day 8, day 15 and day 22 were added. • Section 6.3.2.1 Part A: addition of hematology test requirement on day 8, day 15 and day 22.

Protocol version 2.0	05 January 2018	• DOCUMENT HISTORY section added. • Update to the TRIO Project Team. • PROTOCOL SYNOPSIS, Study Duration: accrual has been extended from 6 to 24 months . • Section 1.3.2, Pembrolizumab: inclusion of new approved indications for pembrolizumab. • Section 5.1, CC-486: reference to CC-486 150 mg tablets removed as only 100 mg tablets are used. • Section 5.3.1, Pre-medication: recommendation for the use of pre-medication based on anti-emetics for CC-486, added as per recommendation by Celgene. • Table 1: Treatment schedule adjustments for pembrolizumab: table revision, specific guidance for myocarditis added • Table 6 and Table 7: clarification added for CA-125 that does not need to be repeated prior to 1st dose of study treatment if done at screening within 7 days of enrollment. • Section 6.4.7.2, Formalin-Fixed Paraffin-Embedded (FFPE) block/partial block from the debulking surgery: possibility to provide 15 FFPE tumor unstained slides instead of a block/partial block added. • Section 9.6, Recording, Processing and Retention of Data: clarification on the study documentation retention which must be done according to ICH-GCP, local regulations or as indicated in the contractual agreement whichever is longer. • Section 9.7, Data Protection: addition of wording specifying that the anonymity of the subjects will be respected with strict adherence to professional standards of confidentiality and the Health Insurance Portability and Accountability Act (HIPPA) Privacy Rule has been added.
Protocol version 1.1	27 July 2016	• Changes in some sections where the protocol was referring to Arm instead of cohort in Part A . • Changes to the wording to improve clarity . • Wrong cross-references corrected .
Protocol version 1.0	13 Jun 2016	Initial version

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STUDY STEERING COMMITTEE

List of members is available in the Steering Committee Charter

INVESTIGATORS

A total of 4 sites from the USA will participate in Part A of the trial. An additional, of approximately, 20 sites (from USA and Germany) will participate in Part B. The list of Investigators participating in the study will be maintained in TRIO's Clinical Trial Management System.

LIST OF ABBREVIATIONS

5-HT3	Three 5-hydroxytryptamine
°C	Degrees Celsius
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase / GPT
AML	Acute myeloid leukemia
ANC	Absolute Neutrophil Count
aPTT/PTT	(activated) Partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase / GOT
BCG	Bacillus Calmette–Guérin
BID	Twice a Day
CAP	Chest, Abdomen, and Pelvis
CIOMS	Council for International Organizations of Medical Sciences
CSR	Clinical Study Report
CT	Computed tomography
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
DNA	Deoxyribonucleic Acid
ECOG	Eastern Cooperative Oncology Group
ECI	Event of clinical interest
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EMA CHMP	European Medicine Agency Committee for Medicinal Products for Human Use
EOC	Epithelial Ovarian Cancer (throughout the protocol EOC may be used interchangeably with EOC/FTC/PPC)
ERV's	Endogenous retroviral transcripts
ESMO	European Society of Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FFT	Fresh-frozen tissue
FTC	Fallopian Tube Cancer
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practices
G-CSF	Granulocyte colony stimulating factor
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HDAC	Histone deacetylase
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IgG4	Immunoglobulin G4
IMP	Investigational Medicinal Product
INR/PT	International Normalized Ratio / Prothrombin time
irCR/PR/PD	Immune-related Complete Response/Partial Response/Progressive Disease
irDCR/PFS	Immune-related Disease Control Rate/Progression Free Survival
irORR	Immune-related Objective Response Rate
irPFS	Immune-related Progression Free Survival
irRECIST	Immune-Related Response Evaluation Criteria In Solid Tumors
IRB	Institutional Review Board
IRR	Infusion-related reaction
ITT	Intent-To-Treat
IV	Intravenous

IWRS	Interactive Web Response System
kg	kilogram
mAb	monoclonal Antibody
MDS	Myelodysplastic Syndromes
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRI	Magnetic Resonance image
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non Small Cell Lung Cancer
NTL	Non Target Lesion
OS	Overall Survival
PD-1	Programmed (cell)Death protein 1
PD-L1	Programmed (cell) Death-Ligand 1
PD-L2	Programmed (cell) Death-Ligand 2
PEM	Pembrolizumab
PICF	Patient Informed Consent Form
PPC	Primary Peritoneal Cancer
PS	Performance status
Q3W	Every 3 weeks
q.d.	Once a Day
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOP	Standard Operating Procedures
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 Diabetes Mellitus
TL	Target Lesion
TORL	Translational Oncology Research Labs
TRIO	Translational Research In Oncology
TSH	Thyroid-stimulating hormone
UCLA	University of California, Los Angeles
UNL	Upper Normal Limit
US	United States
WBC	White Blood Cells
WoCBP	Women of Childbearing Potential

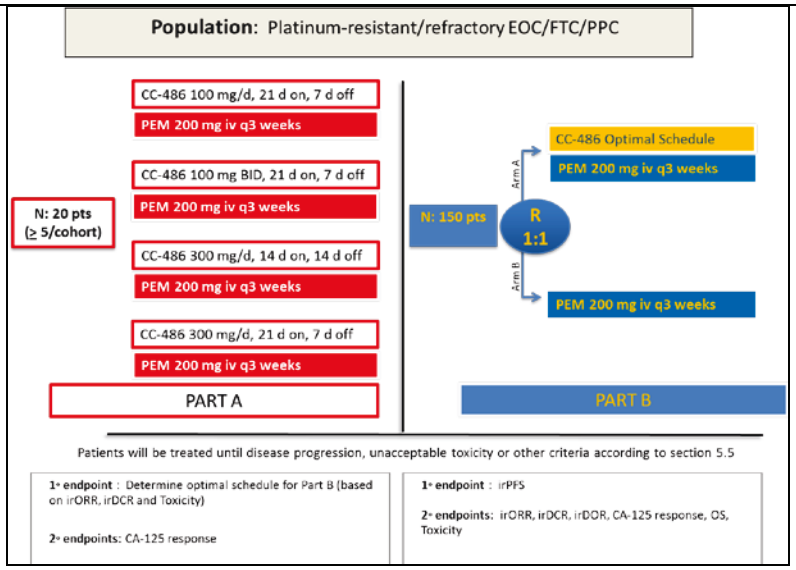
PROTOCOL SYNOPSIS

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) $\geq$ 1.5 x 10^9/L, platelets $\geq$ 100 x 10^9/L, hemoglobin > 9 g/dL (without transfusion or erythropoiesis stimulating agents' dependency). • Serum creatinine $\leq$ 1.5 x upper limit of normal (ULN). • Total serum bilirubin $\leq$ 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.

1. BACKGROUND AND RATIONALE

1.1 Disease Overview

Comprehensive global cancer statistics indicate that there are approximately 200,000 new cases of epithelial ovarian cancer (EOC) diagnosed each year in the world and over 125,000 deaths attributed to the disease.[1] Although the death rate for ovarian cancer has been stable for the last 10 years it remains the cause of more cancer deaths of the female reproductive system than any other. Fallopian tube cancer (FTC) and primary peritoneal carcinoma (PPC) are grouped with EOC because of their similar prognostic, therapeutic, histologic and biologic features as EOC.[2,3]

In more than 75% of the newly identified cases, the disease has already reached an advanced state (stage III or IV) at the time of initial diagnosis.[4] Patients with newly diagnosed EOC are typically primarily treated with a major and extensive surgical procedure with the intent to remove all intra-abdominally visible tumors.[5] After the initial surgery, most patients undergo six cycles of combination chemotherapy with two cytotoxic agents, most commonly a platinum salt (cisplatin or carboplatin) and a taxane (paclitaxel or less frequently docetaxel), administered intravenously or intra-peritoneally.[4–6] Neoadjuvant chemotherapy is also increasingly used.[6] The systemic therapy is administered in hopes of effectively treating any residual or micro-metastatic disease remaining in the abdomen. Despite this rigorous treatment, more than 75% of patients experience a recurrence of their disease within the first 20 months of completing their frontline therapy.[7] Almost all of these recurrences are intra-abdominal and many are treated with further surgical resections (when indicated) and almost all are treated with multiple cycles of “salvage” chemotherapy with the same or other cytotoxic agents as the ones used in the pre/postoperative setting.[8,9] If the disease recurrence has occurred more than 6 months after completion of the initial chemotherapy, usually a platinum/taxane-based regimen is used again and these patients have good probabilities of response to treatment.

Patients whose recurrence occurs within 6 months of initial chemotherapy are considered to have platinum-resistant disease. At first relapse, approximately 25% of patients have platinum-resistant EOC and their prognosis is poor, with relapses occurring within few months after completing salvage therapy and a median overall survival of approximately 12 months.[10,11]

1.2 Overview of Current Treatment for Platinum-Resistant EOC

There are a number of treatment options available for women with platinum-resistant EOC, and the ideal treatment is not known. Due to the added toxicity and lack of high-quality evidence showing improvement in survival for combination chemotherapy, most oncologists choose to treat these patients with sequential single-agent therapy.[12,13]

Agents such as topotecan, paclitaxel, docetaxel, oral etoposide, gemcitabine or pegylated liposomal doxorubicin are associated with response rates typically < 20% and a median PFS of 3-4 months.[14] The addition of bevacizumab to single-agent chemotherapy have shown to improve PFS and ORR and is an acceptable alternative treatment.[14] The choice among these strategies depends upon the clinician's experience, the side effect profile, and prior therapy.

Treatment for platinum-resistant ovarian cancer is far from being curative. Because palliation is the goal of treatment, choosing the proper agent for use in this setting involves balancing the perceived need to obtain an objective response against the importance of maintaining quality of life.

Given the low response rates and short PFS, there is a clear, unmet medical need for more effective treatments for patients with platinum-resistant/refractory relapsed EOC. Since chemotherapeutic approaches have not been able to demonstrate a significant improvement in disease outcomes, these improvements depend upon the optimal integration of novel approaches into clinical trials.

1.3 Investigational Medicinal Product Overview

1.3.1 CC-486

Azacitidine is an analog of the pyrimidine nucleoside cytidine that has effects on cell differentiation, gene expression, and DNA synthesis and metabolism. Azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. The concentration of azacitidine required for maximum inhibition of DNA methylation in vitro does not cause major suppression of DNA synthesis. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanisms. Non-proliferating cells are relatively insensitive to azacitidine.

Since the early 1970s, azacitidine has been investigated in the United States (US) for the treatment of acute leukemia. These investigations indicated azacitidine has activity in the treatment of acute myeloid leukemia (AML). Clinical trials subsequently have been conducted to evaluate the effects of azacitidine in a variety of other malignant and hematologic disorders, including solid tumors, hemoglobinopathies (thalassemia and sickle cell anemia), and myelodysplastic syndromes (MDS). Vidaza® (azacitidine for injection) is approved by the US Food and Drug Administration (FDA) for the following 5 subtypes of the French-American-British classification system of MDS: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia. Vidaza® is also approved by the European Commission (EU) for the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation (HSCT) with the following: intermediate-2 and high-risk MDS according to the International Prognostic Scoring System, chronic myelomonocytic leukemia with 10% to 29% marrow blasts without myeloproliferative disorder, and AML with 20% to 30% blasts and multilineage dysplasia. For these indications, Vidaza® can be administered by the intravenous or subcutaneous routes as designated by country approval. Currently Vidaza® has received marketing authorization in over 80 countries worldwide including US and EU.

CC-486 is an oral formulation of azacitidine that is currently being evaluated in clinical trials, either as a single agent or in combination with other drugs, for the treatment of hematological and solid malignancies. CC-486 is under development and is not approved by any regulatory agency worldwide for any indication.

The safety profile of azacitidine has been well characterized and is based on an extensive amount of patient exposure across a wide range of doses and indications, as well as routes of administration (SC, IV, oral). The vast majority of safety data for azacitidine comes from patients with myelodysplastic syndromes, a setting where marrow tolerance is known to be reduced. Most common adverse reactions (≥ 30%) by SC route are nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia and ecchymosis. The most common adverse reactions by IV route also included petechiae, rigors, weakness and hypokalemia.

For oral azacitidine, the most frequently reported adverse reactions (≥ 30%) are: diarrhea, nausea, constipation, vomiting, fatigue and decreased appetite. Overall, about 50% of patients receiving CC-486 reported at least one treatment-emergent AE of myelosuppression (neutropenia, thrombocytopenia, anemia, and/or general myelosuppression).

The reporting frequencies for the common hematological and non-hematological events were generally highest during Cycles 1 and 2, after which time the frequencies decreased over subsequent treatment cycles. This and other similar findings suggest a lack of cumulative toxicity and that AEs of azacitidine attenuate over time.

1.3.2 Pembrolizumab

The programmed death protein 1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. Binding of PD-1 ligands to PD-1 inhibits T-cell activation triggered through the T-cell receptor. Pembrolizumab (Keytruda®) is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)/kappa isotype designed to directly block the interaction between PD-1 and its ligands, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

Pembrolizumab is approved in various jurisdictions for various indications:

- For the treatment of patients with unresectable or metastatic melanoma and disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor (US, EU, Japan)
- As first-line treatment of patients with metastatic non-small cell lung carcinoma (NSCLC) whose tumors with PD-L1 positive, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.
- As first-line treatment of patients with metastatic non-squamous NSCLC in combination with platinum chemotherapy and pemetrexed (US)
- For the treatment of PD-L1 positive metastatic NSCLC with disease progression on/after platinum-containing chemotherapy (US)
- For the treatment of patients with refractory classical Hodgkin Lymphoma or who have relapsed after greater than or equal to 3 prior lines of therapy (US, EU)
- For the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy (US)
- For the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who are not eligible for cisplatin-containing chemotherapy or patients with locally advanced or metastatic UC who have received platinum-containing chemotherapy (US)
- For the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high or mismatch repair deficient solid tumors who have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- Patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

Pembrolizumab is currently being evaluated in clinical trials in several hematologic malignancies and solid tumors.

Pembrolizumab is generally well tolerated and has demonstrated a favorable safety profile in comparison to chemotherapy. The most common treatment related adverse events observed with pembrolizumab are mostly grade 1-2 and include fatigue, diarrhea, decreased appetite, nausea, and anemia. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern. Important identified risks for pembrolizumab are of an immune mediate nature, including pneumonitis, colitis, thyroid disorders (hypothyroidism/hyperthyroidism), hepatitis, hypophysitis, Type I diabetes mellitus, uveitis, and nephritis. The majority of immune-mediated adverse events are mild to moderate in severity, are manageable with appropriate care, and rarely require discontinuation of therapy.

Refer to the pembrolizumab Investigator´s Brochure (IB) for additional information on the drug.

1.4 Study Rationale

1.4.1 Rationale for Conducting the Study

Recent advances in immunotherapy have led to the development and rapid clinical introduction of monoclonal antibodies directed against two immune checkpoints, CTLA-4 (Cytotoxic T-lymphocyte-associated antigen-4) and PD-1 or PD-L1. All of these agents, and in particular the anti-PD-1 antibodies, have shown clear benefit in the treatment of metastatic melanoma and NSCLC.[15–17] 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. A phase Ib trial with the PD-L1 inhibitor avelumab demonstrated clinical activity (ORR 10.7% (95% CI, 4.7-19.9) and DCR 54.7%) and a low toxicity profile in treatment-refractory unselected patients with EOC.[18] Additionally, a phase Ib study with pembrolizumab demonstrated activity (ORR 11.5% (95% CI, 2.4-30.2) and DCR 34.6%) and a favorable safety profile in heavily pretreated PD-1-positive patients.[19] The observed response and disease control rates in pre-treated patients with relapsed EOC clearly indicate that immune checkpoint inhibition is a strategy that warrants further research in the treatment of EOC.

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.[20,21] 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.

Preclinical 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. 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. There is, thus, a robust concordance for induced increases in genes, highest in ovarian cancer cells, which can trigger increased interferon signaling and concordant upregulation of surface antigens and their assembly proteins and viral defense pathways in 77 epithelial cancer cell lines treated with azacitidine.[22] These upregulated genes include transcript and surface protein levels of PD-L1, the tumor ligand for immune cell PD-1 and high versus low expression in tumor cells of this ligand appears to correlate with good response to anti-PD-1 therapy.[16,22] Most recently, work from two groups indicates a key way in which azacitidine upregulates immune signaling and interferon signaling in cancer cells, including ovarian cancer, is through activation of a double strand RNA (dsRNA) viral defense pathway (Chiappinelli KB, et al, Cell in press, 2015).

All of these above data lead to the hypothesis, inherent to this trial, that through coordinated upregulation of tumor antigens and MHC proteins, interferon pathway induction by dsRNA transcripts including endogenous retroviral transcripts (ERV's), and upregulation of tumor–associated tolerance ligands, DNA demethylating agents may induce T-cell attraction (Figure 1). Immune checkpoint efficacy in this setting may be enhanced when tolerance inducing ligand and receptor interactions are interrupted.

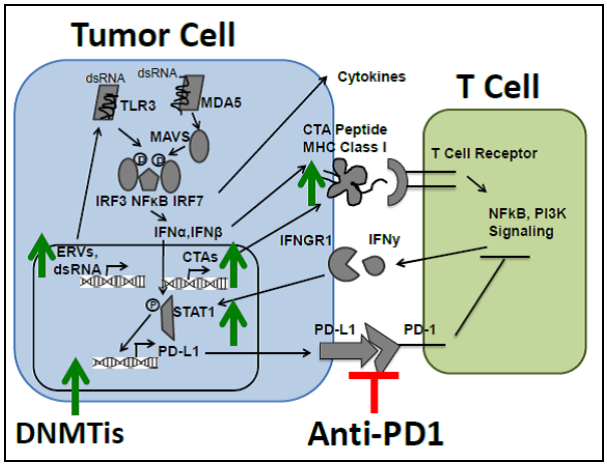


Figure 1: DNA demethylating agents: proposed mechanism of action

Model for how the findings outlined above suggest DNA demethylating agents (DNMTis) may sensitize to immune checkpoint therapies. The DNMTis activate tumor antigens, MHC proteins and their assembly, and the interferon driving viral defense pathway with down stream up-regulation of PD-L1. This concordant signature would attract T-cells and tolerance would then be broken with anti-PD1 therapy.

The levels of the above, ~ 20 gene, viral defense "immune signature" that is upregulated following epigenetic therapy also appears to be a useful biomarker to predict benefit from epigenetic priming during immune checkpoint therapy. This will be tested in tumor biopsy samples, pre- and post-therapy in this trial. In a recent study, high basal levels of the azacitidine-induced viral defense gene signature expression in tumor samples correlated with long-term benefit (Chiappinelli et al., Cell, in press) in patients with advanced melanoma treated with the immune checkpoint inhibitor, anti-CTLA-4.[23] Importantly, for virtually all of these melanoma patients, treatment benefit, high tumor mutational burden and basal viral defense signature are all significantly associated (Chiappinelli et al., Cell, in press) (Figure 2 A). Moreover, low dose azacitidine plus anti-CTLA-4 are significantly more effective at controlling tumor growth compared to each agent alone in the B16 mouse model of melanoma

(Chiappinelli et al., Cell, in press) (Figure 2 B). The hypothesis in the trial is that patients with a low level of the above gene panel will be benefitted by having azacitidine induce a higher level to help sensitize to anti-PD-1.

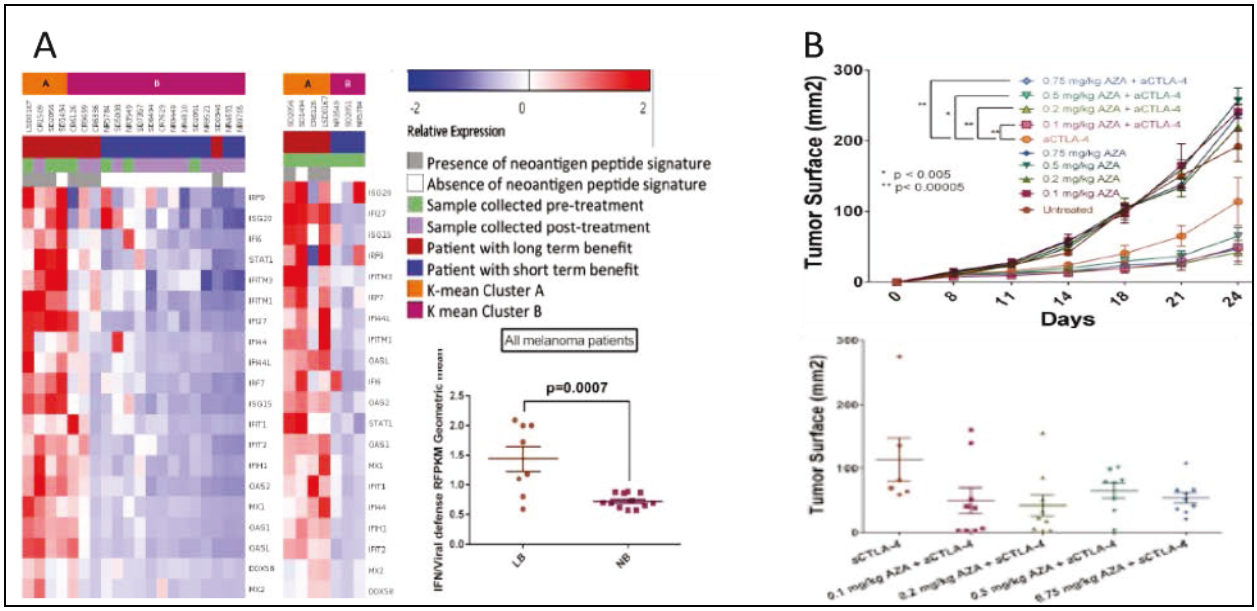


Figure 2: Viral defense gene signature and CC-486 preclinical activity
(From Chiappinelli et al., Cell, in press): **A:** Viral defense gene signature is upregulated in tumors from anti-CTLA-4 treated metastatic melanoma patients who derived durable clinical benefit (complete response, partial response, or progression free-survival > 6 months as previously described[23]) compared to those without benefit. Tumors collected pre-CTLA-4 treatment and shortly post-treatment are shown. **B:** Tumor responses of mice injected with B16-F10 cells and treated with either phosphate-buffered saline, anti-CTLA-4, azacitidine, or both anti-CTLA-4 and azacitidine. Data represent results from one of two independent experiments with identical results, each with n = 10 per arm.

This study will enroll subjects with platinum-resistant/refractory EOC 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 when given as a single agent in relapsed EOC.

1.4.2 Rationale for Regimen and Dose Selection

CC-486 is well tolerated and produces evidence of induced hypomethylation at doses of 100 to 300 mg daily. Doses of 300 mg per day are well tolerated in patients with myelodysplastic syndromes, a setting where bone marrow tolerance is known to be reduced. We expect doses up to 300 mg daily to be well tolerated in patients with EOC, who do not have intrinsic bone marrow disease.

Pembrolizumab will be used at a fixed dose of 200 mg every 3 weeks. The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the

population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that: (1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, (2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and (3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe. A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

In all treatment schedules in the study, CC-486 will be given for 7 days before the first pembrolizumab administration with the intent of hypomethylation being induced at time of first pembrolizumab exposure.

This is not the first study that is assessing the combination of pembrolizumab and azacitidine. A phase II study in colorectal cancer patients is currently recruiting patients and evaluating the combination of pembrolizumab (200 mg every 21 days) and IV azacitidine. Another phase II study is assessing the safety and efficacy of CC-486 (at a dose of 300 mg daily for 14 days) and pembrolizumab in advanced NSCLC. No safety or efficacy results are publicly available at time of release of this protocol.

2. OBJECTIVES

2.1 Part A

2.1.1 Primary Objective

- To establish an optimal schedule of CC-486 combined with pembrolizumab in subjects with platinum-resistant/refractory EOC.

2.1.2 Secondary Objective

- To assess the CA-125 response based on the Gynecological Cancer Intergroup (GCIG) criteria[24].

2.1.3 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.

2.2 Part B

2.2.1 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). irRECIST is a modification of RECIST v1.1 guidelines, to account for the unique response patterns observed with immunotherapy.[25,26] (refer to Appendix 2).

2.2.2 Secondary Objectives

- To assess secondary measures of efficacy for CC-486 combined with pembrolizumab (optimal schedule selected in Part A) relative to pembrolizumab alone.

  Efficacy endpoints:

  - Immune-related Overall Response Rate (irORR)
  - Immune-related Disease Control Rate (irDCR)
  - Immune-related Duration of Response (irDoR)
  - CA-125 response based on GCIG criteria
  - Overall Survival (OS)

- To assess the safety and tolerability of CC-486 combined with pembrolizumab.

2.2.3 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.

3. STUDY DESIGN

This is an open-label, multicenter, multinational trial that will be carried out in two sequential parts (Figure 3).

3.1 Part A

Part A is an open-label, four-cohort, non-randomized, lead-in selection phase in which intravenous (IV) 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 pembrolizumab (200 mg IV q3 weeks in all cohorts) (refer to section 5.3.3 for details on study treatments administration) 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 (e.g. first subject in cohort 1, second subject in cohort 2, etc.). 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. If a subject assigned to a given cohort is not evaluable (i.e. have not completed two CC-486 cycles and/or have not had the first post-baseline tumor assessment and/or both tumor biopsies) then these subjects will be replaced. 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 (or any other withdrawal criteria is met according to section 5.5). Subjects who discontinue treatment for reasons different than irPD will enter the follow-up phase and will continue to be followed with tumor assessment every 12 weeks until irPD. After irPD, and provided that subject has undergone the End of Treatment visit, all subjects will be taken off the study unless presence of serious adverse events (SAEs) or study treatment-related adverse events. In such case these events will be monitored as clinically indicated until the events have resolved (or return to baseline) or in the Investigator's opinion, are unlikely to resolve due to the nature of the condition and/or the subject's underlying disease.

Once 5 subjects in each cohort are considered evaluable, enrollment will be stopped and data from each cohort will be analyzed and the optimal schedule to be taken forward into Part B will be selected according to section 3.3.

Part A includes mandatory tumor core biopsies for biomarkers research and mandatory whole blood sampling for DNA methylation analyses (see section 6.4.7).

3.2 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.

If necessary, a protocol amendment may be released to further define the eligibility criteria, treatment schema, etc. for Part B, based on the analysis of Part A. If there are no changes in the study design, conduct, treatments, safety consideration, etc., this same protocol version will be used for both Part A and Part B.

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:

- Type of relapsed disease: platinum-refractory vs. platinum-resistant (refer to the corresponding definitions in section 4.1)
- 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 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 (or any other withdrawal criteria is met according to section 5.5). Once the subject is discontinued from study treatment and has undergone the End of Treatment visit, she will enter into the follow-up phase. Subjects who discontinue treatment for reasons different than progressive disease will continue to be

followed with tumor assessment every 12 weeks until irPD. After progressive disease, subjects will be followed for assessment of survival status every 6 months (visit or phone contact) until death or for at least 1 year after the End of Treatment visit.

Part B also includes an optional exploratory research component (see section 6.4.7).

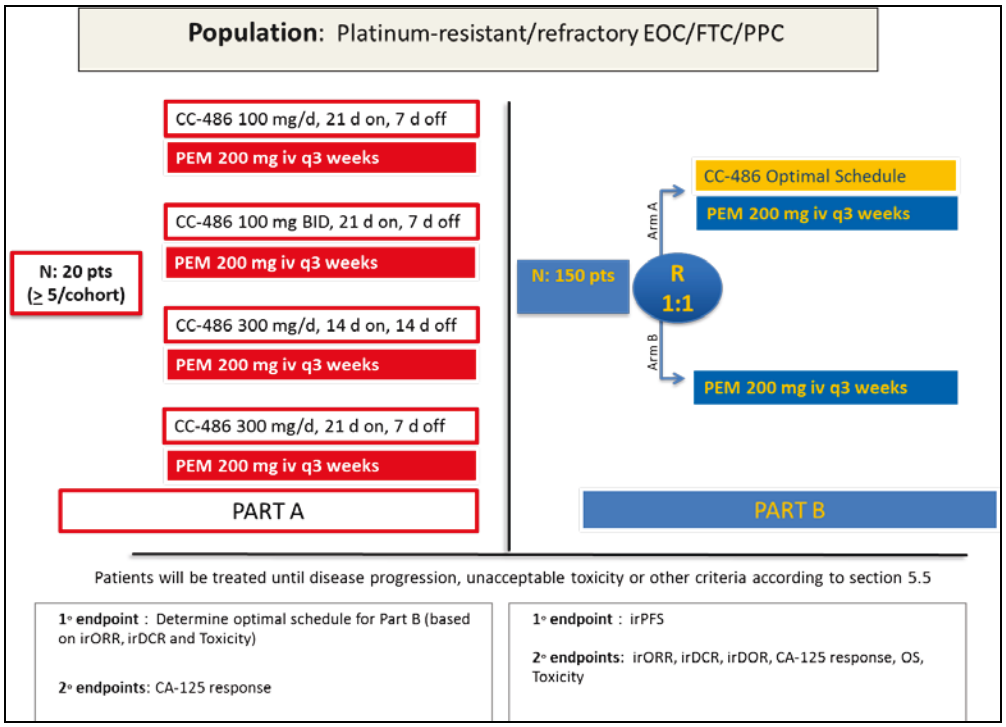


Figure 3: Study schema

3.3 Part A: Determination of the Optimal Schedule for Part B

The optimal schedule to be used in Part B will be selected after analysis of the accumulated safety and efficacy data from Part A by the Steering Committee. The analyses will be conducted once 5 subjects in each cohort are considered evaluable. Subjects will be considered evaluable once they have:

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

Full details of the criteria to be used to guide the Steering Committee in their selection of the optimal regimen will be described in the Steering Committee Charter. In general, however, the following decision criteria will be applied:

- Step 1: Safety and Futility evaluation:

  A cohort will be rejected due to toxicity if any of the below criteria is met:

  - One grade 5 AE related to study drugs
  - More than one subject experiencing a grade 4 AE related to study drugs (other than hypothyroidism)

- More than 2 subjects experiencing a grade 3 AE related to study drugs (other than hypothyroidism)

A cohort will be rejected due to futility if at least one response or stable disease (irPR, irCR or irSD) is not observed in that schedule.

- Step 2: Determination of the optimal schedule: In the cohort(s) not rejected due to toxicity or due to futility, the selection by the Steering Committee of the optimal schedule will be based on the toxicity profile and the irORR of each cohort (irDCR may also be considered for the determination of the optimal schedule). For example, if one cohort has higher irORR and similar toxicity profile compared to another cohort, the first one will be selected as optimal. If two or more cohorts have the same irORR, the optimal schedule will be established based primarily on the more favorable toxicity profile. Additionally, data from the correlative analyses to be done in the biologic samples described in section 6.4.7, may be taken into consideration for determining the optimal schedule.

3.4 Number of Subjects and Investigational Sites

In Part A, at least 5 evaluable subjects per cohort will be included in the study, from 4 participating sites from the USA.

In Part B, 150 subjects will be included, from approximately 25 participating sites from the USA and Germany. The sites participating in Part A will also be participating in Part B.

3.5 Study End

The study will end once the last subject undergoes the last visit and all events required for the final analyses have been observed and collected.

The trial may be prematurely terminated by the sponsor. In this case, subjects deriving clinical benefit from the study treatment at time of trial termination will continue to be provided with study drug by the sponsor/manufacturer.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are applicable both for Part A and B of the study.

Subjects who fail to meet all inclusion criteria or fulfill at least one exclusion criteria cannot be enrolled in the study. The sponsor will not grant any eligibility waivers. If a subject that does not meet the eligibility criteria is incorrectly enrolled in Part A or randomized in Part B, the Investigator should immediately inform the Medical Monitor. The decision about the continuation or discontinuation of these subjects on the study will be based on medical judgment, treatment benefit and safety risks for the subject.

4.1 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 (Appendix 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) $\geq$ 1.5 x 10^9/L, platelets $\geq$ 100 x 10^9/L, hemoglobin > 9 g/dL (without transfusion or erythropoiesis stimulating agents' dependency).
    - Serum creatinine $\leq$ 1.5 x upper limit of normal (ULN).
    - Total serum bilirubin $\leq$ 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.

** Note: Given the patient population in the trial, it is highly unlikely that women of childbearing potential (WoCBP) are enrolled. WoCBP are any women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation. Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal ligation/occlusion. Non-sterile women will be considered of WoCBP if they did not have at least 12 months with no menses without an alternative medical cause*.

4.2 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.

5. TREATMENT

In the TRIO026 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".

In both parts (A and B), subjects will remain on their assigned study treatment until progressive disease based on irRECIST, unacceptable toxicity, consent withdrawal, Investigator's decision that it is in the subject´s best interest to discontinue or other treatment withdrawal criteria is met (section 5.5).

5.1 CC-486

All subjects in Part A and subjects randomized to Arm A of Part B will receive oral CC-486 at the dosing described in sections 5.3.3 and 5.3.4.

At each visit during the treatment phase, subjects should be given container(s) with enough 100 mg tablets for one full CC-486 treatment cycle (defined as 21 or 14 days on-treatment followed by 7 or 14 days off-treatment (depending on the cohort)) of the corresponding schedule/arm (refer to section 5.3).

In Part A, the following number of 100 mg tablets would be needed for a subject to complete one CC-486 cycle of treatment, assuming no dose delays or interruptions or dose reductions from the starting dose level:

- Schedule 1: 21 tablets of 100 mg
- Schedule 2: 42 tablets of 100 mg
- Schedule 3: 42 tablets of 100 mg
- Schedule 4: 63 tablets of 100 mg

The number of tablets may need to be adjusted in case of dose modifications.

For the purpose of this trial, the Single Reference Document to be used for CC-486 is the azacitidine IB.

5.2 Pembrolizumab

Pembrolizumab will be administered in all cohorts in Part A and in both arms in Part B at a fixed dose of 200 mg as a 30 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

In all cohorts in Part A and in Arm A of Part B, the first pembrolizumab infusion will be administered 7 days (± 3 days) after commencing treatment with CC-486 and thereafter all subsequent infusions will be administered every 21 days (± 3 days).

For the purpose of this trial, the Single Reference Document to be used is the pembrolizumab IB.

5.3 Dosage and Administration

5.3.1 Pre-medications

5.3.1.1 Antiemetics for Prevention and Treatment of Emesis

Drugs with the highest therapeutic index for the management of treatment induced nausea and vomiting are the type three 5-hydroxytryptamine (5-HT3) receptor antagonists and the neurokinin-1 receptor (NK1R) antagonists. Additionally, recent data has demonstrated substantial antiemetic activity for the antipsychotic medication olanzapine when used in combination with other antiemetics.

The following antiemetic medication is recommended for CC-486:

- Prophylactic 5-HT3 antagonist should be considered on days when CC-486 is administered.
- Prochlorperazine and/or 5-HT3 inhibitor could also be considered for delayed nausea as needed.
- If subjects experience nausea sub-optimally controlled with prochlorperazine on the days of CC-486 administration, prophylactic 5-HT3 inhibitors may be used.
- If nausea and vomiting persists despite the above measures, more aggressive use of 5-HT3 antagonists or other anti-emetics could be used at the discretion of the treating physician. In cases of nausea and/or vomiting insufficiently controlled by prophylactic treatment with a 5-HT3 receptor antagonist, antiemetic therapy with a combination of an NK1R antagonist and a 5-HT3 receptor antagonist and consideration of olanzapine is recommended.

5.3.1.2 Antidiarrheals

Although premedication for diarrhea prophylaxis is not required, proactive management of first signs of diarrhea is strongly recommended according to section 5.7.3.2. Prophylaxis can be considered as per investigator's best clinical judgement and local practice.

5.3.1.3 Pembrolizumab Premedication

No specific pre-medication is required upfront for pembrolizumab. However pre-medications may be given as per the institutional standard of care.

5.3.2 Preparation

5.3.2.1 CC-486

Not applicable.

5.3.2.2 Pembrolizumab

Preparation should be done in accordance with the Single Reference Document for pembrolizumab and with site´s standard procedures for preparing pembrolizumab.

5.3.3 Study Treatment Administration in Part A

Eligible subjects will receive pembrolizumab 200 mg IV every 21 days (± 3 days) combined with one of the below four schedules of CC-486:

- Schedule 1: CC-486 100 mg q.d. 21 days on, followed by 7 days off-treatment.
- Schedule 2: CC-486 100 mg BID 21 days on, followed by 7 days off-treatment.

- Schedule 3: CC-486 300 mg q.d. 14 days on, followed by 14 days off-treatment.
- Schedule 4: CC-486 300 mg q.d. 21 days on, followed by 7 days off-treatment.

For each subject, the corresponding study treatment schedule will be assigned according the process described in section 6.1.2.1.

On the first CC-486 cycle, after 7 days (± 3 days) of CC-486 monotherapy, the first pembrolizumab administration will be done and thereafter subsequent pembrolizumab infusions will be given every 21 days (± 3 days). CC-486 will continue according to the applicable schedule.

Treatment duration with CC-486 is fixed to 21 consecutive days for schedules 1, 2 & 4, and to 14 consecutive days for schedule 3, regardless of treatment interruptions for any reason. The treatment period with CC-486 must always be followed by the 'off treatment period' defined for each of the treatment schedules.

Subjects will remain on their assigned treatment until progressive disease based on irRECIST, unacceptable toxicity, consent withdrawal, the Investigator concludes that it is in the subject´s best interest to discontinue, or other treatment withdrawal criteria is met (section 5.5).

If a subject is enrolled in Part A but does not receive any study treatment, the reason must be documented in the electronic case report form (eCRF). Baseline data will be collected and subject will undergo the End of Treatment visit (even if no treatment administered) and will be taken off the study.

5.3.3.1 CC-486 intake instructions

CC-486 should be taken at the same time each day (± 2 hours). When taken twice a day, CC-486 should be taken approximately every 12 hours, in the morning and at night. CC-486 may be taken on an empty stomach or with food (a light breakfast or meal of up to approximately 600 calories). Subjects will ingest CC-486 whole tablets with approximately 240 mL (8 ounces) of room temperature water. No tablet should be ingested if it is broken, cracked, or otherwise not intact.

If the subject misses a dose of CC-486, she should take the dose as soon as possible, but not more than 6 hours after the missed scheduled dose. If greater than 6 hours, the missed dose should be skipped and the subject should take the next dose when scheduled. No "make-up dose" or increased dosing should occur.

If vomiting occurs following CC-486 administration, subjects should not take additional drug on that same day. It is recommended that the subject receives an antiemetic (e.g. ondansetron) 30 minutes prior to all subsequent CC-486 doses.

5.3.3.2 CC-486 Intake: Specificities on Day 1 of the First CC-486 cycle (all schedules)

In all schedules, the first CC-486 intake in the study (i.e. on the first CC-486 cycle) should be taken by the subject during the clinic visit and after the whole blood sample for DNA methylation was drawn.

Subject must arrive to the clinic in the fasting state (i.e. no food or drink [except water] for approximately 8 - 10 hours) for the required pre-dose assessments (DNA methylation blood sample and safety evaluations as per section 6.4 if applicable). Once these assessments are completed, subjects will ingest CC-486 with 240 mL of room temperature water in the clinic.

5.3.3.3 Treatment Regimen for Schedule 1

The treatment to be used in the trial is outlined below in Figure 4.

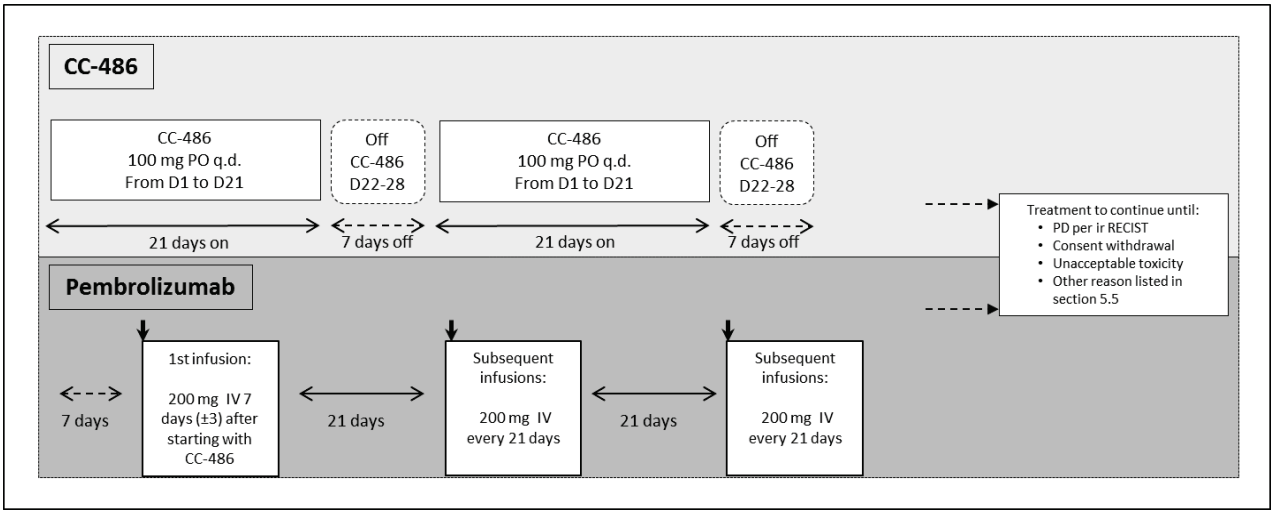


Figure 4: Treatment regimen for Schedule 1

Notes:

- Within 3 days of enrollment, study treatment will begin with CC-486 monotherapy. After 7 days (± 3 days) of CC-486 treatment, the first pembrolizumab administration will be done.
- Pembrolizumab will be administered at a dose of 200 mg as a 30-minutes IV infusion every 21 days (± 3 days). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.
- CC-486 is administered 100 mg orally once daily, 21 days on treatment followed by 7 days off. CC-486 may be taken on an empty stomach or with food (a light breakfast or meal of up to approximately 600 calories). Whole tablets of CC-486 must be taken with approximately 240 mL (8 ounces) of room temperature water.
- On days when both CC-486 and pembrolizumab are administered, pembrolizumab will be infused after CC-486 intake.
- Refer to section 5.7 for treatment schedule adjustments.

5.3.3.4 Treatment Regimen for Schedule 2

The treatment to be used in the trial is outlined below in Figure 5.

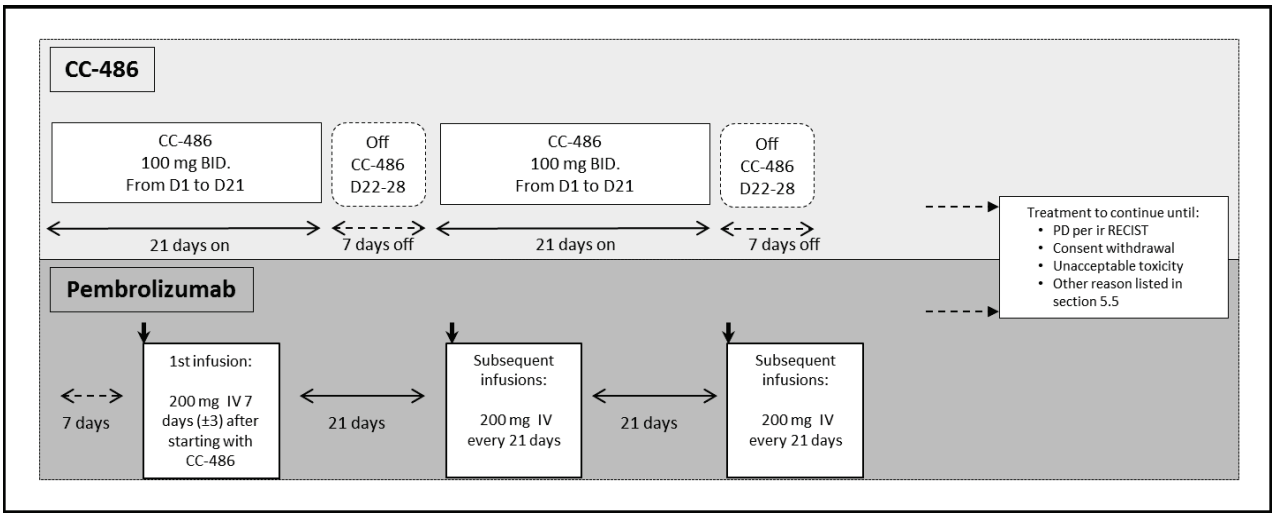


Figure 5: Treatment regimen for Schedule 2

Notes:

- Within 3 days after enrollment, study treatment will begin with CC-486 monotherapy. After 7 days (± 3 days) of CC-486 treatment, the first pembrolizumab administration will be done.
- Pembrolizumab will be administered at a dose of 200 mg as a 30-minutes IV infusion every 21 days (± 3 days). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.
- CC-486 is administered 100 mg orally twice a day (approximately every 12 hours, in the morning and at night), 21 days on treatment followed by 7 days off. CC-486 may be taken on an empty stomach or with food (a light breakfast or meal of up to approximately 600 calories). Whole tablets of CC-486 must be taken with approximately 240 mL (8 ounces) of room temperature water.
- On days when both CC-486 and pembrolizumab are administered, pembrolizumab will be infused after the first CC-486 intake on that day.
- Refer to section 5.7 for treatment schedule adjustments.

5.3.3.5 Treatment Regimen for Schedule 3

The treatment to be used in the trial is outlined below in Figure 6: Treatment regimen for Schedule 3

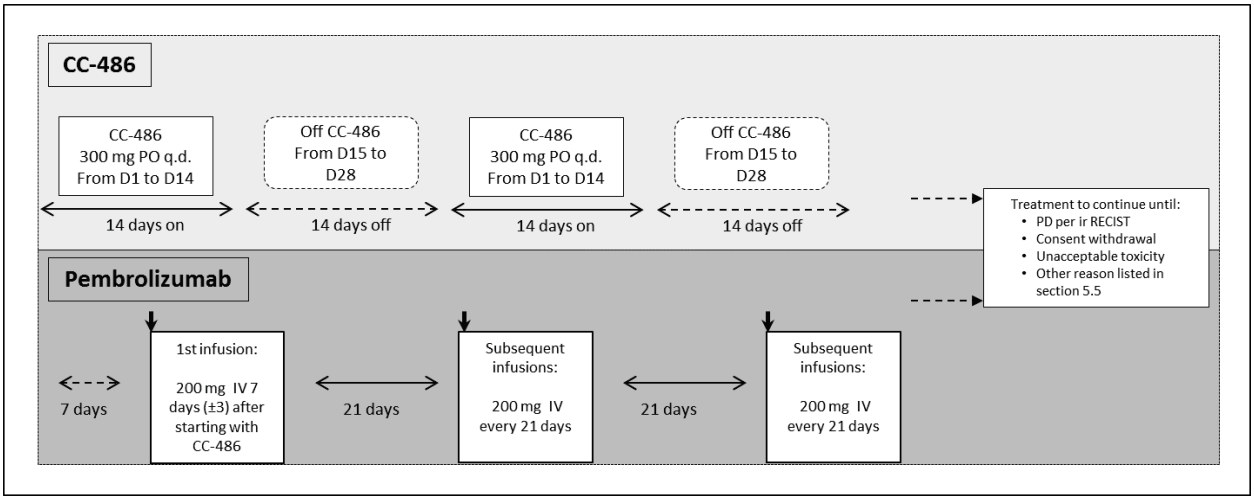


Figure 6: Treatment regimen for Schedule 3

Notes:

- Within 3 days of enrollment, study treatment will begin with CC-486 monotherapy. After 7 days (± 3 days) of CC-486 treatment, the first pembrolizumab administration will be done.
- Pembrolizumab will be administered at a dose of 200 mg as a 30-minutes IV infusion every 21 days (± 3 days). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.
- CC-486 is administered 300 mg orally once daily, 14 days on treatment followed by 14 days off. CC-486 may be taken on an empty stomach or with food (a light breakfast or meal of up to approximately 600 calories). Whole tablets of CC-486 must be taken with approximately 240 mL (8 ounces) of room temperature water.
- On days when both CC-486 and pembrolizumab are administered, pembrolizumab will be infused after CC-486 intake.
- Refer to section 5.7 for treatment schedule adjustments.

5.3.3.6 Treatment Regimen for Schedule 4

The treatment to be used in the trial is outlined below in Figure 7: Treatment regimen for Schedule 4

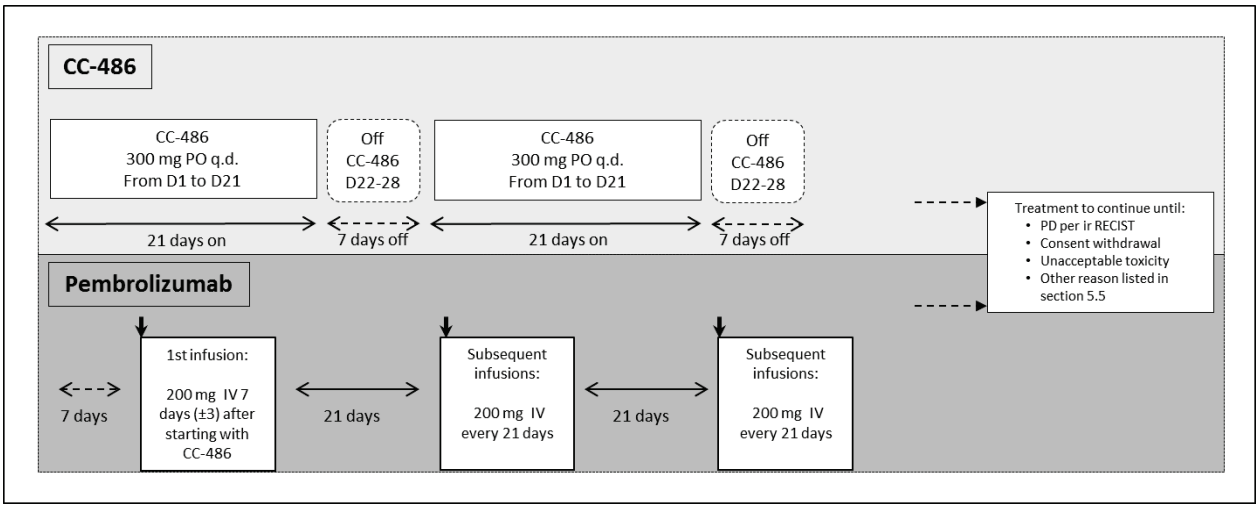


Figure 7: Treatment regimen for Schedule 4

Notes:

- Within 3 days of enrollment, study treatment will begin with CC-486 monotherapy. After 7 days (± 3 days) of CC-486 treatment, the first pembrolizumab administration will be done.
- Pembrolizumab will be administered at a dose of 200 mg as a 30-minutes IV infusion every 21 days (± 3 days). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.
- CC-486 is administered 300 mg orally once daily, 21 days on treatment followed by 7 days off. CC-486 may be taken on an empty stomach or with food (a light breakfast or meal of up to approximately 600 calories). Whole tablets of CC-486 must be taken with approximately 240 mL (8 ounces) of room temperature water.
- On days when both CC-486 and pembrolizumab are administered, pembrolizumab will be infused after CC-486 intake.
- Refer to section 5.7 for treatment schedule adjustments.

5.3.4 Study Treatment Administration in Part B

Subjects will be randomized (1:1) to receive:

- Arm A: Pembrolizumab 200 mg IV every 21 days (± 3 days) combined with CC-486 (optimal schedule selected based on Part A)

  OR

- Arm B: Pembrolizumab 200 mg IV every 21 days (± 3 days)

The optimal schedule after the analysis of Part A will be communicated to the participating sites through a protocol amendment (if required; refer to section 3.2) or through a letter if an amendment is not required.

Subjects will remain on their assigned treatment until progressive disease based on irRECIST, unacceptable toxicity, consent withdrawal, Investigator's decision that it is in the subject´s best interest to discontinue or other treatment withdrawal criteria is met (section 5.5).

If a subject is randomized into Part B but does not receive any study treatment, the reason must be documented in the eCRF. Subjects will remain on study, baseline data will be collected and follow-up will continue as described in the Schedule of Visits and Assessments in section 6.2, unless subject completely withdraws from the study or other criteria for discontinuation from study participation is met according to section 6.5.2.

5.3.4.1 Treatment Regimen in Arm A

Study treatments will be administered to subjects randomized to Arm A according to the applicable schedule and guidance in section 5.3.3.

5.3.4.2 Treatment Regimen in Arm B

Subjects will receive pembrolizumab at a dose of 200 mg as a 30-minutes IV infusion, every 21 days (± 3 days). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

5.3.5 Treatment Compliance

The administration of all study treatments should be recorded in the appropriate sections of the eCRF.

Additionally, for CC-486, treatment compliance will be assessed at each visit during treatment phase. Subjects will complete a diary to document their daily intake. They will be instructed to return all unused drugs (partially used and empty containers) and their diary at each visit. Site staff will perform accountability of the returned drug and will assess compliance of the subject. Site staff must ensure that the subject clearly understands the directions for self-medication and follows the schedule adequately.

5.4 Study Treatments Management

5.4.1 Packaging and Labeling

Clinical supplies will be affixed with a clinical label in accordance with applicable regulatory requirements, and will include a statement regarding it's limitation to investigational use only.

5.4.2 Storage and Handling

Study drugs must be stored in a secure, limited-access location under the storage conditions specified on the label/package insert. Receipt and dispensing of trial medication must be recorded by an authorized person at the site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

5.4.2.1 CC-486

Store as directed on the label.

CC-486 is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling CC-486.

Procedures for proper handling of CC-486 should be applied according to standards established at each site for cytotoxic drugs. If a tablet is broken or damaged, dispose of the drug product and do not use.

5.4.2.2 Pembrolizumab

Storage of pembrolizumab vials and of reconstituted and diluted solutions should be done according to the instructions detailed in the local package insert.

5.4.3 Accountability, Drug Return/Destruction

The Investigator is responsible for keeping accurate records of the clinical supplies received from the sponsor or designee, the amount administered or dispensed to and returned by the subjects, and the amount remaining at the conclusion of the trial.

TRIO will provide appropriate documents (e.g. drug inventory log or similar) that must be completed for drug accountability and return.

5.4.3.1 CC-486

Subjects must return all unused medication and empty containers to the site staff at each visit. Unused/expired CC-486 should be destroyed locally once accountability is performed and drug supplies are reconciled. Procedures for proper disposal of CC-486 should be applied according to standards established at each site for cytotoxic drugs.

5.4.3.2 Pembrolizumab

Unused/expired pembrolizumab will be managed by the sites according to their local requirements.

5.5 Study Treatment Discontinuation

By default, subjects are treated until progressive disease as per irRECIST (Appendix 2) when study treatment must be discontinued. CA-125 increases should not be used to declare disease progression and/or study treatment discontinuation (refer to section 6.4.6.2).

In Part A and in Arm A of Part B, in case there is a need to permanently discontinue one of the study drugs (whichever the reason), the other one will also be discontinued (i.e. monotherapy with CC-486 or with pembrolizumab is not allowed in Part A and in Arm A of Part B).

The Investigator will also discontinue study treatments if any of the following conditions is met:

- Intercurrent illness or a change in subject´s condition or unacceptable toxicity (see section 5.7) that warrants study treatment discontinuation according to Investigator judgment
- Any event, condition, criterion which would warrant discontinuation of pembrolizumab or CC-486 as per section 5.7.
- Any event, condition, reason which would warrant pembrolizumab or CC-486 to be held for more than the maximum acceptable delay as per section 5.7.1.
- Subject completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of pembrolizumab, whichever is later (*Note: 24 months is calculated from the date of first pembrolizumab dose).*
- Need for additional local and/or systemic non-protocol anticancer therapy or subject receives non-protocol anticancer therapy at any time during the study treatment
- Subject’s decision to withdraw study treatments
- Lost to follow up
- Death
- Pregnancy
- Investigator’s decision
- Discontinuation of the study by the sponsor

5.6 Concomitant Treatment and Procedures

Concomitant treatment includes any medication or therapeutic procedure (e.g. prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements, blood transfusions, etc.) used by a subject from the date the Patient Informed Consent Form (PICF) is signed until the End of Treatment visit. After the End of Treatment visit, collection of concomitant therapies will be done according to section 6.4.4.

Concomitant therapies will be assessed at all clinic visits and must be recorded on the appropriate eCRF. Not all concomitant medications need to be recorded in the eCRF. Refer to the CRF Completion Guidelines for guidance on how to report concomitant medications in the TRIO026 study. If the use of any medication during the study is due to an AE, the AE must be recorded on the eCRF and in the subject's source documents.

Any concomitant treatment not listed in section 5.6.2 is considered permitted in the study.

Refer to section 5.6.3 for guidance on the use of radiotherapy during the study.

5.6.1 Contraception

Given the patient population in the trial, it is highly unlikely that WoCBP are enrolled in the TRIO026 study (refer to section 4.1 for the definition of WoCBP).

WoCBP may be included only if they agree to acceptable contraception starting with the screening visit and up to 120 days after the last dose of study treatment.

WoCBP must agree to avoid becoming pregnant by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

- Single method (one of the following is acceptable):
  - intrauterine device (IUD)
  - vasectomy of a subject's male partner
  - contraceptive rod implanted into the skin
- Combination method (requires use of two of the following):
  - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - cervical cap with spermicide (nulliparous women only)
  - contraceptive sponge (nulliparous women only)
  - male condom or female condom (cannot be used together)
  - hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g. calendar, ovulation, symptom-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

5.6.2 Prohibited Treatments

Subjects are prohibited from receiving the following therapies since PICF signature until the End of Treatment visit:

- Investigational agents other than the study treatments.
- Any additional investigational or commercial anticancer agents, such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy, will not be allowed, even if utilized as treatment of non-cancer indications.
- Immunotherapy, including steroids, except for the treatment of potential immune-related AEs during the study.
- Live vaccines. Also, subjects who have received live vaccines within 30 days prior to enrollment in Part A or randomization in Part B are not eligible in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.

5.6.3 Palliative Radiotherapy

Subjects may receive palliative radiotherapy before discontinuing study treatment only for local pain control and only if in the opinion of the treating Investigator, the subject does not have progressive disease. The radiation field cannot encompass a target lesion. Radiation to a target lesion is considered progressive disease and the subject should be removed from study treatment.

5.7 Treatment Schedule Adjustments and Adverse Events Management

5.7.1 General Rules

Regular assessment and monitoring of AEs is required throughout study treatment period and at least up until the End of Treatment visit (refer to section 7.1.1).

Toxicity will be assessed utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. For toxicities not specifically listed in the NCI CTCAE, the following grading will apply for assessing severity:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening
- Grade 5: Death related to AE

Subjects will be instructed to notify their physician immediately for any and all toxicities. Assessment of causality (chronology, confounding factors, concomitant medications, diagnostic tests, and previous experience with the study treatment) should be conducted by the Investigator prior to dose modification and/or delay whenever possible. As a general approach, it is suggested that all AEs be managed with supportive care at the earliest signs of toxicity and before delaying/reducing study drugs, when possible and if clinically appropriate.

All dose modifications should be based on the AE requiring the greatest modification and should be properly documented in source documents. Investigators may take a more conservative approach than the guidelines outlined in the protocol on the basis of clinical judgment that this is in the best interest of the subject.

In case a delay/withhold of one study drug is required, treatment with the other drug may continue according to the protocol schedule if clinically appropriate (applicable for Part A and Arm A of Part B).

Maximum acceptable delays due to adverse events related to study drug(s) are:

- For pembrolizumab: 12 weeks after prior dose of pembrolizumab
- For CC-486: the maximum number of days that dose may be withheld due to toxicity before a subject is permanently discontinued from CC-486 is 14 days (not comprising treatment off-period)

If due to an adverse event related to study drug(s) it is required to delay study treatment for more than the maximum acceptable period, then study treatment should be permanently discontinued and subject should undergo the End of Treatment visit.

Dosing interruptions/delays of one or both study drugs with a maximum duration of 21 days are permitted in the case of medical/surgical events or logistical reasons unrelated to study treatments (e.g. elective surgery, unrelated medical events, subject vacation and/or holidays). Subjects should be placed back on study therapy within 21 days of the scheduled interruption, unless otherwise discussed with the Medical Monitor.

In Part A and in Arm A of Part B, in case there is a need to permanently discontinue one of the study drugs (whichever the reason), the other one will also be discontinued (i.e. monotherapy with CC-486 or with pembrolizumab is not allowed in part A and in Arm A of Part B).

General guidelines on dose delay and modifications for each of the study drugs are detailed in the following subsections.

5.7.2 Pembrolizumab

5.7.2.1 Dose Reductions

No dose reductions are allowed for pembrolizumab.

5.7.2.2 Treatment Schedule Adjustments

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. For assessment and management of irAEs, investigators should refer to the last version of pembrolizumab IB. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 1.

Table 1: Treatment schedule adjustments for pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with 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.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased bilirubin suggestive of hepatitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Stevens Johnson Syndrome	Any grade	Permanently discontinue	Refer the patient for specialized care for assessment and treatment.	Refer the patient for specialized care for assessment and treatment.
Toxic Epidermal Necrolysis	Any grade	Permanently discontinue	Refer the patient for specialized care for assessment and treatment.	Refer the patient for specialized care for assessment and treatment.
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

5.7.2.3 Supportive Care Measures for Pembrolizumab Toxicities

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Immune-mediated adverse reactions can occur after discontinuation of treatment. Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below in this section. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the Investigator does not need to follow the treatment guidance (as outlined below). Refer to section 5.7.2.2 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **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.
    - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

- For T1DM or Grade 3-4 Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with IV corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 2 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 2: Pembrolizumab infusion reaction treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs.	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: - IV fluids - Antihistamines - NSAIDS - Acetaminophen - Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion);	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: - IV fluids - Antihistamines - NSAIDS - Acetaminophen	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	- Narcotics - Oxygen - Pressors - Corticosteroids - Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. **Hospitalization may be indicated.** **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7.3 CC-486

5.7.3.1 Dose Levels

Refer to Table 3: CC-486 dose levels for guidance on dose reduction levels for each schedule. Dose reductions will be allowed from the original start dose except in Schedule 1 where no dose reductions are allowed.

Re-escalation to the higher dose level is not permitted once dose has been reduced due to toxicity with the only exception of cases considered in Table 4.

Table 3: CC-486 dose levels

Dose levels	Schedule 1	Schedule 2	Schedule 3	Schedule 4
Dose level 0 (Starting dose)	100 mg q.d. D1-21	100 mg BID D1-21	300 mg q.d D1-14	300 mg q.d D1-21
Dose level -1	No dose reduction allowed. Discontinue.	100 mg q.d	200 mg q.d.	200 mg q.d.
Dose level -2	Not applicable	Discontinue	100 mg q.d	100 mg q.d
Need for additional dose reduction	Not applicable	Not applicable	Discontinue	Discontinue

q.d.: once a day; BID: twice a day

5.7.3.2 Treatment Schedule Adjustments and Management of CC-486 Toxicities

During CC-486 treatment subjects should receive appropriate supportive care measures as deemed necessary by the Investigator considering the recommendations provided in this section.

Table 4: CC-486 dose modifications for hematologic toxicity

Toxicity	Recommendation
Grade 2-3 neutropenia on any testing*	For Schedule 1, withhold CC-486 until recovery to ≤ Grade 1. After recovery , resume CC-486 at the same dose. If no recovery from neutropenia to ≤ Grade 1 is observed after 14 days of neutropenia diagnosis, permanently discontinue CC-486. For Schedules 2, 3 and 4, temporarily reduce CC-486 one dose level as per Table 3 until cycle completion. If no further reduction is allowed as per Table 3, temporarily withhold CC-486 until next cycle. At next CC-486 cycle: • If recovery to ≤ Grade 1, re-escalate CC-486 to the previous dose (i.e. dose administered prior to the temporary reduction/interruption). • If no recovery from neutropenia to ≤ Grade 1 is observed after 14 days of neutropenia diagnosis, permanently discontinue CC-486.
** If grade ≥ 3 associated with fever at any time, the dose adjustment guidelines for grade 4 neutropenia should be enacted.*	Note: In cases of recurrent neutropenia (grade 3/4) after two temporary dose reductions/interruptions, CC-486 will be permanently discontinued.

Toxicity	Recommendation
Grade 4 neutropenia on a pre CC-486 hematology testing or during CC-486 treatment	All schedules: Withhold CC-486 until next cycle and monitor ANC until recovery to ≤ Grade 1. • If recovery ≤ 7 days: at next cycle, resume CC-486 at the same dose (i.e. dose administered prior to the interruption). • If no recovery > 7 days: permanently discontinue CC-486 Initiation of G-CSF should be considered by the Investigator. If initiated, administer G-CSF per institutional practice or package insert and continue until ANC recovers to ≥ 2.0 x 10^9/L. Note: In cases of recurrent neutropenia (grade 3/4) after two temporary dose reductions/interruptions, CC-486 will be permanently discontinued. In cases where as a consequence of previous toxicity no additional dose reductions are allowed as per Table 3, CC-486 could be temporarily interrupted until next cycle.
Grade 2 thrombocytopenia on any testing	Hold CC-486 until Platelets recover to ≤ Grade 1. Hematology to be tested periodically until recovery. If delay: • ≤ 7 days: resume CC-486 at same dose • 8-14 days: reduce CC-486 one dose level (if allowed per Table 3) except in Schedule 1 where treatment can be resumed at same dose, unless in the opinion of the Investigator it is in the best subject´s interest to discontinue treatment with CC-486. If dose was previously reduced and no further dose reduction is allowed per Table 3 then CC-486 should be permanently discontinued • > 14 days: permanently discontinue
Grade 3 thrombocytopenia on any testing * ** If grade 3 thrombocytopenia with clinically significant bleeding occurs at any time, the dose adjustment guidelines for grade 4 thrombocytopenia should be enacted.*	Hold CC-486 until Platelets recover to ≤ Grade 1. Hematology to be tested periodically until recovery. If delay: • ≤ 7 days: resume CC-486 at same dose • 8-14 days: reduce CC-486 one dose level (if allowed per Table 3) except in Schedule 1 where CC-486 should be permanently discontinued. If dose was previously reduced and no further dose reduction is allowed per Table 3 then CC-486 should be permanently discontinued • > 14 days: permanently discontinue

Toxicity	Recommendation
Grade 4 thrombocytopenia on a pre-CC-486 hematology testing or during CC-486 treatment	Hold CC-486 until Platelets recover to ≤ Grade 1. Hematology to be tested periodically until recovery. If delay: • ≤ 7 days: reduce CC-486 one dose level (if allowed per Table 3) except in Schedule 1 where CC-486 should be permanently discontinued. If dose was previously reduced and no further dose reduction is allowed per Table 3 then CC-486 should be permanently discontinued • No recovery by day 7: permanently discontinue

Notes:

- When neutropenia is concomitantly observed with other toxicity/ies that require a more conservative approach, guidance on dose modifications for other AEs than neutropenia should be followed.
- The initiation of G-CSF is left at the Investigator´s discretion and should only be utilized in accordance to ASCO or ESMO recommendations. In case of G-CSF use, concurrent use (on same days) with CC-486 should be avoided: at least a two day wash-out period should be respected from CC-486 discontinuation and G-CSF initiation.
- In cases of neutropenia without any evidence of infection, prophylactic antibiotic use is left under investigator's discretion.
- If neutropenia is associated with fever and severe diarrhea, subject should be managed appropriately according to the local practice. In case of recurrence of the diarrhea with neutropenia and fever, the continuation of the subject in the study should be discussed on a case-by-case basis with the sponsor's medical monitor

Table 5: CC-486 dose delays/adjustments for non-hematologic toxicity

Toxicity	Recommendation
Grade 3 or 4 Nausea or Vomiting Grade 3 or 4 Diarrhea Grade 3 or 4 Fatigue/Asthenia	Hold until resolution to ≤ Grade 1 and provide optimal medical management according the type and severity of toxicity (also refer to section 5.3.1). If response ≤ 72 hours (3 days) and recovery ≤ 7 days: • Reduce CC-486 one dose level (if allowed per Table 3) except in Schedule 1 where CC-486 should be permanently discontinued. • If dose was previously reduced and no further dose reduction is allowed per Table 3 then CC-486 should be permanently discontinued • If event recurs with same/greater severity after re-challenge at a lower dose level: discontinue CC-486 If no recovery within 7 days: discontinue CC-486/placebo Note: Emesis and diarrhea should be proactively managed in all cases regardless of the grade. Anti-diarrheic treatment (including anti-diarrheic diet and use of loperamide) is recommended for the management of treatment emergent diarrhea in all cases.
Grade 3 or 4 any other clinically significant non-hematologic toxicity	Hold until resolution to ≤ Grade 1 and provide optimal medical management according the type and severity of toxicity. If recovery ≤ 7 days: • Reduce CC-486 one dose level (if allowed per Table 3) except in Schedule 1 where CC-486 should be permanently discontinued. • If dose was previously reduced and no further dose reduction is allowed per Table 3 then CC-486 should be permanently discontinued • If event recurs with same/greater severity after re-challenge at a lower dose level: discontinue CC-486 If no recovery within 7 days: discontinue CC-486/placebo

Toxicity	Recommendation
Renal dysfunction - For any unexplained reductions in serum bicarbonate levels to < 20 mEq/L or unexplained elevations of serum creatinine (or urea) > 20% from baseline	Hold until resolution to baseline level (+/- 20%) and provide optimal medical management. Reduce CC-486 dose in the next cycle of treatment to the next lower dose level except in Schedule 1 where CC-486 should be permanently discontinued. If dose was previously reduced and no further dose reduction is allowed per Table 3 then CC-486 should be permanently discontinued If similar unexplained renal and/or electrolyte disturbances subsequently persist or recur, discontinue CC-486

5.7.3.3 Criteria for CC-486 Discontinuation

CC-486 needs to be permanently discontinued for any of the following:

- Any life-threatening adverse reaction
- Anaphylactic-like reaction related to CC-486 administration
- Necrotising fasciitis
- Any criteria/event listed in section 5.5 or 5.7.3

6. STUDY VISITS AND ASSESSMENTS

6.1 Subject Inclusion

6.1.1 Informed Consent

Prior to any study-specific screening evaluation, the subject or legally acceptable representative (if applicable per local regulation) will be informed of the nature of the study and will be given pertinent information as to the intended purpose, possible benefits, and possible adverse experiences. The procedures and possible hazards to which the subject will be exposed will be explained. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the study.

An approved PICF will then be read and signed by the subject (or legally acceptable representative if applicable) and, when required, a witness, and the Investigator or a person designated by the Investigator, as per local regulations. The subject will be provided with an original copy of the signed PICF.

The subject may partially or completely withdraw from the study at anytime without prejudicing future medical treatment. In any case, the type and extent of withdrawal should be documented on the initial informed consent form, and must be dated and signed by the subject and by the Investigator.

If a potential subject or legally acceptable representative is illiterate or visually impaired, the Investigator must provide an impartial witness to read the PICF to the subject and must allow for

questions. Thereafter, both the subject or legally acceptable representative and the witness must sign the PICF to attest that informed consent was freely given and understood.

The PICF will include a statement by which the subject allows the sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to its data that will be processed according to the confidentiality regulations.

If important new information becomes available that may be relevant to the subject's consent and willingness to continue participation in the study, the PICF will be revised and submitted to IRB/IEC for approval/favorable opinion. The new information will be then discussed with the subject in a timely manner and if she agrees to continue participation in the study, the revised PICF will be signed and dated and the subject will receive an original copy.

In line with each country's applicable regulations, the source should also support the documentation of the consent process, for each subject.

Both parts of this study have an optional component described in the PICF, with a consent section dedicated to this optional component. If a subject opts not to participate in the optional portion, this in no way affects the subject's ability to participate in the main research study.

6.1.2 Registration, Enrollment/Randomization and Treatment Assignment

6.1.2.1 Part A

The following steps for registering and enrolling a subject are chronologically performed:

1. The subject must provide written informed consent prior to performing any study specific procedure not considered standard practice by the institution.
2. The site will ask TRIO for subject's registration immediately after signature of PICF. A unique registration number will be assigned to each subject in the study.
3. The site will proceed to perform the screening procedures according to the Schedule of Assessments and section 6.4. Upon completion of screening procedures, the Investigator or his/her delegate will check if the subject meets all eligibility criteria:
    - Subjects who do not meet all eligibility criteria: sites will have the screen failure form completed in the eCRF with corresponding reason for screen failure captured.
    - Subjects who meet all eligibility criteria: sites will enter the screening data in the eCRF which will be reviewed centrally by TRIO. After the review of the eligibility criteria, TRIO may address, if necessary, some discrepancies that will have to be answered by the site. Once the eligibility central review is completed and discrepancies have been resolved (if applicable) TRIO will provide the confirmation that the subject is eligible and the site will be able to move forward with the subject's enrollment in the eCRF. The site will receive a confirmation of enrollment. If the subject is deemed not eligible following the central eligibility review, the site will be asked to report the screen failure reason in the eCRF.
4. Subjects will be assigned to a cohort in the order they are enrolled in the study. Subjects enrolled in Part A must start study treatment within 3 days of enrollment.

A cohort will remain open to accrual until five subjects treated on that schedule are considered evaluable as per the definition in section 3.3 (subject completed at least 2 CC-486 cycles and have undergone the 1st post-baseline tumor burden assessment and the 2nd tumor biopsy). It is critical that data about the tumor biopsies and 1st tumor burden assessment is entered by the sites in the eCRF in a

timely manner since this is required to close accrual for the corresponding cohort also in a timely manner. TRIO will also review the tumor collection and tumor assessments data and closely follow-up the performance of these procedures.

Details regarding the Registration and Enrollment processes are provided in a specific Instruction Manual related to the Registration and Enrollment.

6.1.2.2 Part B

The following steps for registering and randomizing a subject are chronologically performed:

1. The subject must provide written informed consent prior to performing any study specific procedure not considered standard practice by the institution.
2. The site will register the subject in the IWRS system. The registration needs to be done as soon as the subject signs the PICF. The system will uniquely attribute a registration number to each subject in the study and the site will receive an automated registration confirmation.
3. The site will proceed to perform the screening procedures according to the Schedule of Assessments and to sections 6.3 and 6.4. Upon completion of screening procedures the Investigator or his/her delegate will check if the subject meets all eligibility criteria:
    - Subjects who do not meet the eligibility criteria will be moved to a screen failure category in the IWRS.
    - Subjects who meet all eligibility criteria: the sites will enter the screening data in the eCRF which will be reviewed centrally by TRIO. After the review of the eligibility criteria, TRIO may address, if necessary, some discrepancies that will have to be answered by the site. Once the eligibility central review is completed and discrepancies have been resolved (if applicable) TRIO will provide the confirmation that the subject is eligible and the site will be able to move forward with the subject's randomization in IWRS. Treatment assignment will be done by the system and the site will receive an automated randomization confirmation.

Subjects will be randomized to treatment arms in a 1:1 ratio. To ensure the equal distribution of prognostic factors in the two study arms, subjects will be stratified according to the following parameters:

- Type of relapsed disease: platinum-refractory vs. platinum-resistant (refer to the corresponding definitions in section 4.1)
- Prior treatment regimens for the platinum-refractory/resistant EOC: none vs. 1 or 2

Details regarding the Registration and Randomization processes are provided in a specific Instruction Manual related to the Registration and Randomization processes.

Subjects randomized in Part B must start study treatment within 3 days of randomization.

6.2 Schedule or Visits and Assessments

For both parts of the trial, all study visits and procedures are detailed in the Schedule of Visits and Assessments tables presented in this section. The detailed description of the study visits and assessments is in sections 6.3 and 6.4. Adherence to the schedule of visits and assessments is required and visits should be planned accordingly.

6.2.1 Part A

Table 6: Schedule of visits and assessments in Part A

Protocol Activities	Screening[1]		Treatment Period[2]		End of treatment[3]	Follow-up[4]
	Days -28 to -1	Days -7 to -1	Days 8, 15 and 22			
Informed consent/ Registration[5]	X					
Demographics, medical history	X					
Physical examination (incl. vital signs)		X		At each visit prior to each CC-486 cycle. Vital signs will be assessed as per site´s standard practice	X	According to SoC
ECOG PS		X		At each visit prior to each CC-486 cycle	X	
Serum pregnancy test[6]		X		As clinically indicated		
Hematology[7]		X	X	Within 3 days of every visit prior to each CC-486 cycle and at day 8, day 15 and day 22 of each cycle (± 1 day)	X	
Blood chemistry[7]		X		Within 3 days of every visit prior to each CC-486 cycle	X	
INR or PT AND aPTT/PTT		X		As clinically indicated		
CA-125[8]		X		Within 3 days of every visit prior to each CC-486 cycle	X	X
AEs assessments		X		At each visit prior to each CC-486 cycle	X	X[9]
Concomitant treatments	X[10]			At each visit prior to each CC-486 cycle	X	X[11]
Tumor burden assessments[12]	X			1st assessment: 6 weeks (± 1 week) after first CC-486 intake. Then every 12 weeks (± 1 week)		X
FFPE block from debulking surgery (optional)[13]	X					
Tumor biopsy (mandatory)[14]	X			6 weeks (± 1 week) after first CC-486 intake		
Whole blood for DNA methylation analysis[15]				On Day 1 of the 1st CC-486 cycle and on the pre-treatment visit prior to the 2nd CC-486 cycle		

Notes:

- All assessments should be performed within 3 days of the scheduled visit, unless otherwise specified.
- All pre-treatment tests/procedures should be performed and assessed by the Investigator prior to dosing.

Footnotes:

1: Day -1 is the day before subject enrollment (see footnote 5)

2: Study treatment with CC-486 should start within 3 days of enrollment. The first on-treatment visit should occur on Day 1 of the 1st CC-486 cycle (subject should receive the first CC-486 dose during the visit and after the whole blood sample for DNA methylation was drawn). Afterwards, study visits are scheduled every 4 weeks ± 3 days and should be done during the CC-486 off period as close as possible to restarting the next CC-486 cycle. Additionally, every 21 days (± 3 days) subjects will visit the site to receive pembrolizumab. Refer to section 5.3.3 for details on the administration of each schedule. Study treatment will continue until progressive disease according to irRECIST criteria, unacceptable toxicity, consent withdrawal or the Investigator concludes that is in the subject´s best interest to discontinue (or any other withdrawal criteria is met according to section 5.5). Progression and study treatment discontinuation should not be declared on the basis of CA-125 alone.
In case there is a need to permanently discontinue one of the study drugs, the other one will also be discontinued and the subjects will undergo the End of treatment visit (and begin the Follow-up phase if applicable as per footnote 4).

3: End of Treatment visit must be scheduled 30 days (± 7 days) after the last administration of any study drug. The End of Treatment will be the last study visit for all subjects except those requiring follow-up according to footnote #4.

4: The subjects that will enter the follow-up phase are those who:

- Discontinue treatment for reasons different than irPD. These subjects will continue to be followed up to assess response/progression (with tumor burden assessments and CA-125) every 12 weeks (± 1 week) until irPD. After irPD, and provided that subject has undergone the End of Treatment visit, all subjects will be taken off the study unless requiring AE/SAE follow-up according to the next bullet.
- Discontinue treatment for any reason and have ongoing SAEs (regardless of relationship with study drugs) or study treatment-related AEs at time of the End of Treatment visit. Monitoring of these events will continue as clinically indicated until the events have resolved (or return to baseline) or in the Investigator's opinion, are unlikely to resolve due to the nature of the condition and/or the subject's underlying disease. Frequency of visits will be according to Investigator judgment.

5: There is no window to obtain the signed and dated PICF. Study specific screening assessments not considered standard practice by the institution must start only once the PICF has been signed. Registration takes place as soon as the subject signs the PICF. After screening procedures and if subject meets all eligibility criteria, enrollment will be done according to the process described in section 6.1.2.1.

6: Only in women of childbearing potential. Refer to section 4.1 for definition of women of childbearing potential.

7: Hematology: Hemoglobin, Absolute Neutrophils Count (ANC), Platelets. Blood chemistry: creatinine, AST, ALT, alkaline phosphatase, total bilirubin, glucose, TSH. There is no need to repeat hematology and blood chemistry prior to first dose of study treatment provided that they were done at screening within 7 days of enrollment, unless deemed clinically required by the Investigator. During treatment period hematology will be done within 3 days of every visit prior to each CC-486 cycle and on Days 8, 15 and 22 (± 1 day). Blood chemistry will be done within 3 days of every visit prior to each CC-486 cycle. There is no need to repeat them prior to pembrolizumab administration unless clinically indicated and/or required according to the standard of care at the

institution.

8: There is no need to repeat CA-125 prior to first dose of study treatment provided that it was done at screening within 7 days of enrollment. Whenever possible, CA-125 should be tested at the same laboratory and with the same technique throughout the study. At the End of Treatment visit and during the follow-up, CA-125 will only be tested in subjects without irPD at time of study treatment discontinuation.

9: During the follow-up phase, only SAEs (regardless of the relationship to study drugs) and non-serious AEs related to study treatments are to be reported and/or followed up (refer to section 6.3.4).

10: Concomitant treatments to be collected from date the PICF is signed

11: Only concomitant treatments to treat AEs related to study treatment and SAEs (regardless of their relationship) will be recorded after the End of Treatment visit

12: CT/MRI of chest abdomen and pelvis to be done at each tumor assessment. The schedule of assessments should be fixed according to the calendar, regardless of treatment interruptions. The first post-baseline assessment will be done 6 weeks (± 1 week) after first CC-486 intake. Subsequent assessments should be done thereafter every 12 weeks (± 1 week) taking as a reference the date of the first post-baseline tumor assessment. Tumor burden assessments will be done according to irRECIST criteria until documentation of irPD regardless of the end of study treatment and start of subsequent anticancer therapy or CA-125 values. 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. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed at the Investigator´s discretion. During the follow-up, tumor assessments will only be required in subjects without irPD at time of End of treatment visit.

13: For subjects consenting to this optional tissue acquisition part of the study, a FFPE block/partial block from the EOC debulking surgery will be obtained (or a minimum of 15 unstained slides in case FFPE tissue block cannot be provided).

14: Image-guided core tumor biopsy is mandatory at baseline (within 28 days of study treatment start) and 6 weeks (± 1 week) after first CC-486 intake. The second biopsy must be done during the on-treatment period of the 2nd CC-486 cycle. As much as possible and if clinically indicated, the second biopsy should be scheduled to coincide with the 1st post-baseline tumor burden assessment (both 6 weeks ± 1 week after first CC-486 intake) so the image-guided biopsy is done at the same time the subject undergoes the scans to assess response/progression. If feasible, a fresh-frozen ascites sample will also be collected in subjects with ascites, during the same procedure as the biopsy. Refer to section 6.4.7.1 and the Study Laboratory Manual for additional details.

15: Whole blood for DNA methylation analysis will be obtained via venipuncture. On day 1 of the 1st CC-486 cycle, sample should be obtained prior to the first CC-486 intake.

6.2.2 Part B

Table 7: Schedule of visits and assessments in Part B

Protocol Activities	Screening[1]		Treatment Period[2]	End of treatment[3]	Follow-up[4]
	Days -28 to -1	Days -7 to -1			
Informed consent[5]	X				
Demographics, medical history	X				
Physical examination (incl. Vital signs)		X	At each visit prior to each CC-486 cycle (Arm A) or each PEM infusion (Arm B). Vital signs will be assessed as per site´s standard practice	X	According to SoC
ECOG PS		X	At each visit prior to each CC-486 cycle	X	
Serum pregnancy test[6]		X	As clinically indicated		
Hematology[7]		X	Within 3 days of every visit prior to each CC-486 cycle and at day 8, day 15 and day 22 of each cycle (± 1 day) (Arm A) or each PEM infusion (Arm B)	X	
Blood chemistry[7]		X	Within 3 days of every visit prior to each CC-486 cycle (Arm A) or each PEM infusion (Arm B)	X	
INR or PT AND aPTT/PTT		X	As clinically indicated		
CA-125[8]		X	Within 3 days of every visit prior to each CC-486 cycle (Arm A) or each PEM infusion (Arm B)	X	X
AEs assessments		X	At each visit prior to each CC-486 cycle (Arm A) or each PEM infusion (Arm B)	X	X[9]
Concomitant treatments	X[10]		At each visit prior to each CC-486 cycle (Arm A) or each PEM infusion (Arm B)	X	X[11]
Tumor burden assessments[12]	X		Every 12 weeks (± 1 week)		X
FFPE block from debulking surgery (optional)[13]	X				
Tumor biopsy (optional)[14]	X		6 weeks (± 1 week) after first dose of study treatment		

Notes:

- All assessments should be performed within 3 days of the scheduled visit, unless otherwise specified.
- All pre-treatment tests/procedures should be performed and assessed by the Investigator prior to dosing.

Footnotes:

1: Day -1 is the day before randomization.

2: Study treatment should start within 3 days of randomization. In Arm A, the first on-treatment visit should occur on Day 1 of the 1st CC-486 cycle (when subject should receive the first CC-486 dose during the visit). Afterwards, study visits are scheduled every 4 weeks ± 3 days and should be done during the CC-486 off period as close as possible to restarting the next CC-486 cycle. Additionally, every 21 days (± 3 days) subjects will visit the site to receive pembrolizumab. In Arm B, study visits are scheduled every 21 days ± 3 days, prior to each pembrolizumab infusion. Study treatment will continue until progressive disease according to irRECIST criteria, unacceptable toxicity, consent withdrawal or the Investigator concludes that is in the subject´s best interest to discontinue (or any other withdrawal criteria is met according to section 5.5). Progression and study treatment discontinuation should not be declared on the basis of CA-125 alone.
In Arm A (CC-486 and pembrolizumab), in case there is a need to permanently discontinue one of the study drugs, the other one will also be discontinued and the subjects will undergo the End of treatment visit and begin the Follow-up phase.

3: End of Treatment visit must be scheduled 30 days (± 7 days) after the last administration of any study drug.

4: Once the subject is discontinued from study treatment and has undergone the End of Treatment visit, she will enter in the follow-up phase. Subjects discontinued from study treatment for reasons different than progressive disease per irRECIST (e.g. unacceptable toxicity, physician´s decision) will be followed up (with tumor burden assessments and CA-125) every 12 weeks (± 1 week) until irPD. Once irPD is declared, all subjects will be followed for survival 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.

5: There is no window to obtain the signed and dated PICF. Study specific screening assessments not considered standard practice by the institution must start only once the PICF has been obtained. Subject will be registered in the study immediately after PICF signature.

6: Only in women of childbearing potential. Refer to section 4.1 for definition of women of childbearing potential.

7: Hematology: Hemoglobin, Absolute Neutrophils Count (ANC), Platelets. Blood chemistry: creatinine, AST, ALT, alkaline phosphatase, total bilirubin, glucose, TSH. There is no need to repeat hematology and blood chemistry prior to the first dose of study treatment, provided that they were done at screening within 7 days prior to randomization, unless deemed clinically required by the Investigator. During treatment period: In Arm A, hematology will be done within 3 days of every visit prior to each CC-486 cycle and on Days 8, 15 and 22 (± 1 day). Blood chemistry will be done within 3 days of every visit prior to each CC-486 cycle. There is no need to repeat them prior to pembrolizumab administration unless clinically indicated and/or required according to the standard of care at the institution. In Arm B, hematology and blood chemistry will be done within 3 days of every visit prior to each pembrolizumab infusion.

8: There is no need to repeat CA-125 prior to first dose of study treatment provided that it was done at screening within 7 days of enrollment. Whenever possible, CA-125 should be tested at the same laboratory and with the same technique throughout the study. At the End of Treatment visit and during the follow-up, CA-125 will only be tested in subjects without irPD at time of study treatment discontinuation.

9: During the follow-up phase, only AEs and SAEs related to study treatments that are ongoing by the End of Treatment visit are to be reported and/or followed up (refer to section 6.3.4).

10: Concomitant treatments to be collected from date the PICF is signed

11: Only concomitant treatments to treat AEs/SAEs related to study treatment will be recorded after the End of Treatment visit

12: CT/MRI of chest abdomen and pelvis to be done at each tumor burden assessment. The schedule of assessments should be fixed according to the calendar, regardless of treatment interruptions and taking as a reference the randomization date. Tumor burden assessments will be done according to irRECIST criteria until documentation of irPD regardless of the end of study treatment and start of subsequent anticancer therapy or CA-125 values. 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. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed at the Investigator´s discretion. During the follow-up, tumor assessments will only be required in subjects without irPD at time of End of treatment visit and only until irPD.

13: For subjects consenting to this optional tissue acquisition part of the study, a FFPE block/partial block from the EOC debulking surgery will be obtained (or a minimum of 15 unstained slides in case FFPE tissue block cannot be provided).

14: Image-guided core tumor biopsy is an optional procedure and will be collected in consenting subjects with lesion amenable to biopsy, at baseline (within 28 days of study treatment start) and 6 weeks (± 1 week) after first dose of study treatment. If feasible, a fresh-frozen ascites sample will also be collected in subjects with ascites, during the same procedure as the biopsy. Refer to section 6.4.7.1 and the Study Laboratory Manual for additional details.

6.3 Study Visits and Assessments/Investigations

During all visits below, assessments should be done according to the Schedule of Visits and Assessments (section 6.2). The description/details of the different assessments are found in section 6.4.

6.3.1 Baseline/Screening Period

The baseline/screening period starts with the signature of the PICF and ends when the subject is enrolled in Part A, randomized in Part B or screen failed.

During the screening period the following assessments will be done:

- Demographics, Medical History
- Complete physical examination (including weight)
- Vital signs (according to standard of care)
- ECOG PS
- Laboratory assessments:
    - Hematology: Hemoglobin, Absolute Neutrophils Count (ANC) and Platelets
    - Blood chemistry: creatinine, AST, ALT, alkaline phosphatase, total bilirubin, glucose, TSH
    - Coagulation tests: INR or PT and aPTT/PTT
    - Serum pregnancy test: only in women of childbearing potential (within 7 days of registration)
    - CA-125

  Notes: If for some reason laboratory tests are repeated between these tests done at screening and treatment start, the most recent measurement obtained prior to treatment start must be within the required values according to the inclusion criteria, to begin study treatment.
- Adverse events assessment
- Concomitant medication
- Tumor burden assessments
- Tumor biopsy
- Collection of FFPE block from debulking surgery (optional)

6.3.2 Treatment Period Visits

Study treatment should begin within 3 days of enrollment in Part A or randomization in Part B. All assessments should be performed within 3 days of the scheduled visit, unless otherwise specified. All pre-treatment tests/procedures should be performed and assessed by the Investigator prior to dosing.

During the treatment period, visits will be done as follows:

6.3.2.1 Part A

The first on-treatment visit should occur on Day 1 of the 1st CC-486 cycle (subject should receive the first CC-486 dose during the visit and after the whole blood sample for DNA methylation was drawn as per section 5.3.3.2). Afterwards, visits will be done every 4 weeks ± 3 days, during the CC-486 off period as close as possible to restarting the subsequent CC-486 cycle.

During the treatment period visits the following assessments will be done:

- Physical examination (symptom-oriented)
- ECOG PS
- Adverse events assessment
- Concomitant medication
- Laboratory assessments:
    - Hematology: Hemoglobin, Absolute Neutrophils Count (ANC) and Platelets
    - Blood chemistry: creatinine, AST, ALT, alkaline phosphatase, total bilirubin, glucose, TSH
    - Coagulation tests and pregnancy test: only if clinically indicated
    - CA-125
- Tumor burden assessments: if applicable according to sections 6.2 and 6.4.6.1
- Tumor biopsy: if applicable according to sections 6.2 and 6.4.7.1.
- Whole blood sample for DNA methylation analysis: if applicable according to sections 6.2 and 6.4.7.3

Prior to the first CC-486 cycle, there is no need to repeat hematology, blood chemistry and CA-125 tests provided they were done at screening within 7 days of enrollment, unless deemed clinically required by the Investigator.

In addition to these visits, the subject will visit the clinic at time of each pembrolizumab infusion. There is no need to repeat laboratory tests prior to pembrolizumab administration unless clinically indicated and/or required according to the standard of care at the institution.

Hematology (at least hemoglobin, Absolute Neutrophils Count (ANC) and platelets) will be repeated at day 8, day 15 and day 22 (± 1 day) of each cycle. No clinical visit is required on these days. CC-486 dose adjustments, treatment withhold or treatment discontinuation based on hematology test results will be performed as per section 5.7.3.

6.3.2.2 Part B

In Arm A: The first on-treatment visit should occur on Day 1 of the 1st CC-486 cycle (subject should receive the first CC-486 dose during the visit). Afterwards, visits will be done every 4 weeks ± 3 days, during the CC-486 off period as close as possible to restarting the subsequent CC-486 cycle.

Additionally the subject will visit the clinic at time of each pembrolizumab infusion.

In Arm B: every 21 days ± 3 days, prior to each pembrolizumab infusion

During the treatment period visits the following assessments will be done in both arms:

- Physical examination (symptom-oriented)
- ECOG PS

- Adverse events assessment
- Concomitant medication
- Laboratory assessments:
    - Hematology: Hemoglobin, Absolute Neutrophils Count (ANC) and Platelets
    - Blood chemistry: creatinine, AST, ALT, alkaline phosphatase, total bilirubin, glucose, TSH
    - Coagulation tests and pregnancy test: only if clinically indicated
    - CA-125
- Tumor burden assessments: if applicable according to sections 6.2 and 6.4.6.1
- Tumor biopsy (optional): if applicable according to sections 6.2 and 6.4.7.1.

Prior to the first dose of study treatment, there is no need to repeat hematology, blood chemistry and CA-125 tests provided they were done at screening within 7 days of randomization, unless deemed clinically required by the Investigator.

In Arm A, prior to each pembrolizumab infusion, there is no need to repeat laboratory tests unless clinically indicated and/or required according to the standard of care at the institution.

In Arm A only, hematology (hemoglobin, Absolute Neutrophils Count (ANC) and platelets) will be repeated at day 8, day 15 and day 22 (± 1 day) of each cycle. No clinical visit is required per protocol on these days. CC-486 dose adjustments, treatment withhold or treatment discontinuation based on hematology test results will be performed as per section 5.7.3.

6.3.3 End of Treatment Visit

End of Treatment visit must be scheduled 30 days (± 7 days) after the last administration of the last study drug.

The primary purpose of this visit is to follow-up any AEs ongoing at the time of discontinuation and to assess any new AEs that may have occurred since discontinuation.

During the End of Treatment visit the following assessments will be done:

- Physical examination (symptom-oriented)
- ECOG PS
- Hematology and Blood chemistry
- CA-125 (only in subjects without irPD at time of study treatment discontinuation)
- Adverse events assessment
- Concomitant medication

In Part A only, the End of Treatment will be the last study visit for all subjects except those who:

- Discontinue treatment for reasons different than irPD
- Discontinue treatment for any reason and have ongoing SAEs (regardless of relationship with study treatment) or study treatment-related AEs at time of the End of Treatment visit

6.3.4 Follow-up Visits

6.3.4.1 Part A

The subjects that will enter the follow-up phase are those who:

a) Discontinue treatment for reasons different than irPD: These subjects will enter the follow-up phase and will be followed up to assess response/progression (with tumor burden assessments and CA-125) every 12 weeks (± 1 week) until irPD. After irPD, and provided that subject has undergone the End of Treatment visit, all subjects will be taken off the study unless requiring AE/SAE follow-up according to the paragraph (b) below.

b) Discontinue treatment for any reason and have ongoing SAEs (regardless of relationship with study treatment) or study treatment-related AEs at time of the End of Treatment visit: Monitoring of these events will continue as clinically indicated until the events have resolved (or return to baseline) or in the Investigator's opinion, are unlikely to resolve due to the nature of the condition and/or the subject's underlying disease. Frequency of visits will be according to Investigator judgment.

6.3.4.2 Part B

All subjects will be followed-up.

Subjects discontinued from study treatment for reasons different than progressive disease per irRECIST (e.g. unacceptable toxicity, Investigator´s decision, etc.) will be followed up to assess response/progression (with tumor burden assessments and CA-125) every 12 weeks (± 1 week) until irPD.

Once irPD is declared, all subjects will be followed for survival every 6 months (through visit or phone contact) until death or for at least 1 year after the End of Treatment visit, to assess the survival status.

Any AE or SAE related to study treatments that is ongoing by the End of Treatment visit, must be followed up to resolution or until the events have resolved (or return to baseline) or in the Investigator's opinion, are unlikely to resolve due to the nature of the condition and/or the subject's underlying disease.

6.4 Description of Study Assessments/Investigations

6.4.1 Demographics and Medical History

The Investigator will collect and report in the eCRF demographics and complete history of malignant and clinically-significant non-malignant diseases including known hypersensitivity reactions.

6.4.2 Physical Examination and Vital Signs

At screening physical examinations will include a complete assessment of body systems (i.e. general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, skeletal, and neurologic) per standard of care at the study site or as clinically indicated by symptoms. Weight will also be measured at screening.

During treatment period visits and at the End of Treatment visit, a symptom-directed physical examination will be done.

Vital signs will be assessed as per site´s standard practice.

6.4.3 ECOG Performance Status

Assessment of ECOG PS (Appendix 1) is required to assess subject´s functional status for study eligibility purposes and will be performed throughout the study according to the Schedule of Visits and Assessments (section 6.2).

6.4.4 Adverse Events Assessment and Concomitant Treatments Review

- Adverse events assessment: For information on the assessment and collection of AEs refer to section 7 and to the Schedule of Visits and Assessments in section 6.2.
- Concomitant Treatments: Concomitant treatment includes any medication or therapeutic procedure (e.g. prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements, blood transfusions, etc.) used by a subject from the date the PICF is signed until the End of Treatment visit. After the End of Treatment visit, in Part A, only concomitant therapies to treat AEs related to study treatment and any SAE (regardless of the relationship) will be recorded. In Part B only concomitant treatments to treat AEs/SAEs related to study treatment will be collected after the End of Treatment visit.

6.4.5 Laboratory Safety Assessments

The following laboratory safety assessments will be done according to the Schedule of Visits and Assessments in section 6.2.

- Hematology: hemoglobin, Absolute Neutrophils Count (ANC) and platelets
- Blood chemistry: AST, ALT, Alkaline Phosphatase, Total Bilirubin, Creatinine, Glucose, TSH
- Coagulation tests: INR or PT and aPTT/PTT
- Serum pregnancy test: only in women of childbearing potential

6.4.6 Efficacy Assessments

Efficacy assessments include:

- Evaluation of tumor burden according to the irRECIST to assess irPFS, irORR, irDOR and irDCR
- Serial measurement of CA-125 to monitor for response according to the GCIG criteria in subjects with CA-125 evaluable disease at baseline

6.4.6.1 Schedule/Details of Tumor Burden Assessments

All efficacy endpoints (including the primary and secondary objectives in both Part A and B) are linked to the tumor burden response assessments and therefore the importance of timely and complete disease assessments in this study cannot be understated. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. Frequent off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial.

The schedule of tumor burden assessments should be fixed according to the calendar, regardless of treatment interruptions. Tumor burden assessments will be performed until progressive disease as per irRECIST regardless of the discontinuation of study treatment, the start of a subsequent anticancer therapy or CA-125 values.

The same method of assessment and the same technique used at baseline (CT scan or MRI) to characterize each lesion must be used at each subsequent post-baseline assessment. Review of post-baseline scans and assessment of overall response (according to irRECIST) should be done at the next visit after the scans are performed and prior to indicating subsequent study therapy, to rule out progressive disease that would warrant study treatment discontinuation.

The irRECIST guidelines for measurable, non-measurable, target and non-target and the tumor response criteria are presented in Appendix 2.

6.4.6.1.1 Baseline assessments

Baseline disease assessments should be performed as close as possible to the treatment start and never more than 28 days before enrollment in Part A or randomization in Part B. Disease assessment at screening will be used to determine the measurability of the disease (measurable versus non-measurable) and to document lesions as Target or Non- Target lesions as per irRECIST. Subjects without measurable lesions are not eligible in Part A. Subjects who have no measurable and no non-measurable lesions are not eligible in Part B (i.e. subjects categorized as “No Disease” (irND) according to irRECIST).

Baseline assessment will include at least:

- CT or MRI scan of the chest, abdomen, and pelvis (CAP)
- Any additional imaging as deemed appropriate
- If applicable, clinical assessment of superficial lesions

6.4.6.1.2 Post-baseline assessments

Post-baseline assessments will be done:

- 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 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.

Post baseline assessments will include at least:

- CT or MRI scan of the chest, abdomen, and pelvis (CAP)
- Any other imaging that revealed lesions at baseline
- Any additional imaging as deemed appropriate

6.4.6.2 CA-125 Measurements

CA-125 will be measured in all subjects at baseline, at each pre-treatment visit during the study treatment phase and at the End of Treatment visit. During follow-up, CA-125 will be tested only in subjects without irPD at time of treatment discontinuation and until irPD is declared. CA-125 measurement is not required following irPD. Whenever possible, CA-125 should be tested at the same laboratory and with the same technique throughout the study.

CA-125 will be used to assess tumor response based on the GCIG criteria but will not be used to declare disease progression and/or study treatment discontinuation. Any elevation in CA-125 suggestive of disease progression needs to be confirmed through tumor burden disease assessments as an irPD to declare progression and to warrant study treatment discontinuation. CA-125 elevation alone is not defined as disease progression. If the elevation of CA-125 is not radiographically confirmed as an irPD, study treatment should continue until progression based on irRECIST, unless the Investigator concludes that it is in the best interest of the subjects to discontinue protocol therapy.

6.4.6.2.1 Evaluation of Response according to CA-125

The GCIG has developed criteria for defining response and progression of ovarian carcinoma based on CA-125.[24] The GCIG recommends that for trials of relapsed ovarian cancer the following definition for response according to CA-125 be used.

Definition of response: A response according to CA-125 has occurred if there is at least a 50% reduction in CA-125 levels from a pre-treatment sample. The response must be confirmed and maintained for at least 28 days. Subjects can be evaluated according to CA-125 only if they have a pre-treatment sample that is at least twice the upper limit of normal and within 2 weeks prior to starting treatment (TRIO026 study requires that baseline CA-125 is tested within 7 days prior to enrollment in Part A or randomization in Part B).

To calculate CA-125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the normal range of CA-125 levels will not interfere with the response definition.
- For each subject, it is preferred that the same assay method be used, and the assay must be tested in a quality-control scheme.
- Subjects are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by Human anti-mouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response.

6.4.7 Biological Sampling Procedures

The area of research into the identification of tumor markers and biological processes / targets to aid in the identification of clinical benefit in certain subsets of populations or even in the identification of anticancer therapies to target the marker, is rapidly growing. 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.

As more development and information is revealed in the future, TRIO would like to use these tumor samples for measurement of the new markers. The tumor samples will be stored in the TRIO central laboratory until future use is required. TRIO may collaborate in the future with experts in the field, and the tumor material may be shared with other researchers.

Details on the analyses to be performed on the biologic samples and procedures for sample collection, labeling, storage and shipment/return of biological samples will be described in separate document(s) (e.g. Samples Manual, Samples Plan).

All samples will be submitted to central laboratories (located in the USA) and will be stored for and indefinite time period unless otherwise required by the subject, Investigator, ethics committee and/or regulations.

Refer to the Schedule of Visits and Assessments in section 6.2 for the samples collection time points.

6.4.7.1 Tumor core biopsies: Fresh-frozen tissue (FFT) and Formalin-fixed paraffin-embedded (FFPE) samples

These samples are mandatory in Part A and optional in Part B.

In all subjects participating in Part A, tumor samples will be collected through image-guided core biopsy at baseline and 6 weeks (± 1 week) after first CC-486 intake (provided that the tumor lesion is amenable to a second biopsy). The second biopsy must be done during the on-treatment period of the second CC-486 cycle. As much as possible and if clinically indicated, the second biopsy should be scheduled to coincide with the 1st post-baseline tumor burden assessment (both 6 weeks ± 1 week after first CC-486 intake) so the image-guided biopsy is done at the same time the subject undergoes the scans to assess response/progression.

In Part B, tumor will be collected in the same time points and with the same procedure as in Part A, in subjects consenting to participate in this optional tissue acquisition study, provided they have lesion(s) amenable to biopsy.

A minimum of three cores at each time point is required to perform the molecular analyses. If three cores are taken, two of them will be formalin-fixed paraffin-embedded and one will be fresh-frozen. If a different number of cores is taken, (approximately) half of them will be fresh-frozen and the other half formalin-fixed paraffin-embedded. If only one core can be obtained, this only core will be fresh-frozen.

Once the cores have been removed, the applicable number of cores must be immediately snap-frozen (procedure described in the study Laboratory Manual), while the remaining ones will be formalin-fixed according to site´s procedures.

Both in Parts A and B, if feasible, a fresh-frozen ascites sample will also be collected in subjects with ascites, during the same procedure as the biopsy.

All these samples will be transported to the Translational Oncology Research Labs at the University of California, Los Angeles (TORL-UCLA).

6.4.7.2 Formalin-Fixed Paraffin-Embedded (FFPE) block/partial block from the debulking surgery

For Part A and Part B subjects consenting to this optional tissue acquisition part of the study, a FFPE block/partial block from the EOC debulking surgery will be obtained and submitted to the TORL-UCLA.

FFPE tumor tissue will be used for biomarker research. In case FFPE tissue block cannot be provided, a minimum of 15 unstained slides would be required to be submitted to the TORL-UCLA.

6.4.7.3 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.

6.5 Subject Discontinuation

The Investigator has the right to discontinue a subject from study treatment or withdraw a subject from the study at any time. In addition, subjects have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason.

6.5.1 Discontinuation from Study Treatment

Refer to section 5.5.

6.5.2 Discontinuation from Study Participation

The primary reason for study participation discontinuation should be documented on the eCRF. Reasons for subject´s discontinuation from the study include:

- Death
- Consent withdrawal from entire study participation
- Subject completes the follow-up period as per protocol sections 6.3.3 and 6.3.4
- Subject non-compliance
- Lost to follow-up

Should a subject decide to withdraw consent, all efforts will be made to complete and report the observations as thoroughly as possible. The Investigator should contact the subject by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study. After complete withdrawal of consent, no further study procedure will be performed and no further data will be collected after the date of the subject's withdrawal from study.

Partial withdrawal occurs when the subject withdraws consent but agrees to be contacted for further information on survival. It should be documented in both the medical records and the eCRF that the subject agreed to be contacted for information on survival despite the subject's withdrawal of informed consent. Partial consent withdrawal is not considered a discontinuation from study participation.

In the case a subject does not show up for study visits, site staff should make reasonable contact attempts before declaring the subject as lost to follow-up. These attempts need to be documented in the medical records.

7. SAFETY MONITORING

7.1 Definitions

7.1.1 Period of Observation

At each visit and any contact during the study and follow-up period, the Investigator or designee will inquire about the occurrence of AEs and will document them in the subject file.

The Investigator or designee will report the AEs in the eCRF and to TRIO Drug Safety and Pharmacovigilance Department when required as per the table below:

Table 8: Reporting period of AEs/SAEs

Study period	AEs (non-serious)		Serious Adverse Events/Pembrolizumab Events of Clinical Interest (ECI)	
	Part A	Part B	Part A	Part B
From PICF to first dose	Not required to report	Only if related to study participation	Only if related to study participation	Only if related to study participation
Study treatment period until End of Treatment visit	All (regardless of relationship)	All (regardless of relationship)	All (regardless of relationship)	All (regardless of relationship)
From End of Treatment visit until End of subject participation[1]	Only if related to study treatment	Only if related to study treatment)	All (regardless of relationship)	Only if related to study treatment

[1] The applicable events as per the table that are ongoing at time of the End of Treatment visit should be followed up to resolution or until the event becomes stable (or returns to baseline) or is unlikely to resolve further in the opinion of the Investigator. Regarding SAEs, in Part A all should be reported/followed after the End of Treatment visit, regardless of the relationship with the study drugs. In Part B, only study-drug related SAEs should be followed/reported.

7.1.2 Adverse Event

An AE is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a subject in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Worsening of pre-existing conditions: A pre-existing condition present at baseline, which remains unchanged during the trial, does not need to be recorded as AE.

Any worsening of any pre-existing baseline condition should be reported as an AE in the eCRF. Examples of worsening of a pre-existing condition that should be recorded as an AE are given below:

- Worsening of condition meets the criteria for an AE or SAE
- Action is taken with the investigational drug (e.g. Dose is reduced or treatment is discontinued)
- Treatment is required (concomitant medication is added or changed)
- The Investigator believes a subject has shown a clear deterioration from baseline symptoms

Expected fluctuations or expected deterioration of the EOC (symptoms of disease progression) should not be recorded as an AE.

Changes in vital signs, physical examination and laboratory test results: will only be recorded as an AE in the eCRF if they are judged clinically relevant by the Investigator.

Overdoses: refer to section 7.4.1.

7.1.3 Serious Adverse Event

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]

[1] "Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3] Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, etc.

7.1.3.1 Disease-related events

An event that is part of the natural course of the disease under study (i.e. disease progression) does not need to be reported as an SAE. Progression of the subject's EOC will be recorded in the appropriate pages of the eCRF. Death due to progressive disease is to be recorded on Death Report Form of the eCRF and not as an SAE.

However, if the Investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE. Any new primary cancer must be reported as an SAE.

7.1.3.2 Planned or administrative hospitalization

Subjects may be hospitalized for administrative or social reasons during the trial (e.g. days on which infusion takes place, long distance from home to site…). These and other hospitalizations planned at the beginning of or before the trial do not need to be reported as an SAE in case they have been reported at screening visit in the source data and have been performed as planned.

7.1.3.3 Unexpected Adverse Event

Azacitidine and pembrolizumab IBs provide an overview of the adverse events reported across each drug´s clinical trials in monotherapy and in combination.

Any Serious Adverse Event assessed as related to azacitidine or pembrolizumab but not reported in the listed adverse events' section of the corresponding IB will be documented as a suspected unexpected serious adverse reaction (SUSAR) and will be submitted according to applicable local regulations.

7.1.4 Events of Clinical Interest (ECI) with Pembrolizumab

Selected non-serious and serious pembrolizumab adverse events are also known as ECI and must be reported within 24 hours to the sponsor according to section 7.3.1 during the collection period specified in section 7.1.1.

Any ECI, or follow up to an ECI, that occurs to any subject must be reported immediately to the sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

ECIs for this trial include:

- A pembrolizumab overdose (as defined in section 7.4.1) that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.2 Performing Adverse Event Assessment

7.2.1 Collection of Adverse Event Information

The following information will be collected in the eCRF: Description of event, start/stop date, worst grade experienced (severity), seriousness, action taken on study treatments and relationship to study treatments.

Intensity of adverse event: The intensity of adverse events will be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 in the eCRF or according to the grading defined in section 5.7.1 if the adverse event is not specifically listed in NCI CTCAE.

All adverse clinical experiences, whether observed by the Investigator or reported by the subject, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the subject's outcome. The Investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The Investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the Investigator must provide details about the action taken with respect to the study treatments and about the subject's outcome.

7.2.2 Assessment of Causality

The Investigator will determine the relationship of the study treatments to all AEs as defined in Single Reference Documents for CC-486 and pembrolizumab (see sections 5.1 and 5.2).

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship must be recorded for each adverse event.

Relationship to study drugs will be reported as either "Yes" or "No".

- Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
- No: There is no reasonable causal relationship between the investigational product administered and the AE.

7.3 Reporting of Serious Adverse Events, Events of Clinical Interest and Pregnancies

7.3.1 Reporting of SAEs/ECIs/Pregnancies from the sites to TRIO

SAEs and ECIs will be reported via the Serious Adverse Event Reporting Form. Pregnancies will be reported via the Pregnancy Reporting Form (refer to section 7.4.2 for more information on reporting pregnancies). The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g. an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required.

These forms will be faxed or emailed to TRIO Drug Safety and Pharmacovigilance Department to:

- Email: safety@trioncology.org
- Fax number: North America: + 1 780-702-2273 / Rest of the World: +33. 1.58.10.09.05

Table 9: SAE/ECIs and Pregnancies reporting timelines

	Initial Reports		**Follow-up Information**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs/ECIs	Immediate	SAE Reporting Form	Immediate	SAE Reporting Form
Pregnancy	Immediate	Pregnancy Reporting Form	Immediate	Pregnancy Reporting Form

7.3.2 SAE/ECI/Pregnancies Information Provided by TRIO to Celgene and Merck

TRIO will report all SAEs and pregnancies to Celgene and Merck by forwarding the SAE Reporting Form or Pregnancy Reporting Form via email or other secure method within 24 hours of site awareness. Additionally, any ECI will be provided by TRIO to Merck also within 24 hours of site awareness. The SAEs/ECIs/Pregnancies will be a copy of the SAE or Pregnancy Reporting Form.

7.4 Management of Specific Cases

7.4.1 Overdoses

CC-486 overdose is defined as the accidental or intentional use of CC-486 in a daily dose ≥ 2 times the indicated dose.

Pembrolizumab overdose will be defined as any dose of 1,000 mg or greater (≥ 5 times the indicated dose).

In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. There is no known specific antidote for pembrolizumab and/or CC-486 overdose.

If an adverse event(s) is associated with ("results from") the overdose of a study drug, the adverse event(s) is reported as SAE, even if no other seriousness criteria are met.

If a dose of CC-486 meeting the protocol definition of overdose is taken without any associated adverse event, the overdose should be reported as a non-serious adverse event, using the terminology "accidental or intentional overdose without adverse effect".

If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose should be reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect".

All reports of overdoses associated with SAEs or that are considered ECI must be reported to the sponsor immediately (i.e. no more than 24 hours after learning of the event; section 7.3)

7.4.2 Pregnancy

Given the patient population in the trial, it is extremely unlikely that WoCBP are enrolled and therefore that pregnancies occur in study subjects.

Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of reproductive potential, regardless of disease state) occurring while the subject is on study treatment up to and including 30 days after the subject's last dose, are considered immediately reportable events. The study treatment is to be discontinued immediately.

The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to TRIO on a Pregnancy Reporting Form (see section 7.3.1). The female subject should be referred to an obstetrician-gynecologist (preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the subject until completion of the pregnancy outcome and a follow up Pregnancy Reporting Form must be submitted at that point with the outcome of the pregnancy (either normal or abnormal outcome). If the outcome of the pregnancy was abnormal (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death or congenital anomaly) the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to TRIO Drug Safety and Pharmacovigilance Department immediately, within 24 hours of the Investigator's knowledge of the event using the SAE Reporting Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IMP should also be reported to TRIO immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

The investigator will be responsible to follow-up on all information regarding a reported drug exposure during pregnancy.

7.5 Reporting to Ethics Committees, Regulatory Authorities and other Investigators

Prompt notification of SAEs by the Investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

TRIO will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and are forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE(s) or other specific safety information (e.g. summary or listing of SAEs) from TRIO will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8. STATISTICAL CONSIDERATIONS

8.1 Populations for Analyses

The Intent-to-treat (ITT) will consist of all subjects who were enrolled (Part A)/randomized (Part B) to study treatment, regardless of whether they actually received study medication. All efficacy analyses will be evaluated based on data from this population according to the treatment group they were assigned to at enrollment (Part A)/randomization (Part B) and based on the strata they were originally assigned to at the time of enrollment/randomization.

The Safety population will be used to assess clinical safety and tolerability and will consist of all subjects who were enrolled (Part A)/randomized (Part B) and received at least one dose of study medication. This population will be based on the actual treatment received, if this differs from that to which the subject was enrolled/randomized and will be used for the analysis of safety data.

8.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics data will be listed and summarized by treatment group using the ITT population.

8.3 Protocol Treatment

Duration of treatment, duration of exposure, cumulative dose and relative dose intensity will be summarized by treatment group using the Safety population. The subjects with dose modifications will be presented by treatment group, along with reasons for the dose change.

8.4 Primary Efficacy Endpoints

The efficacy evaluations will be made on the ITT population.

The primary objective of Part A of the trial is to establish an optimal schedule of CC-486 combined with pembrolizumab. Therefore, the primary endpoint will be based on the safety profile as well as on futility evaluation and the irORR/irDCR per irRECIST criteria (refer to section 3.3).

The primary objective of Part B of the trial is to evaluate whether the addition of CC-486 to pembrolizumab (optimal schedule selected in Part A) improves the immune-related Progression free survival (irPFS) compared to pembrolizumab alone.

The primary efficacy endpoints will be analyzed according to the assessment made by the Investigators.

8.5 Secondary Efficacy Endpoints

The efficacy evaluations will be made on the ITT population.

The following secondary endpoint will be assessed for Part A of the trial:

- The CA-125 response based on GCIG criteria

The following secondary endpoints will be assessed for Part B of the trial:

- The Immune-related Overall Response Rate (irORR)
- The Immune-related Disease Control Rate (irDCR)
- The Immune-related Duration of Response (irDoR)
- The CA-125 response based on GCIG criteria (in subjects with CA-125 evaluable disease)
- The Overall survival (OS)

The secondary efficacy endpoints will be analyzed according to the assessment made by the Investigators.

8.6 Safety Endpoints

The assessment of safety will be made on the safety population and will be based mainly on the frequency of adverse events. The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all adverse events to a preferred term and system organ class. Adverse events will be graded using the Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) or according to the grading defined in section 5.7.1 if the adverse event is not specifically listed in NCI CTCAE. Subject's incidence of adverse events will be tabulated by system organ class, preferred term and toxicity grade by treatment arm. Adverse events leading to death or drug discontinuation, drug related and serious adverse events will also be summarized by treatment arm.

Detailed listings for all adverse events will also be provided.

Laboratory parameters: Laboratory parameters, graded according to the NCI CTCAE v4.03, will be summarized at baseline, along visits and at the end of study treatment by treatment arm. Tables of shifts in toxicity will also be provided.

Other Safety Data: Weight and ECOG will be summarized at baseline, along visits and at the end of study treatment by treatment arm. Tables of shifts in toxicity will also be provided when applicable.

8.7 Hypotheses and Sample Size

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 of the combination strategy in EOC. Criteria for Part B Go/No-Go decision and the determination of the optimal schedule can be found in section 3.3. There was no formal sample size calculation for lead-in safety and efficacy selection phase of the trial.

Part B is designed to test the hypothesis that combined epigenetic/checkpoint inhibitor therapy is superior to checkpoint inhibitor therapy 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.

The other efficacy or safety study endpoints will be secondary ones, and thus there will be no multiple testing adjustments required.

8.8 Timing of Analysis

The primary analysis in Part A will be conducted once 5 subjects in each cohort are considered evaluable for response. Subjects will be considered evaluable once they have completed at least 2 CC-486 cycles, have undergone the 1st post-baseline tumor burden assessment and both tumor biopsies performed and adequate paired tissue obtained.

The primary analysis in Part B will be performed once at least 142 events of disease progression or death have been observed, or at the end of study whichever occurs first. The trial may be prematurely terminated by the sponsor. An interim analysis is planned when 50% of expected events are observed (i.e., 71 events); safety analysis will also be performed at this time. There are no plans to terminate the study early; the interim analysis is performed to support ongoing resourcing activities.

In Part B, a follow-up analysis will be performed one year after the primary analysis. Both efficacy and safety analysis will be performed.

9. ADMINISTRATIVE, ETHICAL AND REGULATORY STANDARDS

This is a TRIO-sponsored study, led by Dr. John Glaspy (Professor of Medicine, Jonsson Comprehensive Cancer Center, UCLA, CA, USA) as Study Chair. The study is financially supported by Celgene Corporation.

9.1 Steering Committee

A Study Steering Committee (SSC) will be set-up and operate as per TRIO Standard Operational Procedures (SOPs) which are consistent with the FDA guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, as well as with the EMA CHMP guideline on Data Monitoring Committees. The SSC will have the sole responsibility for the scientific conduct and integrity of the trial. Responsibilities include development and approval of the protocol document, monitoring of accrual, compliance and safety during the conduct of the trial. The SSC will be solely responsible for the analysis, interpretation and public disclosure of the results of the trial in accordance with the statistical plan. The SSC should endeavor to ensure that the study is conducted at all times to the standards set out in Guidelines for Good Clinical Practice (GCP). In all of the deliberations of the SSC, the rights, safety and well being of the study participants are the most important considerations.

9.2 Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, applicable local regulations, the

Council for International Organizations of Medical Sciences (CIOMS), and the ethical principles laid down in the Declaration of Helsinki. This study will be conducted under ethical, scientific and medical standards that protect the rights of participants which include informed consent, independent review, and post-study medical care.

9.3 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate Institutional Review Board (IRB) or an Independent Ethics Committee (IEC) or. The IRB/IEC decision concerning the conduct of the study will be made in writing and kept with the Investigator study file. A copy of this decision will also be provided to TRIO.

Particular attention is drawn to the FDA's requirements for IRBs under 21 CFR Part 56. By signing the "Statement of Investigator" form (Form FDA 1572), the Investigator provides TRIO with the necessary assurance that an IRB is responsible for the initial/continuing review and subsequent approval of the proposed clinical study in accordance with these regulations when applicable.

In compliance with the applicable country regulations, the Investigator is responsible for keeping the IRB/IEC informed of the progress with study renewal at least once a year, or more frequently, as required by the IRB/IEC. The Investigator must also report any serious adverse events, life-threatening problems or deaths to the IRB/IEC as per institutional guidelines and inform the sponsor according to GCP and applicable local regulations. The IRB/IEC must be informed by the Investigator of the termination of the study.

9.4 Compliance with the Protocol and Protocol Amendments

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the Investigator contact TRIO or its agents, if any, to request approval of a protocol deviation, as no such authorized deviations are permitted.

When a deviation occurs in an emergency situation, such as when a departure from the protocol is required to protect the life or physical well being of a participant, TRIO and the reviewing IRB/IEC must be notified as soon as possible after the emergency situation occurred (ICH GCP 4.5.2).

A planned deviation from the protocol that is non-emergent and represents a major change in the protocol as approved by the IRB/IEC must be considered an amendment and treated as such. Even if the Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by TRIO and subsequently approved by the Health Authorities and IRB/IEC, it cannot be implemented. All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR). This includes any modifications to the protocol which may have an impact on the conduct of the study, potential benefit of the subject or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. As previously stated, only amendments that are required to eliminate an immediate hazard to subjects for subject safety can be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any subjects included in this study, even if this action represents a deviation from the protocol.

9.5 Monitoring, Auditing and Inspecting

To ensure compliance with current local regulations and the ICH guidelines, data generated by this study must be available for monitoring, audit or inspection upon request by representatives of the national and local health authorities, TRIO and duly authorized representatives of any entity providing support for this trial. On site, they will notably review adverse events, study records and directly compare them with source documents, review regulatory documents, discuss the conduct of the study with the Investigator, verify study drug accountability, and confirm that the facilities remain acceptable.

9.6 Recording, Processing and Retention of Data

The Investigator is responsible for the preparation and maintenance of adequate case histories designed to record all observations and other relevant data. All subject data reported on the eCRF must be derived from source documents and as such be consistent with the source documents, or the discrepancies must be explained.

Data will be entered and collected via an electronic data capture system (EDC) using eCRFs. EDC is a validated system designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). Study site staff will receive training and have access to a manual for appropriate eCRF completion. All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the Investigator or authorized designee. Only identified and trained users may view the data as their actions become part of the audit trail.

While study sites will be responsible for data entry, TRIO will be responsible for data management of this study, including quality checks.

The eCRF must be completed shortly after the subject's visit. All requested information must be entered on the eCRF. If an item is not available or is not applicable, it must be documented as such. The completed eCRF must be promptly reviewed and approved by the Investigator or authorized designee. In the event of discrepant data, TRIO will request data clarification from the sites. The sites will resolve the discrepancy electronically in the EDC system. eCRF and data clarification documentation will be maintained in the EDC system's audit trail.

At the end of the study, the Investigator will receive subject data, for their site, in a readable format on CD, DVD, or other similar storage format that must be kept with the study records. Acknowledgement of receipt of the storage disc or similar is required.

The investigator should retain the study documentation according to ICH-GCP, local regulations or as indicated in the contractual agreement whichever is longer.

9.7 Data Protection

Subject confidentiality is strictly held in trust by the participating Investigators, their staff, TRIO or affiliates. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects.

Subject and Investigator personal data which may be included in the study database shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data, TRIO shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party. The anonymity of the subjects will be respected with strict adherence to professional

standards of confidentiality and the Health Insurance Portability and Accountability Act (HIPPA) Privacy Rule.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval by TRIO.

The study monitor or TRIO's other authorized representatives will review all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

9.8 Confidentiality and Data Protection

All information concerning the study supplied by TRIO, in connection with this study and/or by any other party collaborating with TRIO, and not previously published, is considered confidential and proprietary information. This information includes but is not limited to the IB, clinical protocol, workbooks (if applicable), case report forms, assay methods, TRIO technical methodology, and other technical and scientific data. This confidential information shall remain the sole property of TRIO and shall not be disclosed to others without prior written consent from TRIO. Information shall not be used except in the performance of this study.

9.9 Withdrawal of Informed Consent for Submitted Biological Samples

If a subject withdraws consent to the use of optional donated biological samples, then the samples will be returned, disposed of/destroyed, and the action documented. In the event that analysis/research has already been performed, TRIO or its representatives, in strict compliance with the applicable country's regulations, should retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

If a subject withdraws this consent, the Investigator has the responsibility to notify TRIO immediately. TRIO will ensure that the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed/repatriated and the action documented and returned to the study site.

9.10 Insurance of Liabilities

If required, the Investigator may forward to the IRB/IEC a copy of the insurance document required by TRIO, in order to cover his/her liabilities, and those of any other participating parties.

9.11 Use of Information and Publication

All information concerning the study drug or in connection with this study, supplied by TRIO and/or by any other party collaborating with TRIO within this study, and not previously published, is considered confidential and proprietary information. This information includes, but is not limited to, the IB, clinical protocol, workbooks (if applicable), case report forms, assay methods, TRIO technical methodology, and basic scientific data. This confidential information shall remain the sole property of TRIO, the respective collaborating party, and shall not be disclosed to others without prior written consent from TRIO. Information shall not be used except in the performance of this study.

To allow for the use of the information derived from this clinical study and to ensure compliance to current regulations, the Investigator is obliged to provide TRIO with complete test results and all data

developed in this study. No publication, abstract or presentation of the study will be made without the approval of the SSC. The SSC will review the manuscript to prevent forfeiture of patent rights to data not in the public domain. Prior to publication, the authorship list will be agreed upon by the SSC. For the purpose of the efficacy and safety analyses, the names on the author list will be given according to the participation in the concept of the study design as well as accrual input (number of eligible subjects accrued) by the Investigators at each center. The maximum number of authors will be determined by the publication policy established by the targeted journal. Abstracts and publications will be submitted to the authors and to the SSC at least 30 days prior to the expected date of submission to the intended publisher.

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11.APPENDICES

APPENDIX 1: Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
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 and 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 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	Dead

APPENDIX 2: Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

Conventional response assessment criteria such as RECIST criteria are not ideal to fully characterize patterns of tumor response to immunotherapy, since patients treated immune-checkpoint inhibitors may present response patterns that are not accurately categorized by these conventional criteria. Often response to immunotherapy is noted to occur after an initial increase in tumor burden. Furthermore, regression of initial lesions may occur despite development of new lesions. Using the RECIST criteria, patients can be classified as having progressive disease when in fact there has been a positive response to the immunotherapy.

Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) is a recently established and published measurement guideline that intends to provide better assessment and more reliable and reproducible study data for targeted immunotherapeutic agents in oncology studies.

1. DEFINITIONS OF MEASURABLE/NON MEASURABLE DISEASE

The RECIST 1.1 definitions for measurable and non-measurable lesions apply. At baseline, all tumor lesions/lymph nodes will be categorized at baseline as measurable or non-measurable.

Measurable Tumor lesions: Must be accurately measured in at least one dimension with a size of:

- ≥ 10mm in the longest diameter by CT/MRI scan (or no less than double the slice thickness) for non-nodal lesions
- ≥ 15mm in the short diameter by CT/MRI for nodal lesions
- ≥ 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

Non-measurable Tumor lesions: include all other lesions as follows:

- Small non-nodal lesions (longest diameter < 10mm or < twice the reconstruction interval)
- Pathological lymph nodes with short axis ≥ 10 but < 15mm
- Lesions considered truly non-measurable: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations:

Lymph nodes: Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15mm by CT/MRI scan. Only the short axis of these nodes will contribute to the baseline Total Measured Tumor Burden (TMTB). The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10mm are considered non-pathological and should not be recorded or followed.

Bone lesions: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are always non-measurable.

Cystic lesions: Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

2. BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

2.1. TARGET LESIONS

All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as Target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

A Total Measured Tumor Burden (TMTB) for all target lesions will be calculated and reported as the baseline TMTB. The TMTB results from adding:

- the longest diameters of all non-nodal target lesions, and
- the short axis for all nodal lesions

The baseline TMTB will be used as reference to further characterize any objective tumor regression/progression in the measurable dimension of the disease.

2.2. NON-TARGET LESIONS

All other lesions (or sites of disease) not selected as Target lesions should be identified as Non-Target lesions and should also be recorded at baseline. There is no limit to the number of Non-Target lesions that can be recorded at baseline. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Measurements are not required and these lesions should be followed as “present”, “absent”, or in rare cases “unequivocal progression”.

Baseline selected Non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent timepoints and become “measurable”. Only true New lesions can be measured and can contribute to the TMTB if measurable.

3. METHODS OF ASSESSMENT

The same method of assessment and the same technique used at baseline to characterize each lesion must be used at each subsequent post-baseline assessment. All measurements should be recorded in metric notation, using calipers if clinically assessed.

3.1. CT AND MRI

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In the TRIO026 study it is recommended that CT examinations of the chest, abdomen, and pelvis will be used to assess tumor burden at baseline and follow-up visits. CT examination with intravenous (i.v.) contrast media administration is the preferred method. Measurability threshold of lesions on CT scan is based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

MRI should be used where CT is not feasible or it is medically contra-indicated. MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality and lesion measurement. For these reasons, CT is the imaging modality of choice.

3.2. CLINICAL LESIONS

In TRIO026, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions only in case they are assessed by CT or MRI scans. In this case, measurement will be based on the CT/MRI and not on clinical examination. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

3.3. CHEST X-RAY

In TRIO026, chest x-ray will not be used for assessment of TL/NTL as they will be assessed by CT/MRI.

3.4. ULTRASOUND

In TRIO026, ultrasound will not be used for assessment of TL/NTL as it is not a reproducible method, does not provide an accurate assessment of tumor size and is operator dependent. Ultrasound examination can be used to identify the presence of new lesions if new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

3.5. ENDOSCOPY AND LAPAROSCOPY

The utilization of these techniques for objective tumor evaluation is not advised.

3.6. CYTOLOGY AND HISTOLOGY

In TRIO026 histology will not be used as part of the tumor response assessment as per irRECIST.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable disease has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

3.7. BONE SCAN

Bone lesions identified on a bone scan at baseline and confirmed as tumor lesions by CT/MRI at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In TRIO026 bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment (if available) is identified on a bone scan performed at any time during the study. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

3.8. FDG-PET SCAN AND PET-CT

In TRIO026, PET scans may be used as a method for identifying new lesions, according with the following algorithm:

- New lesions will be recorded where there is positive FDG uptake not present on baseline FDG-PET scan (if available) or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit.
- If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions in subsequent tumor assessments

Low dose or attenuation correction CT portions of a combined PET–CT are of limited use in efficacy assessments in clinical trials and therefore they should not substitute dedicated diagnostic contrast enhanced CT scans. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for irRECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an Investigator if it is not routinely or serially performed.

4. POST-BASELINE: TMTB

At each post-baseline assessment the TMTB is defined as the sum of:

- Longest diameters of all non-nodal target lesions
- Longest diameters of all NEW non-nodal measurable lesions
- Short axis of all nodal target lesions
- Short axis of all NEW nodal measurable lesions

Definition of New Measurable Lesion

In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

5. POST-BASELINE: NON-TARGET LESIONS ASSESSMENT

Non-Target lesions assessment

The RECIST 1.1 definitions for the assessment of non-target lesions apply:

- Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).
- Non-CR/Non-PD (irNN): Persistence of one or more non-target lesion(s).
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions (note: the appearance of unequivocal new lesions is also considered progression).

The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.

Definition of New Non-Measurable lesions

All new lesions not selected as New Measurable lesions are considered New Non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of New Non-measurable lesions leads to an overall assessment or irPD for the given timepoint. Persisting new Non-measurable lesions prevent irCR.

6. IMMUNE-RELATED OVERALL TUMOR ASSESSMENT AT EACH TIMEPOINT

Immune-related Complete Response (irCR): complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis.

Immune-related Partial Response (irPR): decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.

Immune-related Stable Disease (irSD): failure to meet criteria for irCR or irPR in the absence of irPD.

irNN: no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.

Immune-related Progressive Disease (irPD): minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions.

irNE (Not evaluable): used in exceptional cases where insufficient data exists.

7. CONFIRMATION OF RESPONSE AND PROGRESSION

In TRIO026, imaging for confirmation of response (irCR or irPR) is not required.

On the other side, 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.

8. OTHER CONSIDERATIONS

irPR if no Target Lesions: If new measurable lesions appear in patients with no target lesions at baseline, irPD will be assessed. That irPD timepoint will be considered a new baseline, and all subsequent timepoints will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation.

Symptomatic deterioration: this is not a descriptor of a progressive disease. It may be reason for discontinuation from study treatment but overall response should be based on the objective tumor response according to irRECIST criteria. Subjects with ‘symptomatic deterioration’ requiring

discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumor until objective disease progression is observed.

Doubtful progression: If the Investigator is in doubt as to whether progression has occurred, particularly with regard to non-target lesions or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated, and reassess the subject's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.