CLINICAL STUDY PROTOCOL

ALKS 4230-007/GOG-3063/ENGOT-ov68/APGOT-OV8

Eudra CT: 2021-002326-24

Study title:	A Phase 3, Multicenter, Open-Label, Randomized Study of Nemvaleukin Alfa in Combination With Pembrolizumab Versus Investigator's Choice Chemotherapy in Patients With Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (ARTISTRY-7)	
Document/Date:	Version 5.0	31 Jan 2024
	Version 4.0	14 Aug 2023
	Version 3.0	05 Oct 2022
	Version 2.0	05 Oct 2021
	Version 1.0	19 Aug 2021
Sponsor:	Mural Oncology, Inc. (referred to herein as "Mural") 852 Winter Street Waltham, MA 02451 USA	

PROCEDURES IN CASE OF EMERGENCY

Table 1: Study Contact Information

Role in Study	Name	Address and Telephone Number
Study Lead and Medical Monitor	Rita Dalal, MBBS, MPH	Mural Oncology, Inc. 852 Winter Street Waltham, MA 02451-1420 US Phone Number: +1 (781) 614-0097 Email: rita.dalal@muraloncology.com ARTISTRY-7_Medical_Monitoring@muraloncology.com
SAE and Pregnancy Reporting	PPD	PPD Toll Free Fax: +1 (888) 488-9697 Direct Dial Fax: +1 (919) 654-3849 Email: WILSafety@ppd.com

SAE=serious adverse event, US=United States

2. SYNOPSIS

Name of Sponsor/Company: Mural Oncology, Inc.	
Name of Investigational Product: nemvaleukin alfa	
Title of Study: A Phase 3, Multicenter, Open-Label, Randomized Study of Nemvaleukin Alfa in Combination With Pembrolizumab Versus Investigator's Choice Chemotherapy in Patients With Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (ARTISTRY-7)	
Study Center: A multicenter study conducted globally	
Planned Study Period: Third quarter (Q3) 2021 to Q1 2025	
Phase of Development: 3	
Study Objectives	**Study Endpoints**
Primary Objective: • To evaluate the overall survival (OS) of nemvaleukin in combination with pembrolizumab as compared with chemotherapy in patients with platinum resistant ovarian cancer	**Primary Endpoint:** • OS
Secondary Objectives: • To evaluate the antitumor activity of nemvaleukin in combination with pembrolizumab as compared with chemotherapy • To evaluate the safety of nemvaleukin in combination with pembrolizumab as compared with chemotherapy	**Secondary Endpoints:** • Progression-free survival (PFS) as assessed by Investigator, based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 • Objective response rate (ORR) as assessed by Investigator, based on RECIST v1.1 • Disease control rate (DCR), duration of response (DOR), and time to response (TTR) as assessed by Investigator, based on RECIST v1.1 • Cancer antigen (CA)-125 response as defined by the Gynecologic Cancer InterGroup (GCIG) • Safety as assessed by treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, and electrocardiograms (ECGs)
Exploratory Objectives: • To evaluate the antitumor activity of pembrolizumab monotherapy; to evaluate the antitumor activity of nemvaleukin monotherapy • To evaluate health-related quality of life (HRQoL)	**Exploratory Endpoints:** • PFS, ORR, DOR, TTR, and OS of the monotherapy arms as assessed by Investigator, based on RECIST v1.1 • HRQoL as assessed by the following patient-reported outcome instruments: the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) questionnaire and the EuroQol 5 Dimension 5-Level (EQ-5D-5L) questionnaire

• To determine if any baseline or changes in parameters in tumor tissue and/or peripheral blood may correlate to response to treatment with nemvaleukin in combination with pembrolizumab • To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamic effects of nemvaleukin and/or pembrolizumab in this treatment regimen	• Pretreatment levels, on-treatment levels, and/or changes from pretreatment levels of the following parameters (in tumor specimens and/or peripheral blood): – Combined positive score (CPS) of programmed death ligand-1 (PD-L1), tumor mutational burden (TMB), and other relevant genetic and non-genetic predictive markers (eg, homologous recombination deficiency, breast cancer gene [BRCA] mutation) – Serum concentrations of nemvaleukin (and pembrolizumab as appropriate) – Presence of anti-nemvaleukin antibodies (and anti-pembrolizumab antibodies as appropriate) in serum – Leukocytes including, but not limited to, circulating cluster of differentiation (CD)8+ T cells, regulatory T cells, and natural killer (NK) cells – Serum concentrations of interferon-γ, interleukin (IL)-6, and other soluble proteins

Methodology: This is a Phase 3, multicenter, open-label, randomized study of nemvaleukin in combination with pembrolizumab versus protocol-specific Investigator's choice chemotherapy in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.

All patients will attend a Screening Visit, at which informed consent will be obtained, eligibility will be assessed, and demographics, medical history, prior and concomitant medications, and prior procedures will be reviewed and recorded. If tumor tissue is to be collected for central testing of PD-L1 status prior to Screening, a pre-screening informed consent form will be obtained. For the purposes of confirming the diagnosis of epithelial ovarian cancer (EOC) and for evaluating pretreatment tumor expression of genes and/or proteins of interest (eg, PD-L1 status, TMB, and microsatellite instability), an initial tumor biopsy will be obtained prior to the start of treatment, if such tissue is not already available. Archival tissue can be used in place of pretreatment biopsy. PD-L1 status via central vendor will be required prior to randomization.

Per the original study design, patients were centrally allocated in a randomized fashion (3:1:1:3) to receive either:

- Arm 1: nemvaleukin and pembrolizumab combination therapy
- Arm 2: pembrolizumab monotherapy (closed)
- Arm 3: nemvaleukin monotherapy (closed)
- Arm 4: Investigator's choice chemotherapy. Options for protocol-specific Investigator's choice chemotherapy include one of the following: pegylated liposomal doxorubicin (PLD), paclitaxel, topotecan, or gemcitabine. The Investigator will pre-select the Investigator's choice treatment before the randomization of each patient.

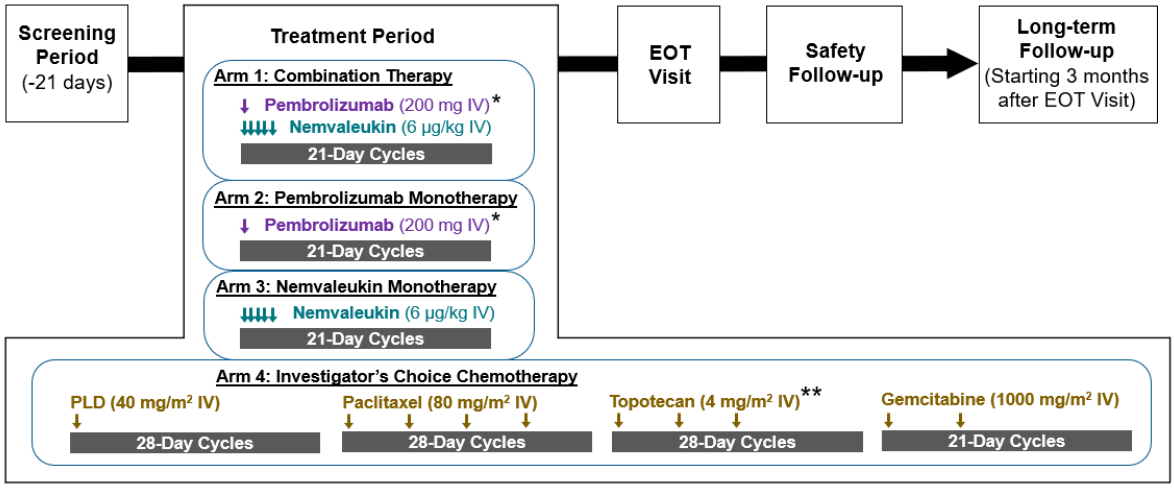
The pembrolizumab monotherapy arm (Arm 2) met its pre-specified futility criteria at the planned futility analysis and was closed to enrollment as of 31 Aug 2023, per the recommendation of the Independent Data Monitoring Committee (IDMC). The nemvaleukin monotherapy arm (Arm 3) did not meet its pre-specified futility criteria at the planned futility analysis and the IDMC recommended continuation. Under protocol version 4.0, the nemvaleukin monotherapy arm (Arm 3) reached its intended enrollment and thus closed. Because no changes have been made to the objectives related to Arm 3 in protocol version 5.0, the Arm 3 number of patients was not recalculated. Therefore, in protocol version 5.0, eligible patients will continue to be enrolled in the remaining 2 arms and will be centrally allocated with a randomization ratio of 1:1 to the Combination and Chemotherapy arms (Arm 1 and Arm 4, respectively).

To ensure equal distribution of prognostic factors in the study arms, patients will be stratified according to the following parameters:

- PD-L1 status (immunohistochemistry CPS ≥10 vs CPS <10)
- Histological subtype (high-grade serous vs non-high-grade serous)
- Investigator's choice chemotherapy (paclitaxel vs other chemotherapies)

Response assessments will include computed tomography (CT) scans and/or magnetic resonance imaging (MRI) every 6 weeks (Year 1) and every 12 weeks (q12w) (Year 2+), with mandatory relevant imaging of chest, abdomen, and/or pelvis. Brain imaging at baseline (and during the study) should be performed when there is a history/suspicion of brain metastasis. Response and PFS will be evaluated per RECIST v1.1 guidelines. For patients who complete treatment or discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging q6w (Year 1 from start of treatment) or q12w (Years 2+ from start of treatment) starting from the last on-treatment assessment until (1) the assessment of progressive disease (PD), (2) the initiation of new anticancer therapy(ies), (3) withdrawal of consent, (4) death, or (5) end of study, whichever occurs first.

Study Design Schematic



EOT=end of treatment, IV=intravenous, PLD=pegylated liposomal doxorubicin.
Note: As of protocol version 5.0, the pembrolizumab and nemvaleukin monotherapy arms (Arm 2 and Arm 3, respectively) are closed to enrollment.
* Treatment with pembrolizumab (Arms 1 and 2) is allowed for up to a maximum of 35 cycles (approximately 2 years).
**Alternatively, topotecan may be administered at 1.25 mg/m^2 on Days 1 through 5 of 21-day cycles.

Number of Patients (Planned): Approximately 376 patients were originally planned in a 3:1:1:3 ratio across 4 arms: 141 patients in Arm 1 (combination therapy), 47 patients in Arm 2 (pembrolizumab monotherapy), 47 patients in Arm 3 (nemvaleukin monotherapy), and 141 patients in Arm 4 (Investigator's choice chemotherapy). Under protocol version 5.0, approximately 450 patients are planned, including approximately 366 patients planned across Arm 1 and Arm 4 (approximately 183 patients in each arm). Under protocol version 5.0, no additional patients will be enrolled in the pembrolizumab monotherapy or nemvaleukin monotherapy arms (Arm 2 and Arm 3, respectively).

Inclusion Criteria: In order to qualify for participation in the study, patients must meet all of the following criteria and, when applicable (per schedule of assessments) the assessment should occur within 10 days prior to expected Cycle 1 Day 1 (C1D1) (closer to C1D1 is highly recommended):

1. Patient is female and ≥18 years of age.
2. Patient or patient's legal representative (as applicable per regional requirements) has provided written informed consent.
3. Patient is willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.
4. Patient has histologically confirmed diagnosis of EOC, fallopian tube cancer, or primary peritoneal cancer and histology subtype: high-grade serous, endometrioid of any grade, clear cell.
5. Patient has platinum-resistant/refractory disease: resistant is defined as disease progression within 180 days following the last administered dose of platinum therapy beyond first-line setting (ie, initial platinum therapy); and refractory is defined as disease progression or lack of response followed by disease progression while receiving the most recent platinum-based therapy (ie, beyond initial therapy). Patient must have progressed radiographically or by GCIG-defined CA-125 criteria on or after their most recent line of anticancer therapy beyond first-line setting.
    a. Note: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression or the date progression was assessed by GCIG-defined CA-125 criteria, whichever comes first.
    b. Note: Patients who have primary platinum-refractory or platinum-resistant disease (disease progression <3 months after completion of first-line platinum-based therapy) are excluded (see Exclusion Criterion 1).
6. Patient must have received at least 1 prior line of platinum-based therapy (as noted below) and no more than 5 prior lines of systemic anticancer therapy in platinum-resistant disease (4 additional lines after the patient developed platinum-resistant/refractory disease). Patient must have received at least 1 line of therapy containing bevacizumab. The following guidelines apply:
    a. Patients who are primary platinum resistant (developed resistance after initial platinum-based therapy) must have received at least 4 cycles of platinum, must have had a response (complete response [CR] or partial response [PR]) and then progressed ≥3 to ≤6 months after the date of the last dose of platinum.
    b. Prior poly adenosine diphosphate-ribose polymerase (PARP) inhibitor is allowed if included within these limits of prior therapy. Prior PARP inhibitor is required for patients with a BRCA mutation.
    c. Adjuvant ± neoadjuvant is considered 1 line of therapy.

d. Maintenance therapy (eg, bevacizumab, PARP inhibitors) will be considered part of the preceding line of therapy (ie, not counted independently).
e. Therapy that changed due to toxicity in the absence of progression will be considered part of the same line (ie, not counted independently).
f. Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance therapy.

7. Patient has at least one measurable lesion that qualifies as a target lesion based on RECIST v1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

8. Patient is willing to provide a tumor tissue sample either collected from a prior biopsy or cytoreductive/debulking surgery occurring at any time since diagnosis or from a fresh biopsy (newly obtained tumor tissue) at Screening. A tumor tissue sample collected at Screening (fresh biopsy) is preferred. Collection of tumor tissue samples from both prior biopsy or cytoreductive/debulking surgery and fresh biopsy are recommended (when possible) to understand changes in the tumor microenvironment during treatment. Central testing of PD-L1 status will be required prior to randomization.

9. Patient has recovered from the effects of any previous chemotherapy, immunotherapy, other prior systemic anticancer therapy, radiotherapy, and/or surgery (ie, residual toxicity no worse than Grade 1 [Grade 2 treatment-associated peripheral neuropathy and/or any grade of alopecia are acceptable assuming all other inclusion criteria are met]).

10. Patient who has received prior systemic anti-neoplastic agent(s) must wait at least 5 half-lives or 4 weeks (whichever is shorter) following prior therapy before enrollment into the study or 4 weeks if the half-life of a given investigational agent is not known.

11. Patient has an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1 and an estimated life expectancy of at least 3 months.

12. Patient has adequate hematologic reserve, as evidenced by:

    a. Absolute neutrophil count of ≥1,500/µL;
    b. Absolute lymphocyte count of ≥500/µL;
    c. Platelet count of ≥100,000/µL; and
    d. Hemoglobin of ≥9 g/dL (patient may be transfused to this level if necessary, but transfusion must occur >1 week prior to the first dose of study drug[s] and hemoglobin maintained to an acceptable level [≥9 g/dL] prior to first dose).

    Note: Administration of granulocyte colony-stimulating factor (G-CSF) or erythropoietin stimulating factor is permitted according to approved indications and scientific recommendations. Administration of long-acting G-CSF must occur >2 weeks prior to the first dose of study drug(s). Administration of short-acting G-CSF must occur >1 week prior to the first dose of study drug(s).

13. Patient has adequate hepatic function, as evidenced by aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values ≤3 × the upper limit of normal (ULN) and serum total bilirubin values of ≤1.5 × ULN (≤2 × ULN for patients with known Gilbert's syndrome). For patients with documented baseline liver metastasis, the following limits will apply: ≤5 × ULN for ALT/AST and ≤2 × ULN for bilirubin.

14. Patient has adequate renal function, as evidenced by a calculated creatinine clearance of ≥45 mL/min by the Cockcroft-Gault equation or a serum creatinine ≤1.5 × ULN. Creatinine clearance assessed by the Cockcroft-Gault equation is preferred over serum creatinine when assessing patient eligibility.
15. Patient has international normalized ratio (INR) and/or prothrombin time and activated partial thromboplastin time (aPTT) ≤1.5 × ULN unless the patient is receiving anticoagulant therapy, in which case INR and/or prothrombin time and aPTT must be within the desired therapeutic range of intended use for such anticoagulants.
16. Patient agrees to abide by the contraceptive requirements detailed in the protocol (Appendix 1).
17. Women of childbearing potential (WOCBP) must have a negative pregnancy test (serum or urine). (See Appendix 1 of the protocol for the definition of WOCBP.)

Exclusion Criteria: In order to qualify for participation in the study, patients must not meet any of the following criteria and, when applicable (per schedule of assessments) the assessment should occur within 10 days prior to expected C1D1 (closer to C1D1 is highly recommended):

1. Patient has primary platinum-refractory disease or primary platinum resistance: primary platinum-refractory disease is defined as disease progression during initial platinum-based therapy; and primary platinum resistance is defined as disease progression <3 months after completion of initial platinum-based therapy.
2. Patient has histologically confirmed diagnosis of EOC with mucinous or carcinosarcoma subtype.
3. Patient has nonepithelial tumor (eg, germline or stromal cell tumor) or ovarian tumor with low malignant potential (ie, borderline or low-grade serous tumor).
4. Patient requires recurrent (≥1 per month) fluid drainage (eg, paracentesis, thoracentesis, pericardiocentesis) or patient requires fluid drainage of ≥500 mL within 4 weeks of the expected date of the first dose of study drug.
5. Patient has received prior IL-2-based or IL-15-based cytokine therapy; patient has had exposure, including intralesional, to IL-12 or analogs thereof.
6. Patient has prior exposure to any anti-programmed death receptor-1 (PD-1)/PD-L1 therapy.
7. Patient requires or has taken systemic corticosteroids (>10 mg of prednisone daily, or equivalent) within 14 days prior to the first dose of study drug(s); however, replacement doses, topical, ophthalmologic, and inhalational steroids are permitted.

   Note: patients requiring the use of a steroid during the Screening Period at a dose level of <10 mg of prednisone (or equivalent) per day are not excluded as long as the event requiring the use of the steroid has recovered to acceptable grade.
8. Patient has taken nonsteroid systemic immunomodulatory agents (eg, etanercept, adalimumab, etc) within 28 days prior to the first dose of study drug(s) or anticipates any use of these therapies during the study period.

9. Patient has undergone any major surgical procedure within 3 weeks prior to Screening. Patients who have not recovered from any previous surgery that occurred more than 3 weeks prior to Screening are also excluded.
10. Patient has undergone prior solid organ and/or non-autologous hematopoietic stem cell or bone marrow transplant.
11. Patient has received a live or live-attenuated vaccine(s) within 30 days prior to the first dose of study drug(s). Note: Coronavirus Disease 2019 (COVID-19) vaccine is allowed; see guidance on COVID-19 vaccines in the body of the protocol.
12. Patient has had any active infection and/or a fever ≥38.5°C (≥101°F) within 7 days prior to the first dose of study drug(s) requiring systemic therapy. Antibiotics given for peri-procedural prophylaxis or given presumptively for a limited time (eg, until infection was ruled out), as well as topical or intraocular antibiotics, shall not be exclusionary.
13. Patient has active autoimmune disease(s) requiring systemic treatment within the past 2 years or a documented history of clinically severe autoimmune disease that has required chronic or frequent systemic steroids. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is allowed.
14. Patient has underlying chronic lung disease, chronic obstructive pulmonary disease, metastatic lung disease, pleural effusions, or other lung disorders (eg, pulmonary embolism) with a baseline room air oxygen saturation of <92% at Screening and/or dyspnea (≥Grade 3) which requires oxygen therapy.
15. Has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
16. Patient has any other concurrent uncontrolled illness or laboratory findings that may interfere with the planned treatment, affect patient compliance, such as recent serious trauma, or mental illness or substance use, which may interfere with the ability of the patient to cooperate and participate in the study.
17. Patient is at high risk of treatment-related complications (see protocol for examples).
18. Patient has had an active second malignancy within the previous 2 years. This criterion does not apply to patients with adequately treated basal cell or squamous cell skin cancer, carcinoma *in situ* of the cervix, urothelial carcinoma *in situ*, or ductal carcinoma *in situ* of the breast that has undergone full surgical resection.
19. Patient is currently pregnant, breastfeeding, or is planning to become pregnant or to begin breastfeeding during the study period or within 120 days after last study drug administration.
20. Patient has active or symptomatic central nervous system (CNS) metastases unless all the following have been met: such metastases have been treated by surgery and/or radiation therapy, and/or gamma knife and have remained radiographically stable (or shrinking) on 2 consecutive imaging examinations performed at least 6 weeks apart; and steroids have been tapered to a dose of 10 mg of prednisone (or equivalent) or less for at least 2 weeks prior to first dose of study drug(s); and the patient is neurologically stable. Patients with history of brain metastases or a suspicion of brain metastases must have a brain MRI at baseline.

21. Patient has known or suspected hypersensitivity to pembrolizumab, nemvaleukin, PLD, paclitaxel, topotecan, gemcitabine, or to any of their excipients.

    Note: hypersensitivity to one or more of the chemotherapy choices is not exclusionary as long as the Investigator is able to select 1 of the 4 chemotherapy options for which the patient is known not to be hypersensitive.

22. Patient has active uncontrolled coagulopathy.
23. Patient has QT interval corrected by the Fridericia Correction Formula values of >470 msec; patient who is known to have congenital prolonged QT syndromes; or patient who is on medications known to cause prolonged QT interval on ECG.
24. Patient is known to be positive for human immunodeficiency virus (HIV).
    - For sites in Czech Republic only: patients test positive for HIV at Screening.
25. Patients with known active hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) are excluded; however, a patient with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) may be enrolled provided that HBV DNA is negative. Patients with known active hepatitis C (eg, hepatitis C virus [HCV] RNA [qualitative] are detected) are excluded; however, a patient with cured hepatitis C (negative HCV RNA status) may be enrolled.
    - For sites in Czech Republic only: patients test positive for HBV or HCV at Screening.
26. History of bowel obstruction, history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 3 months before the first dose of study drug is administered. Clinical symptoms of bowel obstruction should be ruled out by appropriate imaging studies during the Screening Period and prior to randomization in the study. Patients with a functioning ostomy can be included in the study.
27. Patients who are investigational site staff members directly involved in the conduct of the study or their immediate family members as well as site staff members otherwise supervised by the Investigator, or patients who are employed by Mural or companies/vendors hired to be directly involved in the conduct of the study (immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted) unless the investigational site staff or staff at Mural or companies/vendors working on behalf of Mural are recusing themselves from the study activities.

Investigational Product, Dosage, and Mode of Administration: Nemvaleukin drug product is supplied at a concentration of 1 mg/mL in a single-dose vial of lyophilized powder. Patients receiving nemvaleukin will be administered nemvaleukin at 6 µg/kg/day for 5 consecutive days, every 21 days (q21d), via a 30-minute intravenous (IV) infusion.

Pembrolizumab is supplied as single-dose vials of either lyophilized powder or solution. Patients receiving pembrolizumab will be administered pembrolizumab at 200 mg q21d via a 30-minute IV infusion.

For patients randomized to Arm 1, nemvaleukin will be administered prior to pembrolizumab.

Reference Therapy, Dosage, and Mode of Administration: Treatment of protocol-specific Investigator's choice is to include any of the single-agent chemotherapies listed below, with the dosing schedule provided below. Chemotherapy agents will be sourced via institution and documented accordingly. Institutional guidelines can be followed for duration of infusion to avoid or manage the hypersensitivity reactions. Note: Single-agent chemotherapy must be selected prior to randomization.

- PLD: 40 mg/m^2; IV infusion of 1 mg/min (Cycle 1), 60-minute infusion (Cycles 2+); Day 1 of 28-day cycles
- Paclitaxel: 80 mg/m^2; IV infusion over 60 min; Days 1, 8, 15, and 22 of 28-day cycles
- Topotecan: 4 mg/m^2; IV infusion over 30 min; Days 1, 8, and 15 of 28-day cycles. Alternatively, 1.25 mg/m^2; IV infusion over 30 min; Day 1 through 5 of 21-day cycles
- Gemcitabine: 1,000 mg/m^2; IV infusion over 30 min; Days 1 and 8 of 21-day cycles

Duration of Treatment and Duration of Study: Duration of treatment depends on the arm in which the patient is enrolled. Patients will receive treatment with nemvaleukin for as long as they are experiencing disease control and are tolerating treatment well, or until any other criteria for treatment discontinuation are met. Patients who discontinue either nemvaleukin or pembrolizumab due to unacceptable toxicity that cannot be managed by dose modification must discontinue both study treatments. Patients who require treatment hold for either nemvaleukin or pembrolizumab due to unacceptable toxicity, based on recommendation in Table 9, may hold both study treatments. However, holding one agent is feasible if the Investigator's causality assessment clearly attributes the adverse event (AE) to only one of the components. Treatment with pembrolizumab (Arms 1 and 2) will be allowed for up to a maximum of 35 treatments (35 cycles; approximately 2 years). Patients in the nemvaleukin and pembrolizumab combination therapy (Arm 1) may continue nemvaleukin as monotherapy without pembrolizumab beyond 35 cycles upon discussion with the Sponsor and not meeting any other criteria for discontinuation.

Patients will receive chemotherapy for as long as they are experiencing disease control and are tolerating treatment well, or until any other criteria for treatment discontinuation are met.

Patients will be followed for survival for up to 3 years after initiation of treatment or until closure of study, whichever comes first.

Statistical Methods: In general, summary statistics (n, mean, standard deviation, median, minimum, and maximum values for continuous variables and number and percentage of patients in each category for categorical variables) will be provided for evaluated variables by treatment arms. Study drug is defined as nemvaleukin and/or pembrolizumab, or Investigator's choice chemotherapy.

All individual patient-level data will be presented as data listings. Missing data will not be imputed.

Baseline is defined as the last non-missing value prior to each respective patient's first dose of study drug.

The Chemotherapy Arm consists of multiple agents depending on the Investigator's choice; all these agents together will be considered as one Chemotherapy Arm. The statistical comparison or testing will only be conducted between the Combination Arm and the Chemotherapy Arm. No statistical comparison or testing will be conducted against or between the monotherapy arms.

Study Populations

- Intent-to-Treat (ITT) Population: The ITT Population will include all randomized patients regardless of the study drug received.

- Safety Population: The Safety Population will include all randomized patients who received any exposure to nemvaleukin, pembrolizumab, or Investigator's choice chemotherapy.
- Pharmacodynamic Population: The Pharmacodynamic Population will consist of all patients who received at least 1 dose of nemvaleukin, pembrolizumab, or Investigator's choice chemotherapy and have at least 1 available post-baseline pharmacodynamic measurement.
- Pharmacokinetic Population: The PK Population will consist of all patients who received at least 1 dose of nemvaleukin or pembrolizumab and have at least 1 measurable serum concentration of nemvaleukin or pembrolizumab at any scheduled PK time point.

Patient Disposition

The number of patients in the ITT Population and the reasons for discontinuation will be summarized.

Patient disease and baseline characteristics will be summarized using frequency distribution or descriptive statistics, as appropriate.

Demographics and baseline characteristics such as age, race, weight, ECOG status, prior line(s) of therapy, vital signs, and clinical laboratory data will be summarized with descriptive statistics.

Medical history (including cancer history) will be summarized.

Antitumor Activity (Efficacy) Analyses

Antitumor activity analyses will be based on the ITT Population, unless specified otherwise.

Antitumor activity and efficacy data (including ORR, DCR, DOR, PFS, TTR, and OS) will be summarized.

Evaluation of antitumor outcomes will be based on both central review and Investigator review of the radiographic measurements as defined according to RECIST v1.1.

Analysis of Primary Efficacy Endpoint: OS

The primary endpoint was changed from PFS to OS in protocol version 5.0 because it is considered the most appropriate primary endpoint to objectively demonstrate clinical benefit in the target population (El Bairi et al, 2023).

OS is defined as the time from randomization to death due to any cause. For patients without documentation of death, patients will be censored at the last known contact date or the date of study cut-off, whichever comes earlier.

The treatment difference in survival will be assessed by the stratified log-rank test, and p-value will be reported. A stratified Cox proportional hazard model will be used for modeling the treatment effect between the Combination and the Chemotherapy arms (Arm 1 and Arm 4, respectively). The Efron method will be used for handling the ties. The hazard ratio (HR) and its associated 95% confidence interval (CI) will be reported.

OS will be displayed by Kaplan-Meier curves. Median OS and its 95% CI will be provided. The 1-year and 2-year OS rate will be estimated using the Kaplan-Meier method.

A statistical comparison will be conducted between the Combination Arm (Arm 1) and the Chemotherapy Arm (Arm 4); the monotherapy arms (either nemvaleukin alone or pembrolizumab alone) are included in the study for reference only.

The statistical hypothesis test, where HR is:

H_0 (Null Hypothesis): HR (combination/chemotherapy) = 1

H_a (Alternative Hypothesis): HR (combination/chemotherapy) < 1

Analysis of Secondary Efficacy Endpoints

Progression-Free Survival:

PFS is defined as the time from randomization to the first documentation of objective tumor progression (by RECIST v1.1) or death due to any cause.

For patients who have PD while on study treatment, the date of disease progression will be the date of the first assessment at which PD is objectively documented per RECIST v1.1 by the Investigator. If the patient discontinues study treatment for reasons other than documented PD per RECIST v1.1, then the date of disease progression will be the date of the first assessment at which PD is objectively documented per RECIST v1.1 by the Investigator during the Follow-Up Period and prior to start of new anticancer treatment. Death is considered as a confirmed PD event. In case PD or death are observed immediately after 2 or more missed consecutive tumor assessments, PFS will be censored at the date of the last tumor assessment immediately before 2 or more missed consecutive tumor assessments. All remaining patients will be censored at the last known date at which the patient was considered progression-free.

A stratified Cox proportional hazard model will be used for modeling the treatment effect between the Combination and the Chemotherapy arms (Arm 1 and Arm 4, respectively). The Efron method will be used for handling the ties. The HR and its associated 95% CI will be reported.

The median PFS will be provided along with the 95% CI. In addition, Kaplan-Meier curves will be provided. The 6-month, 9-month, or 1-year PFS rate will be estimated using the Kaplan-Meier method.

Objective Response Rate:

ORR is defined as the proportion of patients in the analysis population who have a CR or PR.

The best overall response is the best response recorded after initiation of study treatment until initial documented disease progression or start of a new anticancer treatment, whichever occurs first, taking into account the requirements for confirmation of CR or PR, unless otherwise specified.

The analysis of ORR between the Combination and the Chemotherapy arms (Arm 1 and Arm 4, respectively) will be conducted by the Cochran-Mantel-Haenszel (CMH) test based on randomization stratification factors. The ORR difference and its associated 95% CI will be reported.

Duration of Response:

DOR is defined as the time from the first documentation of CR or PR to the first documentation of objective tumor progression or death due to any cause. Patients who never achieve CR or PR prior to starting any new anticancer treatment will be excluded from the analysis. DOR is based on a non-randomized subset of patients (specifically, patients who achieve an objective response). Therefore, a formal hypothesis testing will not be performed for this endpoint.

The distribution of DOR will be estimated using the Kaplan-Meier method. The median estimate of DOR will be provided along with 95% CI. Kaplan-Meier curves will also be provided.

The censoring rule for DOR is the same as that of PFS.

Disease Control Rate:

DCR is defined as the proportion of patients with objective evidence of CR, PR, or stable disease (SD). For SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

DCR will be analyzed using the CMH test based on randomization stratification factors. The DCR difference and its associated 95% CI will be reported.

Time to Response:

TTR is defined as the time from randomization to the first documentation of CR or PR. Patients who never achieve CR or PR prior to starting any new anticancer treatment will be excluded from the analysis. No censoring observation will occur by definition. TTR is based on a non-randomized subset of patients (specifically, patients who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes.

Cancer Antigen 125 Response:

CA-125 response is defined as at least a 50% reduction in CA-125 levels from baseline and the response must be confirmed and maintained for at least 28 days. The number of responders will be analyzed using the CMH test based on randomization stratification factors. The response difference and its associated 95% CI will be reported.

In addition, the change from baseline value in CA-125 will be summarized with descriptive statistics.

Safety Analyses

The safety endpoints will be analyzed based on the Safety Population. Safety evaluations will be based on AEs, vital signs, weight, clinical laboratory tests, and ECGs. Safety data (AEs, vital sign measurements, ECGs, and clinical laboratory results) will be summarized using descriptive statistics for all treatment arms. Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities Preferred Terms and System Organ Classes and graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

TEAEs are defined as AEs that that have an onset on or after the day of the first dose of study drug or increases in severity after the first dose of study drug. TEAEs will be summarized by system organ class, preferred term, severity grade, and by relationship to study drug (nemvaleukin, pembrolizumab, both nemvaleukin and pembrolizumab, or chemotherapy). The summary tables will include the number and percentage of patients with TEAEs overall, by system organ class, and by preferred terms within each system organ class. Similar tables will be prepared for AEs of special interest, serious AEs (SAEs), TEAEs leading to treatment discontinuation, and additional categories of AEs as defined in the Statistical Analysis Plan. Disease progression will not be captured as an AE or SAE. Death due to disease progression will not be captured as an SAE.

Results of vital signs and clinical laboratory tests will be summarized by visit for the absolute value and by change from baseline. In addition, hematologic and chemistry laboratory parameters will be graded according to the NCI CTCAE where applicable. The shifts from baseline NCI CTCAE grades to maximum and final post-baseline grades will be assessed.

Patient-reported Outcomes: Health-related Quality of Life

Evaluation of HRQoL will be based on the analyses of the FACT-O and EQ-5D-5L questionnaire items and scales.

Sample Size Considerations

The primary endpoint was changed from PFS to OS in protocol version 5.0; therefore, the sample size was recalculated based on OS assumptions.

Approximately 366 patients are planned to be randomized in a 1:1 ratio into the Combination and the Chemotherapy arms (Arm 1 and Arm 4, respectively). It is expected that approximately 286 deaths will have been observed between the Combination and the Chemotherapy arms at the final OS analysis. The study has an approximate 85% power to detect an OS HR of 0.7 (the Combination arm versus the Chemotherapy arm at an alpha level of 2.5% (1-sided). The sample size calculation is based on the following assumptions: 1) 2.5% alpha is allocated to the OS endpoint; 2) OS follows an exponential distribution with a median of 10 months and 14.3 months in the Chemotherapy arm and

Combination arm, respectively; 3) the HR is 0.7, corresponding to a 4.3 month increase in the median OS; 4) an enrollment period of 25 months; and 5) a yearly dropout rate of 5%.

Under protocol version 5.0, approximately 450 patients are planned, including approximately 366 patients planned across Arm 1 and Arm 4 (approximately 183 patients in each arm). Under protocol version 5.0, no additional patients will be enrolled in the pembrolizumab monotherapy or nemvaleukin monotherapy arms (Arm 2 and Arm 3, respectively).

Multiple Comparisons/ Multiplicity

The overall type I error for this study is controlled at 2.5% (1-sided), fully allocated to OS. The statistical comparison is only performed between the Combination and Chemotherapy arms (Arm 1 and Arm 4, respectively).

The Lan-DeMets O'Brien-Fleming alpha-spending function is constructed to implement group sequential boundaries for OS hypothesis testing to control the type I error.

Efficacy boundaries are based on the assigned type I error rate and the projected number of events at study milestones. The actual boundaries will be determined from the actual number of events at the time of the specified interim analysis using the alpha-spending function.

There will be no type I error rate adjustment for the interim futility analyses performed for each of the monotherapy arms since the monotherapy arms are not included for any statistical comparisons.

Interim Analyses

The interim analyses planned in this study are described below. All the analyses will be conducted by an independent statistician under the guidance of an IDMC. The Sponsor's study team members will be blinded for any aggregate antitumor efficacy data or results by assigned treatment group during the study conduct. More details can be found in the IDMC charter.

Interim futility analysis of ORR in each monotherapy arm

The monotherapy arms (either nemvaleukin alone or pembrolizumab alone) are included in the study as reference arms to isolate the component effect; thus, no statistical comparison or testing will be conducted against or between the monotherapy arms.

Interim analyses will be conducted separately when the 24th patient enrolls into the nemvaleukin monotherapy arm and the 12th patient enrolls into the pembrolizumab monotherapy arm; these analyses will be conducted by an independent statistician. The interim analysis on the ORR will provide a statistical recommendation for early stopping due to futility. The pembrolizumab monotherapy arm (Arm 2) met its pre-specified futility criteria at the planned futility analysis and was closed to enrollment as of 31 Aug 2023, per the recommendation of the IDMC.

The stopping boundary is summarized below.

Monotherapy Arm:	**Interim Analysis at:**	**Recommend Stopping Enrollment if:**
Pembrolizumab Monotherapy Arm (closed as of 31 Aug 2023)	First 12 dosed patients	0 or 1 response (confirmed PR or CR)
Nemvaleukin Monotherapy Arm	First 24 dosed patients	0 response (confirmed or unconfirmed PR or CR or durable SD lasting for ≥3 months)

If the futility criteria are met, further enrollment into the arm will stop; patients in the arm receiving benefit (SD or better) may remain on study until progression. Crossover to another treatment arm is not allowed. (Note: all patients who progress at any time will be immediately discontinued from treatment.)

There will be no type I error rate adjustment at the primary efficacy analysis caused by this futility analysis, as the monotherapy arms are not included for any statistical comparisons.

Interim Analysis of OS

One planned efficacy interim analysis of OS will be performed when approximately 215 death events (at approximately 75% information fraction) are observed in the 2 arms (the Combination and the Chemotherapy arms).

Subgroup Analyses

Subgroup analyses relevant to baseline characteristics and disease will be performed (eg, prior treatments, ECOG status, biomarkers, stratification factors, age, region, race, disease stage, and number of prior lines of therapy).

Table 2: Schedule of Assessments for Arms 1 and 3 (Arm 1 Nemvaleukin + Pembrolizumab; Arm 3 Nemvaleukin Monotherapy)

Procedure (Arms 1 and 3)	**SCN**	**Cycles 1 and 2**						**Cycle 3+ up to 1 Year**					**Cycles After 1 Year**					**EOT**	**30-Day Safety**	**LTFU q3 Months (±15d)**	**Comments**
Cycle Day		**1**	**2**	**3**	**4**	**5**	**8**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**	**	**FU***	****	
Visit Window (days)	D −21 to −1	* −3	±1	±1	±1	±1	±1	* −3	±1	±1	±1	±1	* −3	±1	±1	±1	±1	+7	±7		
Pre-SCN informed consent	X[a]																				D −35 to D −22; if needed to allow sufficient time for PD-L1 testing
Informed consent	X																				
Eligibility criteria	X																				Assessed by the Investigator; must be met ≤10 days before C1D1
Demographics and medical history	X																				
Prior medication, procedures, and anticancer therapy(ies)	X																				
Decision of Investigator's choice chemotherapy	X																				
PD-L1 status[b]	X																				Assessed by central laboratory using tumor tissue sample at SCN; local assessment can be used in some cases [b]
Tumor assessment[c]	X	q6w						q6w					q12w					X[d]	X[d]	X[d]	q6w (±7 days) from C1D1 dose during the 1st year, and q12w (±7 days) thereafter
CA-125[c]	X	q6w						q6w					q12w								
Tumor tissue sample[e]	X[e]						X[f]														At SCN required for central PD-L1 status; may be collected before SCN using pre-SCN ICF; D8 refers to C2 only
Physical examination	X	X						X					X					X	X		Full exam at SCN; focused/directed exam while on treatment
Vital signs[g]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		At nemvaleukin predose, end of infusion (±5 min), and at 0.5 hr (±5 min), 1 hr (±15 min) and 2 hr (±15 min) post-infusion
Weight and height[h]	X	X		X		X		X		X		X	X		X		X	X	X		Weight and height at C1D1 ≤10 days; weight only on other dosing days

Procedure (Arms 1 and 3)	**SCN**	**Cycles 1 and 2**						**Cycle 3+ up to 1 Year**					**Cycles After 1 Year**					**EOT** **	**30-Day Safety FU****	**LTFU q3 Months (±15d) ******	**Comments**
Cycle Day		**1**	**2**	**3**	**4**	**5**	**8**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**				
Visit Window (days)	D −21 to −1	* −3	±1	±1	±1	±1	±1	* −3	±1	±1	±1	±1	* −3	±1	±1	±1	±1	+7	±7		
ECOG status	X	X						X					X					X			
Single ECG	X	as clinically indicated																X			
LVEF	X																				C1D1 ≤10 days; only when PLD was selected as physician's choice of chemotherapy
Hematology[i]	X	X[i]		X		X		X				X	X					X			10 to 3 days prior to C1D1
Biochemistry[i]	X	X[i]		X		X		X				X	X					X			
Pregnancy test[j]	X	X						X					X					X	X[j]	X[j]	Local laboratory; 30-day Safety FU and LTFU tests only applicable to sites in France and Norway
Urinalysis[i k]	X	X[i]						X					X					X	X		10 to 3 days prior to C1D1; C4, and then every 4 cycles
Thyroid test (TSH, total T3 or free T3, and free T4)	X	X						X					X					X			10 to 3 days prior to C1D1; after SCN, TSH at each cycle, T3 and T4 only if needed; after 1 year, every 3 cycles
Adrenal function test (cortisol and ACTH)	X	X						X					X								10 to 3 days prior to C1D1; at each cycle in the 1st year; after 1 year, every 3 cycles
Coagulation panel	X																				INR and aPTT; 10 to 3 days prior to C1D1
EQ-5D-5L[l m]		X						q6w					q12w					X	X	X[m]	Before any study-related discussions or procedures
FACT-O[l]		X				X		X					q12w					X	X		
Administration of nemvaleukin[n]		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X				6 µg/kg; 21-day cycles; 30-min IV infusion
ctDNA[o]		X					X[f]	X[o]										X			Do not collect after C3; predose (C1D1 ≤10 days; CxD1 ≤24 hr)
Immunophenotyping (PBMC, TBNK, T_{reg})		X[o]					X[f]	X[o]										X			

Procedure (Arms 1 and 3)	SCN	Cycles 1 and 2						Cycle 3+ up to 1 Year					Cycles After 1 Year					EOT **	30-Day Safety FU***	LTFU q3 Months (±15d) ****	Comments
Cycle Day		**1**	**2**	**3**	**4**	**5**	**8**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**				
Visit Window (days)	D −21 to −1	* −3	±1	±1	±1	±1	±1	* −3	±1	±1	±1	±1	* −3	±1	±1	±1	±1	+7	±7		
Serum for soluble proteins[p] (PIP and IL-2RA)		X	X																		D1: predose (C1D1 ≤10 days; C2D1 ≤24 hr) and at 2 hr postdose (nemvaleukin); D2: ≤2 hr predose (nemvaleukin)
PK (nemvaleukin)		X[q]						X[q]					X[q]					X[q]	X[q]		Predose (C1D1 ≤10 days; CxD1 ≤24 hr) and at infusion completion
Immunogenicity (ADA) (nemvaleukin)		X[r]						X[r]					X[r]					X[r]	X[r]		Predose (C1D1 ≤10 days; CxD1 ≤24 hr)
AEs and concomitant meds	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X[s]	X[s]	Concomitant meds are to be followed as long as AEs are followed
Subsequent anticancer therapy																		X	X	X	
Overall survival																				X	
HIV, HBV, HCV tests	X																				Only applicable to sites in Czech Republic; local test
ARM 1 Only																					
Administration of pembrolizumab		X						X					X								After nemvaleukin administration; 200 mg; 21-day cycles; 30-min IV infusion; for a maximum of 35 cycles (≈2 years)
PK (pembrolizumab)		X[t]						X[t]										X[t]	X[t]		D1 of C1, C2, C4, and C8; predose (C1D1 ≤10 days; CxD1 ≤24 hr); and at infusion completion
Immunogenicity (ADA) (pembrolizumab)		X[u]						X[u]										X[u]	X[u]		D1 of C1, C2, C4, and C8; predose (C1D1 ≤10 days; CxD1 ≤24 hr)

ACTH=adrenocorticotropic hormone, ADA=antidrug antibody, AE=adverse event, aPTT=activated partial thromboplastin time, C=Cycle, CA-125=cancer antigen 125, CPS=combined positive score, ctDNA=circulating tumor DNA, D=Day, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, eCRF=electronic case report form, EOC=epithelial ovarian cancer, EOT=end of treatment, EQ-5D-5L=EuroQol 5 Dimension 5-Level, FACT-O=Functional Assessment of Cancer Therapy – Ovarian, FU=follow-up, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, ICF=Informed Consent Form, IL-2RA=interleukin 2 receptor alpha, INR=international normalized ratio, IV=intravenous, LTFU=long-term follow-up, LVEF=left ventricular ejection fraction, meds=medications, PBMC=peripheral blood mononuclear cell, PD-L1=programmed death ligand 1, PIP=pro-inflammatory panel, PK=pharmacokinetics, PLD=pegylated liposomal doxorubicin, PR=partial response, q12w=every 12 weeks, q3=every 3, q6w=every 6 weeks, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, SCN=Screening, TBNK=T cell, B cell, and natural killer cell,

T_{reg}=regulatory T-cell, T3=triiodothyronine, T4=thyroxine, TSH=thyroid-stimulating hormone, US=United States, VAS=Visual Analog Scale, WOCBP=women of childbearing potential.

* Assessments on D1 have a visit window of −3 days unless noted otherwise in the table footnote or in the comments' column.

** EOT Visit should be scheduled within 7 days from the day a decision was made to discontinue study treatment.

*** The Safety Follow-up assessments apply to all patients dosed and will be scheduled at least 30 days (±7 days) following the EOT Visit.

**** Patients will be contacted by the Investigator for phone visits during the Long-term Follow-up Period. Assessment to be performed every 3 months (±15 days) or more frequently to assess for survival status starting from the EOT Visit, for up to 3 years from first dose of study drug.

[a] The assessment window for the pre-screening ICF is D −35 to D −22. Pre-screening ICF can be completed before main ICF to allow sufficient time for assessment of PD-L1 by central laboratory in advance. This time should take into account the time needed to schedule and perform the biopsy and the transit time to the central laboratory.

[b] Central PD-L1 results are required for randomization. Under extreme circumstances the medical monitor may pre-approve the use of local PD-L1 result for randomization if: (1) tissue was submitted for central assessment, and the laboratory was given at least 10 business days to run the assay, but the results did not become available in the expected timeframe for randomization; and (2) local assessment was performed using DAKO 22C3 assay and allows PD-L1 status categorization (CPS ≥10 vs CPS <10).

[c] Tumor assessment should include all appropriate procedures to document the full extent of the patient's neoplastic disease according to RECIST v1.1. The same procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient. Tumor assessment and CA-125 should be performed q6w (±7 days) from C1D1 dose during the first year of study participation and q12w (±7 days) thereafter. Scans used for screening disease assessment that were performed previously as part of routine clinical management are acceptable to use if they are of diagnostic quality, have anatomic extent to cover the entirety of disease involvement, were performed within 28 days prior to C1D1, and the method used for the scan can be maintained throughout the study. When applicable, tumor assessment should be performed prior to dosing. A confirmatory scan for the first demonstration of a PR or better should be performed no sooner than 4 weeks (highly recommended) and no later than 6 weeks. See Section 10.2.1 for details on acceptable methods of tumor imaging and guidance for patients with history or suspicion of brain metastases.

[d] For patients who complete treatment or discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging q6w (Year 1 from start of treatment) or every 12 weeks (Years 2+ from start of treatment) from C1D1 until (1) the assessment of progressive disease, (2) the initiation of new anticancer therapy(ies), (3) withdrawal of consent, (4) death, or (5) end of study, whichever occurs first.

[e] Fresh (newly obtained) or archival tumor tissue sample may be collected for central immunohistochemistry testing of PD-L1 status prior to Screening after signing the pre-screening ICF. A tumor tissue sample collected at Screening (fresh biopsy) is preferred. Alternatively, a patient may provide a tumor tissue sample from prior cytoreductive surgery, or any archival tumor tissue collected since diagnosis of EOC. If surgery is planned during the study, collection of tissue and blood samples is recommended with appropriate documented consent under the optional biopsy collection procedures.

[f] In patients with accessible lesions, an additional on-treatment tumor biopsy is highly recommended on C2D8 (+4 days). See Section 10.4.2.2 for additional details. An additional immunophenotyping sample and an additional ctDNA sample will also be collected in patients with the optional biopsy performed on C2D8 (+4 days). Both the additional immunophenotyping sample and the additional ctDNA sample should be collected on the same day (±3 days) as the optional biopsy. For all patients randomized at sites in the US and Canada, a mandatory immunophenotyping sample will be collected on C1D8 (+2 days) and C2D8 (+2 days).

[g] Vital signs include blood pressure, pulse, respiratory rate, and body temperature.

[h] Height will be obtained at Screening only. Weight may be recorded within 10 days before expected dosing on C1D1 and within 3 days before dosing for other dosing days.

[i] Hematology, biochemistry, and urinalysis samples must be collected 10 to 3 days prior to expected C1D1 (ie, from D −10 to D −3) for central laboratory results to be available for review to assess eligibility. Local laboratory results can be used for eligibility if the central laboratory test results are at risk of arriving outside the expected timeframe for randomization. In this case, sites are still required to review central laboratory results when they become available. If a central laboratory result does not meet the eligibility criteria but the local laboratory result does, the local laboratory result that supports the patient's eligibility should be entered into the eCRF. Otherwise, samples must be collected as noted in the schedule of assessments.

[j] All WOCBP must have a negative pregnancy test (serum or urine) performed by local laboratory within 3 days before the first dose of every cycle. If pregnancy testing is performed within these intervals before dosing, sampling does not need to be repeated on the day of dosing. For patients at sites in France and Norway: after treatment discontinuation, pregnancy testing in heterosexually active WOCBP must continue to be assessed monthly for 30 days in Arm 3 and for 120 days in Arm 1.

[k] If dipstick assessment result is abnormal, relevant work-up is per Investigator discretion (see Appendix 3).

[l] The questionnaires must be completed before any study-related discussions or procedures.

[m] VAS only. Investigator or appropriately delegated designee will record the patient's response.

[n] Any time nemvaleukin is administered, antipyretics are recommended prior to administration, during dosing of IV nemvaleukin, and subsequently as needed. Patient must be well hydrated prior to start of treatment.

[o] ctDNA and immunophenotyping samples are to be collected on C1D1 (within 10 days before dosing and can be drawn on different days than safety labs [ie, hematology, biochemistry, and urinalysis]), C2D1 and C3D1 (within 24 hours before dosing), and EOT.

[p] For D1, serum for soluble proteins (PIP) is to be collected for C1 within 10 days before dosing on D1 and the samples must be drawn on the same day as other laboratory samples (ie, ctDNA and immunophenotype), for all other cycles within 24 hours before dosing on D1, and at 2 hours (±15 minutes) postdose. For D2, serum for soluble proteins is to be collected within 2 hours (±15 minutes) prior to dosing. IL-2RA is only to be collected predose on C1D1.

[q] Samples will be collected on D1 of each cycle for Cycles 1-8 as follows: for C1 within 10 days before dosing on D1 and must be drawn on the same day as other laboratory samples, for all other cycles within 24 hours before dosing on D1 and at the completion of the 30-minute (±5 minutes) nemvaleukin infusion. Additional samples will be collected at EOT and at Safety Follow-up. Samples should be drawn from the arm opposite of the arm used to infuse study drug. Do not take samples from a central line used to infuse study drug.

[r] Samples will be collected on D1 of each cycle for Cycles 1-8 as follows: for C1 within 10 days before dosing on D1 and must be drawn on the same day as other laboratory samples (ie, ctDNA, immunophenotyping, and PK), for all other cycles within 24 hours before dosing on D1. Additional samples will be collected at EOT and at Safety Follow-up. Samples should be drawn from the arm opposite of the arm used to infuse study drug. Do not take samples from a central line used to infuse study drug.

[s] During the Follow-up Period, patients will be contacted by the Investigator for in-office visit/phone visits to review any AEs/SAEs and concomitant medications at 30 days after the EOT. In addition, SAEs will be collected for patients in Arm 1 through 90 days after the EOT during Survival Follow-up visits. For all patients, if new anticancer therapy is initiated, AE and concomitant medication collection will stop. Any AE or SAE with an onset 30 days (Arm 3) or 90 days (Arm 1) after the EOT will not be collected or reported unless the Investigator assesses the event to be related to the study drug.

[t] Applies to Arm 1 only. Samples will be collected on D1 of Cycles 1, 2, 4, and 8 as follows: predose (for C1 within 10 days before dosing on D1 and must be drawn on the same day as other laboratory samples [ie, ctDNA, immunophenotyping, and PK], for all other cycles, D1 samples can be drawn within 24 hours before the start of pembrolizumab infusion) and at the completion of the pembrolizumab infusion (+30 minutes). Additional samples will be collected at EOT and Safety Follow-up. Samples should be drawn from the arm opposite of the arm used to infuse study drug. Do not take samples from a central line used to infuse study drug.

[u] Applies to Arm 1 only. Samples will be collected on D1 of Cycles 1, 2, 4, and 8 as follows: predose, for C1 within 10 days before dosing on D1 and must be drawn on the same day as other laboratory samples, for all other cycles samples can be drawn within 24 hours before the start of pembrolizumab infusion.

Additional samples will be collected at EOT and Safety Follow-up. Samples should be drawn from the arm opposite of the arm used to infuse study drug. Do not take samples from a central line used to infuse study drug.

Table 3: Schedule of Assessments for Arm 2 (Pembrolizumab Monotherapy)

Procedure (Arm 2)	SCN	Cycles 1 and 2						Cycle 3+ up to 1 Year					Cycles After 1 Year					EOT **	30-Day Safety FU***	LTFU q3 Months (±15d) ****	Comments
Cycle Day		**1**	**2**	**3**	**4**	**5**	**8**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**				
Visit Window (days)	D −21 to −1	* −3	±1	±1	±1	±1	±1	* −3	±1	±1	±1	±1	* −3	±1	±1	±1	±1	+7	±7		
Pre-SCN informed consent	X[a]																				D −90 to D −22; if needed to allow sufficient time for PD-L1 testing
Informed consent	X																				
Eligibility criteria	X																				Assessed by the Investigator, must be met ≤10 days before C1D1
Demographics and medical history	X																				
Prior medication, procedures, and anticancer therapy(ies)	X																				
Decision of Investigator's choice chemotherapy	X																				
PD-L1 status[b]	X																				Assessed by central laboratory using tumor tissue sample at SCN; local assessment can be used in some cases [b]
Tumor assessment[c]	X	q6w						q6w					q12w					X[d]	X[d]	X[d]	q6w (±7 days) from C1D1 dose during the 1st year, and q12w (±7 days) thereafter
CA-125[c]	X	q6w						q6w					q12w								
Tumor tissue sample[e]	X[e]						X[f]														At SCN required for central PD-L1 status; may be collected before SCN using pre-SCN ICF; D8 refers to C2 only
Physical examination[g]	X	X						X					X					X	X		Full exam at SCN; focused/directed exam while on treatment
Vital signs[h]	X	X						X					X					X	X		At predose, end of infusion (±5 min), at 0.5 hr (±5 min), and 1 hr (±15 min)
Weight and height[i]	X	X						X					X					X	X		Weight and height at C1D1 ≤10 days; weight only on other dosing days
ECOG status	X	X						X					X					X			

Procedure (Arm 2)	SCN	Cycles 1 and 2						Cycle 3+ up to 1 Year					Cycles After 1 Year					EOT **	30-Day Safety FU***	LTFU q3 Months (±15d) ****	Comments
Cycle Day		**1**	**2**	**3**	**4**	**5**	**8**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**				
Visit Window (days)	D −21 to −1	* −3	±1	±1	±1	±1	±1	* −3	±1	±1	±1	±1	* −3	±1	±1	±1	±1	+7	±7		
Single ECG	X	as clinically indicated																X			
LVEF	X																				C1D1 ≤10 days; only when PLD was selected as physician's choice of chemotherapy
Hematology[j]	X	X[j]						X					X					X			10 to 3 days prior to C1D1
Biochemistry[j]	X	X[j]						X					X					X			
Pregnancy test[k]	X	X						X					X					X	X[k]	X[k]	Local laboratory; 30-day Safety FU and LTFU tests only applicable to sites in France and Norway
Urinalysis[j l]	X	X[j]						X					X					X	X		10 to 3 days prior to C1D1; C4, and then every 4 cycles
Thyroid test (TSH, total T3 or free T3, and free T4)	X	X						X					X					X			10 to 3 days prior to C1D1; after SCN, TSH at each cycle, T3 and T4 only if needed; after 1 year, every 3 cycles
Adrenal function test (cortisol and ACTH)	X	X						X					X								10 to 3 days prior to C1D1; at each cycle in the 1st year; after 1 year, every 3 cycles
Coagulation panel	X																				INR and aPTT; 10 to 3 days prior to C1D1
EQ-5D-5L[m n]		X						q6w					q12w					X	X	X[n]	Before any study-related discussions or procedures
FACT-O[m]		X						X					q12w					X	X		
Administration of pembrolizumab		X						X					X								200 mg; 21-day cycles; 30-min IV infusion; for a maximum of 35 cycles (≈2 years)
ctDNA[o]		X					X[f]	X[o]										X			D8 refers to C2 only; do not collect after C3; predose (C1D1 ≤10 days; CxD1 ≤24 hr)
Immunophenotyping (PBMC, TBNK, T_{reg})		X[o]					X[f]	X[o]										X			
Serum for soluble proteins[p] (PIP and IL-2RA)		X																			Predose (C1D1 ≤10 days; C2D1 ≤24 hr) and at 2 hr postdose

Procedure (Arm 2)	SCN	Cycles 1 and 2						Cycle 3+ up to 1 Year					Cycles After 1 Year					EOT **	30-Day Safety FU***	LTFU q3 Months (±15d) ****	Comments
Cycle Day		**1**	**2**	**3**	**4**	**5**	**8**	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**				
Visit Window (days)	D −21 to −1	* −3	±1	±1	±1	±1	±1	* −3	±1	±1	±1	±1	* −3	±1	±1	±1	±1	+7	±7		
AEs and concomitant meds	X	X						X					X					X	X[q]	X[q]	Concomitant meds are to be followed as long as AEs are followed
Subsequent anticancer therapy																		X	X	X	
Overall survival																				X	
HIV, HBV, HCV tests	X																				Only applicable to sites in Czech Republic; local test

ACTH=adrenocorticotropic hormone, AE=adverse event, aPTT=activated partial thromboplastin time, C=Cycle, CA-125=cancer antigen 125, CPS=combined positive score, ctDNA=circulating tumor DNA, D=Day, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, eCRF=electronic case report form, EOC=epithelial ovarian cancer, EOT=end of treatment, EQ-5D-5L=EuroQol 5 Dimension 5-Level, FACT-O=Functional Assessment of Cancer Therapy – Ovarian, FU=follow-up, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, ICF=Informed Consent Form, IL-2RA=interleukin 2 receptor alpha, INR=international normalized ratio, IV=intravenous, LTFU=long-term follow-up, LVEF=left ventricular ejection fraction, meds=medications, PBMC=peripheral blood mononuclear cell, PD-L1=programmed death ligand 1, PIP=pro-inflammatory panel, PLD=pegylated liposomal doxorubicin, PR=partial response, q12w=every 12 weeks, q3=every 3, q6w=every 6 weeks, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, SCN=Screening, TBNK=T cell, B cell, and natural killer cell, T_{reg}=regulatory T-cell, T3=triiodothyronine, T4=thyroxine, TSH=thyroid-stimulating hormone, VAS=Visual Analog Scale, WOCBP=women of childbearing potential.

* Assessments on D1 have a visit window of −3 days unless noted otherwise in the table footnote or in the comments' column.

** EOT Visit should be scheduled within 7 days from the day a decision was made to discontinue study treatment.

*** The Safety Follow-up assessments apply to all patients dosed and will be scheduled at least 30 days (±7 days) following the EOT Visit.

**** Patients will be contacted by the Investigator for phone visits during the Long-term Follow-up Period. Assessment to be performed every 3 months (±15 days) or more frequently to assess for survival status starting from the EOT Visit, for up to 3 years from first dose of study drug.

[a] The assessment window for the pre-screening ICF is D −90 to D −22. Pre-screening ICF can be completed before main ICF to allow sufficient time for assessment of PD-L1 by central laboratory in advance. This time should take into account the time needed to schedule and perform the biopsy and the transit time to the central laboratory.

[b] Central PD-L1 results are required for randomization. Under extreme circumstances the medical monitor may pre-approve the use of local PD-L1 result for randomization if: (1) tissue was submitted for central assessment, and the laboratory was given at least 10 business days to run the assay, but the results did not become available in the expected timeframe for randomization; and (2) local assessment was performed using DAKO 22C3 assay and allows PD-L1 status categorization (CPS ≥10 vs CPS <10).

[c] Tumor assessment should include all appropriate procedures to document the full extent of the patient's neoplastic disease according to RECIST v1.1. The same procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient. Tumor assessment and CA-125 should be performed q6w (±7 days) from C1D1 dose during the first year of study participation and q12w (±7 days) thereafter. Scans used for screening disease assessment that were performed previously as part of routine clinical management are acceptable to use if they are of diagnostic quality, have anatomic extent to cover the entirety of disease involvement, were performed within 28 days prior to C1D1, and the method used for the scan can be maintained throughout the

study. When applicable, tumor assessment should be performed prior to dosing. A confirmatory scan for the first demonstration of a PR or better should be performed no sooner than 4 weeks (highly recommended) and no later than 6 weeks. See Section 10.2.1 for details on acceptable methods of tumor imaging and guidance for patients with history or suspicion of brain metastases.

[d] For patients who complete treatment or discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging q6w (Year 1 from start of treatment) or every 12 weeks (Years 2+ from start of treatment) from C1D1 until (1) the assessment of progressive disease, (2) the initiation of new anticancer therapy(ies), (3) withdrawal of consent, (4) death, or (5) end of study, whichever occurs first.

[e] Fresh (newly obtained) or archival tumor tissue sample may be collected for central immunohistochemistry testing of PD-L1 status prior to Screening after signing pre-screening ICF. A tumor tissue sample collected at Screening (fresh biopsy) is preferred. Alternatively, a patient may provide a tumor tissue sample from prior cytoreductive surgery, or any archival tumor tissue collected since diagnosis of EOC. If surgery is planned during the study, collection of tissue and blood samples is recommended with appropriate documented consent under the optional biopsy collection procedures.

[f] In patients with accessible lesions, an additional on-treatment tumor biopsy is highly recommended on C2D8 (+4 days). See Section 10.4.2.2 for additional details. An additional immunophenotyping sample and an additional ctDNA sample will also be collected in patients with the optional biopsy performed on C2D8 (+4 days). Both the additional immunophenotyping sample and the additional ctDNA sample should be collected on the same day (±3 days) as the optional biopsy.

[g] A full physical examination is to be performed at Screening. Focused/directed physical examinations for the areas of disease or AEs are to be performed at all other visits.

[h] Vital signs include blood pressure, pulse, respiratory rate, and body temperature. On days when study drug is not administered, vital signs may be collected at any time.

[i] Height will be obtained at Screening only. Weight may be recorded within 10 days before expected dosing on C1D1 and within 3 days before dosing for other dosing days.

[j] Hematology, biochemistry, and urinalysis samples must be collected 10 to 3 days prior to expected C1D1 (ie, from D −10 to D −3) for central laboratory results to be available for review to assess eligibility. Local laboratory results can be used for eligibility if the central laboratory test results are at risk of arriving outside the expected timeframe for randomization. In this case, sites are still required to review central laboratory results when they become available. If a central laboratory result does not meet the eligibility criteria but the local laboratory result does, the local laboratory result that supports the patient's eligibility should be entered into the eCRF. Otherwise, samples must be collected as noted in the schedule of assessments.

[k] All WOCBP must have a negative pregnancy test (serum or urine) performed by local laboratory within 3 days before the first dose of every cycle. If pregnancy testing is performed within these intervals before dosing, sampling does not need to be repeated on the day of dosing. For patients at sites in France and Norway: after treatment discontinuation, pregnancy testing in heterosexually active WOCBP must continue to be assessed monthly for 120 days.

[l] If dipstick assessment result is abnormal, relevant work-up is per Investigator discretion (see Appendix 3).

[m] The questionnaires must be completed before any study-related discussions or procedures.

[n] VAS only. Investigator or appropriately delegated designee will record the patient's response.

[o] ctDNA and immunophenotyping samples are to be collected on C1D1 (within 10 days before dosing and can be drawn on different days than safety labs [ie, hematology, biochemistry, and urinalysis]), C2D1 and C3D1 (within 24 hours before dosing), and EOT.

[p] For D1, serum for soluble proteins (PIP) is to be collected for C1 within 10 days before dosing on D1 and the samples must be drawn on the same day as other laboratory samples (ie, ctDNA and immunophenotype), for all other cycles within 24 hours before dosing on D1, and at 2 hours (±15 minutes) postdose. IL-2RA is only to be collected predose on C1D1.

[q] During the Follow-up Period, patients will be contacted by the Investigator for in-office visit/phone visits to review any AEs/SAEs and concomitant medications at 30 days after the EOT. In addition, SAEs will be collected through 90 days after the EOT during Survival Follow-up visits. For all patients, if

new anticancer therapy is initiated, AE and concomitant medication collection will stop. Any AE or SAE with an onset 90 days after the EOT will not be collected or reported unless the Investigator assesses the event to be related to the study drug.

Table 4: Schedule of Assessments for Arm 4 (Investigator's Choice Chemotherapy)

Procedure (Arm 4)	SCN	Cycles 1 and 2								Cycle 3+ up to 1 Year								Cycles After 1 Year								EOT **	30-Day Safety FU***	LTFU q3 Months (±15d) ****
Cycle Day		1	2	3	4	5	8	15	22	1	2	3	4	5	8	15	22	1	2	3	4	5	8	15	22			
Visit Window (days)	D −21 to −1	* −3	±1	±1	±1	±1	±1	±1	±1	* −3	±1	±1	±1	±1	±1	±1	±1	* −3	±1	±1	±1	±1	±1	±1	±1	+7	±7	
Pre-SCN informed consent	X[a]																											
Informed consent	X																											
Eligibility criteria[b]	X																											
Demographics and medical history	X																											
Prior medication, procedures, and anticancer therapy(ies)	X																											
Decision of Investigator's choice chemotherapy	X																											
PD-L1 status[c]	X																											
Tumor assessment[d]	X	q6w								q6w								q12w								X[e]	X[e]	X[e]
CA-125[d]	X	q6w								q6w								q12w										
Tumor tissue sample[c]	X[c]						X[f]																					
Physical examination[g]	X	X								X								X								X	X	
Vital signs[h]	X	per institutional standard or labeling information of chemotherapy regimen																								X	X	
ECOG status	X	X								X								X								X		
Single ECG	X	as clinically indicated																								X		
Pregnancy test[i]	X	X								X								X								X	X[i]	X[i]
Thyroid test[j]	X																											
Adrenal function test[j]	X																											
Urinalysis[k l]	X	X[k]								X[l]								X[l]								X	X	
Coagulation panel[j]	X																											

Procedure (Arm 4)	**SCN**	**Cycles 1 and 2**								**Cycle 3+ up to 1 Year**								**Cycles After 1 Year**								**EOT** **	**30-Day Safety FU****	**LTFU q3 Months (±15d)** ****
Cycle Day		**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**			
Visit Window (days)	D −21 to −1	* −3	±1	±1	±1	±1	±1	±1	±1	* −3	±1	±1	±1	±1	±1	±1	±1	* −3	±1	±1	±1	±1	±1	±1	±1	+7	±7	
EQ-5D-5L[m n]		X								q6w								q12w								X	X	X[n]
FACT-O[m]		X								X								q12w								X	X	
ctDNA[o]		X					X[f]			X[o]																X		
Subsequent anticancer therapy																										X	X	X
Overall survival																												X
HIV, HBV, HCV tests (sites in Czech Republic only)	X																											
ARM 4 PLD (40 mg/m^2); 28-day Cycles (Administered on D1)																												
Administration of PLD		X								X								X										
Weight and height[p]	X	X								X								X								X	X	
Hematology[k]	X	X[k]					X			X								X								X		
Biochemistry[k]	X	X[k]					X			X								X								X		
LVEF	X	X[q]								X[q]								X[q]								X		
AEs and concomitant meds	X	X								X								X								X	X[r]	X[r]
ARM 4 paclitaxel (80 mg/m^2); 28-day Cycles (Administered on D1, D8, D15, and D22)																												
Administration of paclitaxel		X					X	X	X	X					X	X	X	X					X	X	X			
Weight and height[p]	X	X					X	X	X	X					X	X	X	X					X	X	X	X	X	
Hematology[k]	X	X[k]					X	X	X	X						X	X	X						X	X	X		
Biochemistry[k]	X	X[k]					X	X	X	X						X	X	X						X	X	X		
AEs and concomitant meds	X	X					X	X	X	X					X	X	X	X					X	X	X	X	X[r]	X[r]

Procedure (Arm 4)	**SCN**	**Cycles 1 and 2**								**Cycle 3+ up to 1 Year**								**Cycles After 1 Year**								**EOT** **	**30-Day Safety FU****	**LTFU q3 Months (±15d)** ****
Cycle Day		**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**			
Visit Window (days)	D −21 to −1	* −3	±1	±1	±1	±1	±1	±1	±1	* −3	±1	±1	±1	±1	±1	±1	±1	* −3	±1	±1	±1	±1	±1	±1	±1	+7	±7	
ARM 4 topotecan 4 mg/m^2; 28-day Cycles (Administered on D1, D8, and D15)																												
Administration of topotecan		X					X	X		X					X	X		X					X	X				
Weight and height[p]	X	X					X	X		X					X	X		X					X	X		X	X	
Hematology[k]	X	X[k]					X	X		X						X		X						X		X		
Biochemistry[k]	X	X[k]					X	X		X						X		X						X		X		
AEs and concomitant meds	X	X					X	X		X					X	X		X					X	X		X	X[r]	X[r]
ARM 4 topotecan 1.25 mg/m^2; 21-day Cycles (Administered D1 to D5)																												
Administration of topotecan		X	X	X	X	X				X	X	X	X	X				X	X	X	X	X						
Weight and height[p]	X	X	X	X	X	X				X	X	X	X	X				X	X	X	X	X				X	X	
Hematology[k]	X	X[k]		X		X				X				X				X								X		
Biochemistry[k]	X	X[k]		X		X				X				X				X								X		
AEs and concomitant meds	X	X		X		X				X		X		X				X		X		X				X	X[r]	X[r]
ARM 4 gemcitabine 1,000 mg/m^2; 21-day Cycles (Administered D1 and D8)																												
Administration of gemcitabine		X					X			X					X			X					X					
Weight and height[p]	X	X					X			X					X			X					X			X	X	
Hematology[k]	X	X[k]					X			X								X								X		
Biochemistry[k]	X	X[k]					X			X								X								X		
AEs and concomitant meds	X	X					X			X					X			X					X			X	X[r]	X[r]

ACTH=adrenocorticotropic hormone, AE=adverse event, C=Cycle, CA-125=cancer antigen 125, CPS=combined positive score, ctDNA=circulating tumor DNA, D=Day, ECG=electrocardiogram, ECHO=echocardiogram, ECOG=Eastern Cooperative Oncology Group, eCRF=electronic case report form, EOC=epithelial ovarian cancer, EOT=end of treatment, EQ-5D-5L=EuroQol 5 Dimension 5-Level, FACT-O=Functional Assessment of Cancer Therapy – Ovarian, FU=follow-up, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, ICF=Informed Consent Form, IV=intravenous, LTFU=long-term follow-up, LVEF=left ventricular ejection fraction, meds=medications, MUGA=multiple gated acquisition, PD-L1=programmed death

ligand 1, PLD=pegylated liposomal doxorubicin, PR=partial response, q12w=every 12 weeks, q3=every 3, q6w=every 6 weeks, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, SCN=Screening, T3=triiodothyronine, T4=thyroxine, TSH=thyroid-stimulating hormone, VAS=Visual Analog Scale, WOCBP=women of childbearing potential.

* Assessments on D1 have a visit window of −3 days unless noted otherwise in the table footnote.

** EOT Visit should be scheduled within 7 days from the day a decision was made to discontinue study treatment.

*** The Safety Follow-up assessments apply to all patients dosed and will be scheduled at least 30 days (±7 days) following the EOT Visit.

**** Patients will be contacted by the Investigator for phone visits during the Long-term Follow-up Period. Assessment to be performed every 3 months (±15 days) or more frequently to assess for survival status starting from the EOT Visit, for up to 3 years from first dose of study drug.

[a] The assessment window for the pre-screening ICF is D −35 to D −22. Pre-screening ICF can be completed before main ICF to allow sufficient time for assessment of PD-L1 by central laboratory in advance. This time should take into account the time needed to schedule and perform the biopsy and the transit time to the central laboratory.

[b] Eligibility requirements should be assessed by the Investigator and must be met within 10 days prior to expected C1D1.

[c] Fresh (newly obtained) or archival tumor tissue sample may be collected for central immunohistochemistry testing of PD-L1 status prior to SCN after signing the pre-screening ICF. A tumor tissue sample collected at SCN (fresh biopsy) is preferred. Alternatively, a patient may provide a tumor tissue sample from prior cytoreductive surgery, or any archival tumor tissue collected since diagnosis of EOC. If surgery is planned during the study, collection of tissue and blood samples is recommended with appropriate documented consent under the optional biopsy collection procedures. Central PD-L1 results are required for randomization. Under extreme circumstances the medical monitor may pre-approve the use of local PD-L1 result for randomization if: (1) tissue was submitted for central assessment, and the laboratory was given at least 10 business days to run the assay, but the results did not become available in the expected timeframe for randomization; and (2) local assessment was performed using DAKO 22C3 assay and allows PD-L1 status categorization (CPS ≥10 vs CPS <10).

[d] Tumor assessment should include all appropriate procedures to document the full extent of the patient's neoplastic disease according to RECIST v1.1. The same procedure used to define measurable or non-measurable lesions must be used throughout the study for each patient. Tumor assessment and CA-125 should be performed q6w (±7 days) from C1D1 dose during the first year of study participation and q12w (±7 days) thereafter. Scans used for screening disease assessment that were performed previously as part of routine clinical management are acceptable to use if they are of diagnostic quality, have anatomic extent to cover the entirety of disease involvement, were performed within 28 days prior to C1D1, and the method used for the scan can be maintained throughout the study. When applicable, tumor assessment should be performed prior to dosing. A confirmatory scan for the first demonstration of a PR or better should be performed no sooner than 4 weeks (highly recommended) and no later than 6 weeks. See Section 10.2.1 for details on acceptable methods of tumor imaging and guidance for patients with history or suspicion of brain metastases.

[e] For patients who complete treatment or discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging q6w (Year 1 from start of treatment) or every 12 weeks (Years 2+ from start of treatment) from C1D1 until (1) the assessment of progressive disease, (2) the initiation of new anticancer therapy(ies), (3) withdrawal of consent, (4) death, or (5) end of study, whichever occurs first.

[f] In patients with accessible lesions, an additional on-treatment tumor biopsy is highly recommended on C2D8 (+4 days). See Section 10.4.2.2 for additional details. An additional ctDNA sample will also be collected in patients with the optional biopsy performed on C2D8 (+4 days). The additional ctDNA sample should be collected on the same day (±3 days) as the optional biopsy.

[g] A full physical examination is to be performed at SCN. Focused/directed physical examinations for the areas of disease or AEs are to be performed at all other visits.

[h] Vital signs include blood pressure, pulse, respiratory rate, and body temperature. For Investigator's choice chemotherapy, monitor vital signs per institutional standard or labeling information of chemotherapy regimen.

[i] All WOCBP must have a negative pregnancy test (serum or urine) performed by local laboratory within 3 days before the first dose of every cycle. If pregnancy testing is performed within these intervals before dosing, sampling does not need to be repeated on the day of dosing. For patients at sites in France and Norway: after treatment discontinuation, pregnancy testing in heterosexually active WOCBP must continue to be assessed monthly for the recommended duration of the contraception in the approved label and/or institutional guidelines for the specific Investigator's choice chemotherapy.

[j] Samples for thyroid test, adrenal function test, and coagulation panel are to be collected 10 to 3 days prior to expected C1D1 (ie, from D −10 to D −3). TSH, total T3 or free T3, free T4, total cortisol, and ACTH are to be collected at Screening for all patients.

[k] Hematology, biochemistry, and urinalysis samples must be collected on the same day 10 to 3 days prior to expected C1D1 (ie, from D −10 to D −3) for central laboratory results to be available for review to assess eligibility. Local laboratory results can be used for eligibility if the central laboratory test results are at risk of arriving outside the expected timeframe for randomization. In this case, sites are still required to review central laboratory results when they become available. If a central laboratory result does not meet the eligibility criteria but the local laboratory result does, the local laboratory result that supports the patient's eligibility should be entered into the eCRF. Otherwise, samples can be collected as noted in the schedule of assessments. Mid-cycle laboratory assessments beyond C3 can be performed as per institutional guidance.

[l] Urinalysis must be collected at C4D1 and every 4 cycles thereafter (ie, C8D1, C12D1, etc). If dipstick assessment result is abnormal, relevant work-up is per Investigator discretion (see Appendix 3).

[m] The questionnaires must be completed prior to any study related discussions with patients and prior to any study procedures (when applicable).

[n] VAS only. Investigator or appropriately delegated designee will record the patient's response.

[o] ctDNA is to be collected on C1D1 (within 10 days before dosing and can be drawn on different days than safety labs [ie, hematology, biochemistry, and urinalysis]), C2D1 and C3D1 (within 24 hours before dosing), and EOT.

[p] Height will be obtained at Screening only. Weight may be recorded within 10 days before expected dosing on C1D1 and within 3 days before dosing for other dosing days.

[q] LVEF assessment at baseline can be done during the Screening Period within 10 days of expected C1D1 for patients where PLD was selected as physician's choice of chemotherapy. C1D1 assessment does not need to be performed if baseline assessment was performed as per protocol. On-treatment LVEF assessment is to be performed every 4 cycles (ie, C5D1, C9D1, etc; within 3 days of the first dose of the cycle) and only applies to patients who are randomized to Investigator's Choice Chemotherapy Arm to receive PLD. The same assessment technique (MUGA or ECHO) should be conducted throughout treatment. If patient LVEF drops below normal or by at least 15% from baseline, treatment with PLD should be discontinued.

[r] During the Follow-up Period, patients will be contacted by the Investigator for in-office visit/phone visits to review any AEs/SAEs and concomitant medications at 30 days after the EOT. For all patients, if new anticancer therapy is initiated, AE and concomitant medication collection will stop. Any AE or SAE with an onset 30 days after the EOT will not be collected or reported unless the Investigator assesses the event to be related to the Investigator's choice chemotherapy.

Note: Investigator's choice chemotherapy to be administered as follows: for PLD (40 mg/m^2), Day 1 of 28-day cycles, 1 mg/min for Cycle 1, and 60-minute infusions for Cycles 2+; for paclitaxel (80 mg/m^2; 60-minute IV infusion), Days 1, 8, 15, and 22 of 28-day cycles; for topotecan, either Days 1, 8, and 15 of 28-day cycles (4 mg/m^2; 30-minute IV infusion) or Days 1 through 5 of 21-day cycles (1.25 mg/m^2; 30-minute IV infusion); for Gemcitabine (1,000 mg/m^2; 30-minute IV infusion), Day 1 and 8 of 21-day cycles.

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Table 5: List of Abbreviations and Definition of Terms

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ALK-P	alkaline phosphatase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
BRCA	breast cancer gene
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CA-125	cancer antigen 125
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
CLS	capillary leak syndrome
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPS	combined positive score
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
CSA	clinical study agreement
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte associated protein 4
DCR	disease control rate
DNA	deoxyribonucleic acid

Abbreviation	Definition
DOR	duration of response
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EOT	end of treatment
EQ-5D-5L	EuroQol 5 Dimension 5-Level
FACT-O	Functional Assessment of Cancer Therapy – Ovarian
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IL-2R	interleukin-2 receptor
INR	international normalized ratio
irAE	immune-related adverse event

Abbreviation	Definition
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	Intent-to-Treat
IV	intravenous
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
ORR	objective response rate
OS	overall survival
PARP	poly adenosine diphosphate-ribose polymerase
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PLD	pegylated liposomal doxorubicin
PR	partial response
PROC	platinum-resistant ovarian cancer
PT	preferred term
q12w	every 12 weeks
q21d	every 21 days
q3w	every 3 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rhIL-2	recombinant human IL-2
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	stable disease
SOA	Schedule of Assessments

Abbreviation	Definition
SOC	System Organ Class
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TMB	tumor mutational burden
T_{regs}	regulatory T cells
TSH	thyroid stimulating hormone
TTR	time to response
ULN	upper limit of normal
US	United States
VAS	Visual Analogue Scale
WOCBP	women of childbearing potential

5. INTRODUCTION

5.1. Ovarian Background and Current Treatment Standards

Ovarian, fallopian tube, and primary peritoneal cancers identified as EOCs are life-threatening diseases and comprise the seventh most common cause of cancer mortality in women (Bray et al, 2018). In the US in 2020, an estimated 21,750 women will be newly diagnosed with ovarian cancer, and an estimated 13,940 women will die from the disease (Siegel et al, 2020). Standard frontline treatment for EOC is platinum-based chemotherapy with or without an antiangiogenic, such as bevacizumab, which may be followed by maintenance therapy with bevacizumab, a PARP inhibitor, or both, depending on biomarker status. Antiangiogenic agents (eg, bevacizumab) and PARP inhibitors (eg, olaparib, niraparib etc) are the 2 molecularly-targeted therapies approved in recurrent EOC worldwide. The additional treatment option for EOC has increased the survival of patients with recurrent EOC and at least half of them will likely receive more than 3 lines of therapy. There is high unmet medical need in patients with no standard treatment option after their third line (3+ disease) treatment. More efforts to identify new treatment options for this increasing number of patients with "chronic" disease are needed (Pujade-Lauraine and Combe 2016). Activity of the platinum-based regimens is clinically meaningful for a majority of patients, although disease recurrence is common, and most patients will eventually become resistant to the platinum therapy. These patients are known as recurrent, PROC patients. For patients who become resistant to or who are refractory to platinum, the standard of care is single-agent non-platinum chemotherapy, which offers a low likelihood of durable response. In the most recent AURELIA study, physician's choice chemotherapy (PLD, paclitaxel, topotecan, or gemcitabine) generated objective responses in 12% of PROC patients with a PFS of 3.4 months (Pujade-Lauraine et al, 2014).

Recently, there have been multiple failed Phase 3 studies in the EOC and PROC spaces with novel targeted agents and immune checkpoint inhibitors. The FORWARD I study showed a higher response rate for mirvetuximab soravtansine than for chemotherapy (22% vs 12%, *P*=0.015), but failed to meet its primary endpoint of PFS (HR=0.98, *P*=0.897) or OS (HR=0.815, *P*=0.248); a selected subgroup with high folate receptor expression showed promising activity, and a larger study is ongoing to confirm these results (Immunogen Inc 2019; Moore et al, 2019). In early studies, anti-PD-1 or anti-PD-L1 monotherapies were also shown to be ineffective for treating EOC, in general; these therapies generate objective responses in <15% of platinum-sensitive and -resistant ovarian cancer patients, with a median PFS of 2.1 months (Gonzalez-Martin and Sanchez-Lorenzo 2019; Matulonis et al, 2019). Most recently, 3 large Phase 3 studies treating EOC with immune checkpoint inhibitors failed to meet their primary endpoints. IMagyn050/GOG 3015/ENGOT-OV39, a Phase 3 study in the frontline setting, recently reported failure to meet its primary endpoint of PFS for atezolizumab plus bevacizumab and chemotherapy, versus bevacizumab and chemotherapy alone (Moore et al, 2020). In addition, in the PROC disease state, avelumab alone or in combination with standard of care (PLD) did not improve survival in the Phase 3 JAVELIN 200 study (Pujade-Lauraine et al, 2019). NINJA, a Phase 3 study of monotherapy nivolumab versus gemcitabine or PLD (GEM/PLD), also failed to improve OS (HR=1.03, *P*=0.808) (Omatsu et al, 2020). Median PFS was 2.04 (95% CI, 1.91 to 2.20) months with nivolumab and 3.84 (95% CI, 3.58 to 4.17) months with GEM/PLD (HR=1.46; 95% CI, 1.15 to 1.85; *P*=0.002), while ORR was 8% (95% CI, 3.5 to 13.9) versus 13% (95% CI, 7.6 to 20.8), respectively. Additionally, a Phase 2 study of

pembrolizumab, KEYNOTE-100, showed modest responses of 7.4% to 9.9%, with a median PFS of only 2.1 months; higher PD-L1 expression was correlated with higher response (Matulonis et al, 2019). There are a number of immune checkpoint inhibitor studies ongoing in EOC that will further determine if checkpoint inhibitors alone or in combination with standard of care or other novel agents have the potential to treat the disease (Grywalska et al, 2019). These ongoing studies and studies like these will allow us to further understand the potential of immunotherapy in the treatment of EOC.

Epithelial ovarian cancers, in general, have immunogenic properties, with over half of patients demonstrating tumor-infiltrating lymphocytes. Tumors with expression of PD-L1 show enhanced response to PD-1/L1 inhibitors relative to those without expression (Kandalaft et al, 2011). Interestingly, EOC tumors with immune infiltrates typically demonstrate a high proportion of T_{regs}, which could establish immunosuppressive phenotypes. Additionally, EOC tumors often harbor a lower TMB and frequency of PD-L1 expression as compared to other tumor types more responsive to checkpoint inhibition therapies (eg, bladder cancer, melanoma). The available data suggest that single-agent checkpoint inhibitors show only modest activity in EOC (Gatalica et al, 2014; Woo et al, 2001). Additionally, smaller studies of high dose IL-2 generated response rates of approximately 25% in platinum-pretreated ovarian cancer patients (Edwards et al, 1997; Vlad et al, 2010). The most promising immunotherapy activity to date in ovarian cancer is with the combination of the anti-PD-1 nivolumab and the anti-CTLA-4 ipilimumab in platinum-resistant disease. This combination therapy was associated with an ORR of 34% (doubling the results of nivolumab monotherapy), yet there was no significant difference in PFS between the combination therapy and nivolumab alone, thus demonstrating a lack of true durability of responses (Zamarin et al, 2020).

5.2. Nemvaleukin Preliminary Clinical Evidence

Intravenous nemvaleukin alfa ('nemvaleukin', ALKS 4230) monotherapy and the combination of IV nemvaleukin with pembrolizumab have shown preliminary evidence of clinical benefit in multiple tumor types in the open-label Phase 1/2 ARTISTRY-1 (ALK4230-A101) study.

In Part A of the ARTISTRY-1 study (dose escalation, data cut-off 29 Oct 2021), approximately 46 patients were treated with escalating dose levels from 0.1 to 10 µg/kg. Of the 46 patients, 12 heavily pretreated patients (median of 3 [1 to 8] prior lines of therapy) were treated with nemvaleukin monotherapy at 6 µg/kg (recommended Phase 2 dose). The patients enrolled at the 6 µg/kg dose level had a mix of tumor indications, including 4 patients with melanoma, 3 patients with colorectal carcinoma, and 1 patient with RCC. SD by RECIST v1.1 was reported in patients enrolled at dose levels of 0.3 µg/kg to 8 µg/kg. Among the 12 patients treated in the 6 µg/kg dose level cohort, 9 were evaluable for disease assessment, and the best response among them was SD by RECIST v1.1 in 4 patients.

In Part B of the ARTISTRY-1 study (dose expansion, monotherapy, data cut-off 29 Oct 2021), 74 patients (47 melanoma, 27 RCC) were treated with nemvaleukin monotherapy at 6 µg/kg (recommended Phase 2 dose). Of the 46 evaluable patients with melanoma (30 cutaneous melanoma, 6 mucosal melanoma, and 10 other melanomas; per RECIST v1.1), 4 patients achieved a PR: 1 confirmed PR in mucosal melanoma, 1 unconfirmed PR in mucosal melanoma, 1 confirmed PR in cutaneous melanoma, and 1 unconfirmed PR in cutaneous melanoma. Two additional PRs occurred after the data cut-off date: 1 confirmed PR and 1 PR awaiting

confirmation, both in patients with cutaneous melanoma. In addition, SD was observed in 31 patients with melanoma (2 with mucosal melanoma). Of the 22 evaluable patients with RCC, 4 achieved a PR (3 confirmed and 1 unconfirmed) and 10 patients had SD.

In Part C of the ARTISTRY-1 study (dose expansion, combination therapy, data cut-off 29 Oct 2021), 165 patients (including 42 rollover patients from Part A and Part B) received a combination of nemvaleukin and pembrolizumab (the majority of the patients received 3 or 6 ug/kg of nemvaleukin q3w and 200 mg of pembrolizumab q3w). Of those, 137 patients had evaluable on-study disease assessment scans (per RECIST v1.1). Of the 137 evaluable patients, there were 4 CRs, 18 PRs, and 60 SDs. As of 29 Oct 2021, 43 patients were still on treatment in the ARTISTRY-1 study.

As of 29 Oct 2021, 15 heavily pretreated ovarian cancer patients were enrolled in Cohort 1 (Part C). Of the 15 patients, 14 patients were evaluable and had PROC. Among the 14 evaluable PROC patients, there were 2 CRs, 2 PRs (1 confirmed, 1 unconfirmed), and 1 prolonged SD reported resulting in an ORR of 28.6% and a DCR of 71.4%. The median DOR was 53.4 weeks among the PROC patients.

As of 21 Apr 2022, nemvaleukin safety data has been evaluated in 279 patients for the IV route of administration – both as monotherapy and in combination with pembrolizumab (ARTISTRY-1, ARTISTRY-3, ARTISTRY-6, and ION-01-ALKS 4230 studies). The most frequent (≥30%) TEAEs occurring at 6 µg/kg q21d nemvaleukin (IV administration) were Pyrexia, Neutropenia, Chills, Nausea, Fatigue, Anaemia, Aspartate aminotransferase increased, and Alanine aminotransferase increased. In general, a similar incidence of TEAEs was reported for both the IV monotherapy and IV combination therapy.

Overall, the safety profile of nemvaleukin IV is consistent with its mechanism of action and is similar to what is expected in the relapsed/refractory solid cancer patient population. Nemvaleukin IV as monotherapy and in combination with pembrolizumab was well tolerated. No apparent added toxicity was observed for nemvaleukin in combination with pembrolizumab compared with pembrolizumab alone.

5.3. Background on Nemvaleukin

Nemvaleukin is an engineered fusion protein composed of a circularly permuted IL-2 and IL-2Rα designed to selectively activate the intermediate-affinity IL-2R, but not the high-affinity IL-2R. The IL-2Rα domain of nemvaleukin serves to sterically impede the binding of nemvaleukin to the high-affinity IL-2R yet still allow binding to the intermediate-affinity IL-2R (Lopes et al, 2020a). IL-2 plays a pivotal role in immune homeostasis due to its ability to stimulate numerous lymphocyte subsets including NK cells, effector CD4+ and CD8+ T cells, and T_{regs}. Low concentrations of IL-2 induce signaling through the high-affinity IL-2R comprised of IL-2Rα, IL-2Rβ, and common γ chain (γ_c), preferentially expressed on T_{regs}. Higher concentrations of IL-2 are necessary to induce signaling through the intermediate-affinity IL-2R, composed of IL-2Rβ and γ_c, and predominantly expressed on memory CD8+ T cells and NK cells, which play an important role in driving antitumor immune responses (Sim and Radvanyi 2014). Recombinant human IL-2 is approved for treatment of metastatic melanoma and RCC (Proleukin USPI), but AEs including CLS limit its therapeutic use, potentially mediated through interaction with the high-affinity IL-2R expressed on vascular endothelial cells (Huh et al, 2012; Krieg et al, 2010). Furthermore, antitumor efficacy of IL-2 may also be limited by preferential

expansion of immunosuppressive T_{regs}, which may limit anticancer activity of rhIL-2 (Malek and Bayer 2004). Despite the poor tolerability of immunotherapy with rhIL-2, it remains one of the few treatment regimens for metastatic melanoma and RCC that elicits a complete and durable response in a subset of patients. Thus, selective activation of the intermediate-affinity IL-2R by nemvaleukin has the potential to provide enhanced tumor killing as well as improved safety and tolerability.

In vitro and *in vivo* nonclinical pharmacodynamics data support selective signaling through the intermediate-affinity IL-2R by nemvaleukin, leading to the activation and expansion of effector cells, including CD8+ T cells and NK cells, while minimizing the activation and expansion of immunosuppressive T_{regs}. Additional nonclinical data demonstrate that administration of IV or SC nemvaleukin results in equivalent tumor growth inhibition in a mouse syngeneic tumor model. Overall, preclinically, administration of nemvaleukin results in the selective activation and expansion of effector cells with minimal activation and expansion of immunosuppressive CD4+ T_{regs} compared to rhIL-2 (Lopes et al, 2020b).

Harnessing of the IL-2 pathway has potential to provide benefit to patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer based on results of a Phase 2 study of intraperitoneal rhIL-2 administered to patients with platinum-resistant or platinum-refractory ovarian cancer (Vlad et al, 2010). Of 24 patients assessed for response, there were 6 (4 complete, 2 partial) responses for an overall response rate of 25.0% [95% CI of 11-45]. The median survival of the 31-patient cohort was 2.1 years (95% CI, 1.3 to 4.4), but for the 6 patients with responses the median survival was not reached at the time of publication (range 24 to 120+ months). There were also significant associations between on-treatment changes in T cell counts and survival, suggesting that a therapy that can activate and expand effector T cell responses can provide benefit to patients with advanced ovarian cancer.

5.4. Background on Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death 1 ligand 2. Based on nonclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across several indications. For more details on specific indications refer to the IB.

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ T_{regs} correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and RCC. Tumor-infiltrating lymphocytes can be expanded *ex vivo* and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley et al, 2005; Hunder et al, 2008).

The 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. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling on engagement of its ligands (PD-L1 and/or programmed cell death 1 ligand 2) (Greenwald et al, 2005; Okazaki et al, 2001).

The structure of murine PD-1 has been resolved (Zhang et al, 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T cell signaling cascade (Chemnitz et al, 2004; Okazaki et al, 2001; Riley 2009; Sheppard et al, 2004). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Francisco et al, 2010; Parry et al, 2005). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in epithelial ovarian, fallopian tube, or primary peritoneal cancer.

5.5. Rationale for Dose Selection

The selection of IV nemvaleukin dose of 6 µg/kg/day given on 5 consecutive days is based on several considerations, including pharmacodynamic effects on immune cell expansion, safety, and preliminary exposure-response analysis as well as IV nemvaleukin monotherapy activity. Data from the ARTISTRY-1 study was used for dose selection. Do note that current data from the 3 µg/kg dose level of nemvaleukin in combination with pembrolizumab is more mature as compared to the data from the 6 µg/kg dose level in combination with pembrolizumab in Part C of ARTISTRY-1 as enrollment in the 3 µg/kg in combination with pembrolizumab group started in December 2018, while enrollment in the 6 µg/kg in combination with pembrolizumab group only started in January 2020.

- Data from Part A (dose escalation) of ARTISTRY-1 indicated that systemic exposure to nemvaleukin increased with increase in dose, which correlated with a dose-dependent increase in absolute counts of NK cells and CD8+ T cells, with a minimal, non-dose-dependent effect on T_{regs}. A greater expansion of CD8+ T cells and NK cells was observed at 6 µg/kg as compared with 3 µg/kg with a similar safety profile at 6 µg/kg.
- Preliminary dose/exposure – response analysis indicated that higher systemic exposure is likely to be associated with a higher probability of observing clinical activity. Given the high unmet need in the PROC patient population, the 6 µg/kg dose is anticipated to improve the likelihood of observing beneficial clinical response with a manageable safety profile.

- Although 6 µg/kg was selected as the recommended Phase 2 dose for IV nemvaleukin, dose escalation continues in ARTISTRY-1 with the 8 µg/kg dose level being tolerated to date, thus providing additional safety margin for the selected dose.
- Selection of 6 µg/kg was also supported by IV nemvaleukin monotherapy activity in both RCC and mucosal melanoma at the 6 µg/kg dose in Part B (monotherapy expansion) of ARTISTRY-1 with 5 objective responses observed to date.

Taken all together, the overall benefit/risk assessment supports the selected dosing regimen for IV nemvaleukin 6 µg/kg/day for 5 consecutive days every 3 weeks, either as monotherapy or in combination with pembrolizumab (200 mg q3w) for ARTISTRY-7.

The planned dose of pembrolizumab for this study is 200 mg q3w. Based on the totality of data generated in the KEYTRUDA development program, 200 mg q3w is an appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. To date in the nemvaleukin development program, the combination of nemvaleukin and pembrolizumab has not shown any additive toxicity to the known safety profile of either agent. Furthermore, in ARTISTRY-1, the ovarian cohort showed a favorable and acceptable benefit/risk profile using these doses and dosing regimen of nemvaleukin and pembrolizumab.

5.6. Benefit-Risk Assessment

It is believed that the selectivity of nemvaleukin for the intermediate-affinity IL-2R but not the high-affinity IL-2R will improve the safety and tolerability profile as compared to human recombinant IL-2, a therapeutic with established clinical efficacy, and may also result in enhanced antitumor effects against a variety of cancer types. Nemvaleukin has been evaluated in approximately 315 patients across the nemvaleukin development program and the emerging safety profile is favorable in the setting of patients with advanced solid tumors. Pembrolizumab is an approved agent with an established safety profile. To date in the nemvaleukin development program, the combination of nemvaleukin and pembrolizumab has not shown any additive toxicity to the known safety profile of either agent. In ARTISTRY-1, the ovarian cohort evaluating nemvaleukin and pembrolizumab combination regimen has shown favorable results. Furthermore, there exist no effective/ approved therapies for PROC, a highly unmet need. Thus, the benefit/risk profile evaluation of the nemvaleukin and pembrolizumab combination regimen in patients with PROC is favorable.

5.7. Clinical Hypotheses

The preliminary activity seen in ARTISTRY-1 together with the scientific evidence and rationale provided above clearly demonstrate that single-agent checkpoint inhibition is not sufficient to reliably achieve meaningful efficacy in EOCs. Novel immunotherapies like nemvaleukin in combination with a checkpoint inhibitor could provide additional immunologic stimulation to achieve clinically significant tumor killing, resulting in improved outcomes for these difficult to treat tumors. The primary study hypothesis is that the combination of nemvaleukin plus pembrolizumab will generate a significantly improved OS compared to current standard of care chemotherapies with an acceptable safety profile.

6. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints are listed in Table 6.

Table 6: Study Objectives and Endpoints

Study Objectives	Study Endpoints
Primary Objective: • To evaluate the OS of nemvaleukin in combination with pembrolizumab as compared with chemotherapy in patients with platinum resistant ovarian cancer	**Primary Endpoint:** • OS
Secondary Objectives: • To evaluate the antitumor activity of nemvaleukin in combination with pembrolizumab as compared with chemotherapy • To evaluate the safety of nemvaleukin in combination with pembrolizumab as compared with chemotherapy	**Secondary Endpoints:** • PFS as assessed by Investigator, based on RECIST v1.1 • ORR as assessed by Investigator, based on RECIST v1.1 • DCR, DOR, and TTR as assessed by Investigator, based on RECIST v1.1 • CA-125 response as defined by the GCIG • Safety as assessed by TEAEs, clinical laboratory parameters, vital signs, and ECGs
Exploratory Objectives: • To evaluate the antitumor activity of pembrolizumab monotherapy; to evaluate the antitumor activity of nemvaleukin monotherapy • To evaluate HRQoL • To determine if any baseline or changes in parameters in tumor tissue and/or peripheral blood may correlate to response to treatment with nemvaleukin in combination with pembrolizumab • To evaluate the PK, immunogenicity, and pharmacodynamic effects of nemvaleukin and/or pembrolizumab in this treatment regimen	**Exploratory Endpoints:** • PFS, ORR, DOR, TTR, and OS of the monotherapy arms as assessed by Investigator, based on RECIST v1.1 • HRQoL as assessed by the following PRO instruments: the FACT-O questionnaire and the EQ-5D-5L questionnaire • Pretreatment levels, on-treatment levels, and/or changes from pretreatment levels of the following parameters (in tumor specimens and/or peripheral blood): – CPS of PD-L1, TMB, and other relevant genetic and non-genetic predictive markers (eg, HRD, BRCA mutation) – Serum concentrations of nemvaleukin (and pembrolizumab as appropriate)

Study Objectives	Study Endpoints
	– Presence of anti-nemvaleukin antibodies (and anti-pembrolizumab antibodies as appropriate) in serum – Leukocytes including, but not limited to, circulating CD8+ T cells, T_{regs}, and NK cells – Serum concentrations of interferon-γ, IL-6, and other soluble proteins

BRCA=breast cancer gene, CA-125=cancer antigen 125, CD=cluster of differentiation, CPS=combined positive score, DCR=disease control rate, DOR=duration of response, ECG=electrocardiogram, EQ-5D-5L=EuroQol 5 Dimension 5-Level, FACT-O=Functional Assessment of Cancer Therapy – Ovarian, GCIG=Gynecologic Cancer InterGroup, HRD=homologous recombination deficiency, HRQoL=health-related quality of life, IL=interleukin, NK=natural killer, ORR=objective response rate, OS=overall survival, PD-L1=programmed death ligand 1, PFS=progression-free survival, PK=pharmacokinetic(s), PRO=patient-reported outcome, RECIST=Response Evaluation Criteria in Solid Tumors, TEAE=treatment-emergent adverse event, TMB=tumor mutational burden, T_{regs}=regulatory T cells, TTR=time to response

7. STUDY POPULATION

7.1. Patient Inclusion Criteria

In order to qualify for participation in the study, patients must meet all of the following criteria. Inclusion criteria should be assessed by the Investigator and, when applicable (per SOA) the assessment should occur within 10 days prior to expected C1D1 (closer to C1D1 is highly recommended).

1. Patient is female and ≥18 years of age.
2. Patient or patient's legal representative (as applicable per regional requirements) has provided written informed consent.
3. Patient is willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.
4. Patient has histologically confirmed diagnosis of EOC, fallopian tube cancer, or primary peritoneal cancer and histology subtype: high-grade serous, endometrioid of any grade, clear cell.
5. Patient has platinum-resistant/refractory disease: resistant is defined as disease progression within 180 days following the last administered dose of platinum therapy beyond first-line setting (ie, initial platinum therapy); and refractory is defined as disease progression or lack of response followed by disease progression while receiving the most recent platinum-based therapy (ie, beyond initial therapy). Patient must have progressed radiographically or by GCIG-defined CA-125 criteria on or after their most recent line of anticancer therapy beyond first-line setting.
    a. Note: Progression should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression or the date progression was assessed by GCIG-defined CA-125 criteria, whichever comes first.
    b. Note: Patients who have primary platinum-refractory or platinum-resistant disease (disease progression <3 months after completion of first-line platinum-based therapy) are excluded (see Exclusion Criterion 1).
6. Patient must have received at least 1 prior line of platinum-based therapy (as noted below) and no more than 5 prior lines of systemic anticancer therapy in platinum-resistant disease (4 additional lines after the patient developed platinum-resistant/refractory disease). Patient must have received at least 1 line of therapy containing bevacizumab. The following guidelines apply:
    a. Patients who are primary platinum resistant (developed resistance after initial platinum-based therapy) must have received at least 4 cycles of platinum, must have had a response (CR or PR) and then progressed ≥3 to ≤6 months after the date of the last dose of platinum.
    b. Prior PARP inhibitor is allowed if included within these limits of prior therapy. Prior PARP inhibitor is required for patients with a BRCA mutation.
    c. Adjuvant ± neoadjuvant is considered 1 line of therapy.

d. Maintenance therapy (eg, bevacizumab, PARP inhibitors) will be considered part of the preceding line of therapy (ie, not counted independently).
e. Therapy that changed due to toxicity in the absence of progression will be considered part of the same line (ie, not counted independently).
f. Hormonal therapy will be counted as a separate line of therapy unless it was given as maintenance therapy.

7. Patient has at least one measurable lesion that qualifies as a target lesion based on RECIST v1.1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.
8. Patient is willing provide a tumor tissue sample either collected from a prior biopsy or cytoreductive/debulking surgery occurring at any time since diagnosis or from a fresh biopsy (newly obtained tumor tissue) at Screening. A tumor tissue sample collected at Screening (fresh biopsy) is preferred. Collection of tumor tissue samples from both prior biopsy or cytoreductive/debulking surgery and fresh biopsy are recommended (when possible) to understand changes in the tumor microenvironment during treatment. Central testing of PD-L1 status will be required prior to randomization.
9. Patient has recovered from the effects of any previous chemotherapy, immunotherapy, other prior systemic anticancer therapy, radiotherapy, and/or surgery (ie, residual toxicity no worse than Grade 1 [Grade 2 treatment-associated peripheral neuropathy and/or any grade of alopecia are acceptable assuming all other inclusion criteria are met]).
10. Patient who has received prior systemic anti-neoplastic agent(s) must wait at least 5 half-lives or 4 weeks (whichever is shorter) following prior therapy before enrollment into the study or 4 weeks if the half-life of a given investigational agent is not known.
11. Patient has an ECOG status of 0 or 1 and an estimated life expectancy of at least 3 months.
12. Patient has adequate hematologic reserve, as evidenced by:
    a. Absolute neutrophil count of ≥1,500/µL;
    b. Absolute lymphocyte count of ≥500/µL;
    c. Platelet count of ≥100,000/µL; and
    d. Hemoglobin of ≥9 g/dL (patient may be transfused to this level if necessary, but transfusion must occur >1 week prior to the first dose of study drug[s] and hemoglobin maintained to an acceptable level [≥9 g/dL] prior to first dose).

    Note: Administration of G-CSF or erythropoietin stimulating factor is permitted according to approved indications and scientific recommendations. Administration of long-acting G-CSF must occur >2 weeks prior to the first dose of study drug(s). Administration of short-acting G-CSF must occur >1 week prior to the first dose of study drug(s).
13. Patient has adequate hepatic function, as evidenced by AST and ALT values ≤3 × the ULN and serum total bilirubin values of ≤1.5 × ULN (≤2 × ULN for patients with known Gilbert's syndrome). For patients with documented baseline liver metastasis, the following limits will apply: ≤5 × ULN for ALT/AST and ≤2 × ULN for bilirubin.

14. Patient has adequate renal function, as evidenced by a calculated creatinine clearance of ≥45 mL/min by the Cockcroft-Gault equation or a serum creatinine ≤1.5 × ULN. Creatinine clearance assessed by the Cockcroft-Gault equation is preferred over serum creatinine when assessing patient eligibility.
15. Patient has INR and/or prothrombin time and aPTT ≤1.5 × ULN unless the patient is receiving anticoagulant therapy, in which case INR and/or prothrombin time and aPTT must be within the desired therapeutic range of intended use for such anticoagulants.
16. Patient agrees to abide by the contraceptive requirements detailed in the protocol (Appendix 1).
17. WOCBP must have a negative pregnancy test (serum or urine). (See Appendix 1 for the definition of WOCBP.)

7.2. Patient Exclusion Criteria

In order to qualify for participation in the study, patients must not meet any of the following criteria. Exclusion criteria should be assessed by the Investigator and, when applicable (per SOA) the assessment should occur within 10 days prior to expected C1D1 (closer to C1D1 is highly recommended).

1. Patient has primary platinum-refractory disease or primary platinum resistance: primary platinum-refractory disease is defined as disease progression during initial platinum-based therapy; and primary platinum resistance is defined as disease progression <3 months after completion of initial platinum-based therapy.
2. Patient has histologically confirmed diagnosis of EOC with mucinous or carcinosarcoma subtype.
3. Patient has nonepithelial tumor (eg, germline or stromal cell tumor) or ovarian tumor with low malignant potential (ie, borderline or low-grade serous tumor).
4. Patient requires recurrent (≥1 per month) fluid drainage (eg, paracentesis, thoracentesis, pericardiocentesis) or patient requires fluid drainage of ≥500 mL within 4 weeks of the expected date of the first dose of study drug.
5. Patient has received prior IL-2-based or IL-15-based cytokine therapy; patient has had exposure, including intralesional, to IL-12 or analogs thereof.
6. Patient has prior exposure to any anti-PD-1/PD-L1 therapy.
7. Patient requires or has taken systemic corticosteroids (>10 mg of prednisone daily, or equivalent) within 14 days prior to the first dose of study drug(s); however, replacement doses, topical, ophthalmologic, and inhalational steroids are permitted.

   Note: patients requiring the use of a steroid during the Screening Period at a dose level of <10 mg of prednisone (or equivalent) per day are not excluded as long as the event requiring the use of the steroid has recovered to acceptable grade.
8. Patient has taken nonsteroid systemic immunomodulatory agents (eg, etanercept, adalimumab, etc) within 28 days prior to the first dose of study drug(s), or anticipates any use of these therapies during the study period.

9. Patient has undergone any major surgical procedure within 3 weeks prior to Screening. Patients who have not recovered from any previous surgery that occurred more than 3 weeks prior to Screening are also excluded.
10. Patient has undergone prior solid organ and/or non-autologous hematopoietic stem cell or bone marrow transplant.
11. Patient has received a live or live-attenuated vaccine(s) within 30 days prior to the first dose of study drug(s). Note: COVID-19 vaccine is allowed; see guidance on COVID-19 vaccines in Section 7.3.2).
12. Patient has had any active infection and/or a fever ≥38.5°C (≥101°F) within 7 days prior to the first dose of study drug(s) requiring systemic therapy. Antibiotics given for peri-procedural prophylaxis or given presumptively for a limited time (eg, until infection was ruled out), as well as topical or intraocular antibiotics, shall not be exclusionary.
13. Patient has active autoimmune disease(s) requiring systemic treatment within the past 2 years or a documented history of clinically severe autoimmune disease that has required chronic or frequent systemic steroids. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is allowed.
14. Patient has underlying chronic lung disease, chronic obstructive pulmonary disease, metastatic lung disease, pleural effusions, or other lung disorders (eg, pulmonary embolism) with a baseline room air oxygen saturation of <92% at Screening and/or dyspnea (≥Grade 3) which requires oxygen therapy.
15. Has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
16. Patient has any other concurrent uncontrolled illness or laboratory findings that may interfere with the planned treatment, affect patient compliance, such as recent serious trauma, or mental illness or substance use, which may interfere with the ability of the patient to cooperate and participate in the study.
17. Patient is at high risk of treatment-related complications, such as:
    - Unstable, poorly controlled, or severe hypertension
    - Clinically significant pericardial effusion
    - New York Heart Association Class III or Class IV congestive heart failure (Appendix 2); high risk cardiovascular disease, defined as unstable angina. NOTE: If the Investigator plans to use PLD in the event the patient is randomized to Arm 4, patient has LVEF, as assessed by multiple gated acquisition scans or echocardiogram, below the institutional lower limit of normal.
    - Myocardial infarction, or cerebrovascular accident within 6 months of first dose of study drug(s)
    - Uncontrolled diabetes mellitus that has required 2 or more hospitalizations in the last year and/or emergent management within the last 6 months

- Severe peripheral vascular disease
- A non-healing wound, ulcer, or bone fracture

18. Patient has had an active second malignancy within the previous 2 years. This criterion does not apply to patients with adequately treated basal cell or squamous cell skin cancer, carcinoma *in situ* of the cervix, urothelial carcinoma *in situ*, or ductal carcinoma *in situ* of the breast that has undergone full surgical resection.
19. Patient is currently pregnant, breastfeeding, or is planning to become pregnant or to begin breastfeeding during the study period or within 120 days after last study drug administration.
20. Patient has active or symptomatic CNS metastases unless all the following have been met: such metastases have been treated by surgery and/or radiation therapy, and/or gamma knife and have remained radiographically stable (or shrinking) on 2 consecutive imaging examinations performed at least 6 weeks apart; and steroids have been tapered to a dose of 10 mg of prednisone (or equivalent) or less for at least 2 weeks prior to first dose of study drug(s); and the patient is neurologically stable. Patients with history of brain metastases or a suspicion of brain metastases must have a brain MRI at baseline.
21. Patient has known or suspected hypersensitivity to pembrolizumab, nemvaleukin, PLD, paclitaxel, topotecan, gemcitabine, or to any of their excipients.

    Note: hypersensitivity to one or more of the chemotherapy choices is not exclusionary as long as the Investigator is able to select 1 of the 4 chemotherapy options for which the patient is known not to be hypersensitive.
22. Patient has active uncontrolled coagulopathy.
23. Patient has QT interval corrected by the Fridericia Correction Formula values of >470 msec; patient who is known to have congenital prolonged QT syndromes; or patient who is on medications known to cause prolonged QT interval on ECG.
24. Patient is known to be positive for HIV.
    - For sites in Czech Republic only: patients test positive for HIV at Screening.
25. Patients with known active hepatitis B (eg, HBsAg reactive) are excluded; however, a patient with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) may be enrolled provided that HBV DNA is negative. Patients with known active hepatitis C (eg, HCV RNA [qualitative] are detected) are excluded; however, a patient with cured hepatitis C (negative HCV RNA status) may be enrolled.
    - For sites in Czech Republic only: patients test positive for HBV or HCV at Screening.
26. History of bowel obstruction, history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 3 months before the first dose of study drug is administered. Clinical symptoms of bowel obstruction should be ruled out by appropriate imaging studies during the Screening Period and prior to randomization in the study. Patients with a functioning ostomy can be included in the study.

27. Patients who are investigational site staff members directly involved in the conduct of the study or their immediate family members as well as site staff members otherwise supervised by the Investigator, or patients who are employed by Mural or companies/vendors hired to be directly involved in the conduct of the study (immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted) unless the investigational site staff or staff at Mural or companies/vendors working on behalf of Mural are recusing themselves from the study activities.

7.3. Study Requirements and Restrictions

7.3.1. Contraception and Pregnancy

7.3.1.1. Patient Eligibility Requirements

Patient agrees to abide by the contraception and egg donation requirements detailed in Section 7.3.1.2.

A WOCBP must have a negative pregnancy test (urine or serum) performed by local laboratory within 3 days before the first dose of study drug is administered in every cycle. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. If the serum pregnancy test is positive at Screening, the patient must be excluded from participation in the study. If the serum pregnancy test is positive prior to dosing in subsequent cycles, then the patient must be discontinued from study treatment (see Section 7.5.1).

7.3.1.2. Contraception and Egg Donation Requirements During the Study

All WOCBP must refrain from donating eggs and must practice sexual abstinence (as defined in Appendix 1) or use a contraceptive method that is highly effective (as described in Appendix 1) for the duration of the study and for at least 30 days (Arm 3) or 120 days (Arm 1, Arm 2) after the final dose of study drug. All heterosexually active WOCBP enrolled in Arm 4 (Investigator's choice chemotherapy) must use contraceptive as per approved label and/or institutional guidelines for specific chemotherapy.

7.3.1.3. If a Pregnancy Occurs

If a patient becomes pregnant while participating in the study, she will be discontinued from study treatment immediately. The EOT and Safety Follow-up Visits will be scheduled, and a Pregnancy Report Form will be reported (Section 10.3.1.6) within 24 hours of awareness of the pregnancy, irrespective of whether an AE has occurred. Pregnancies that occur from the time of randomization through 120 days following last dose of study treatment or up to the start of new anticancer therapy, whichever is earlier, must be reported by the Investigator. The pregnancy will be followed until completion or termination. Additional follow-up may be required up to approximately the first year after the completion of the pregnancy.

If the outcome of the pregnancy meets the criteria for classification as a SAE it should be reported following the SAE procedure (see Section 10.3.1.6). Note: Only SAEs that occur in study patients will be reported in the clinical database.

7.3.2. Concomitant and Prohibited Medications

All intercurrent medical conditions will be treated at the discretion of the Investigator according to acceptable community standards of medical care. All concomitant medications and treatments will be documented on the eCRF.

Any use of the following medications on study by patients is prohibited:

- Any other investigational treatment.
- Any other anti-neoplastic therapy including, but not limited to, cytotoxic chemotherapy, immunotherapy, any antibody therapy, other targeted agents, or hormonal therapy.
- Radiotherapy, including systemically administered radioisotopes; however, limited field, palliative radiotherapy to a nontarget lesion at a site anatomically distinct from target lesion site(s) is allowed with notification to the Medical Monitor.
- Immunomodulatory agents, including but not limited to interferons or ILs.
- Live or live-attenuated vaccines within 30 days prior to the first dose of study drug, while participating in the study, and within 30 days after the last dose of study drug; however, inactivated vaccines are allowed.
  - For sites in Czech Republic only: live or live-attenuated vaccines within 30 days prior to the first dose of study drug, while participating in the study, and within 90 days after the last dose of study drug; however, inactivated vaccines are allowed.
- For Arms 1, 2, 3 only: Pharmacologic doses of systemic corticosteroids (>10 mg of prednisone daily, or equivalent); exception: systemic glucocorticoids are permitted only for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology (refer to Section 9.3.1). Note: study intervention interruption is required while the patient is receiving steroids >10 mg prednisone daily or equivalent. Restart of study intervention should be discussed with the medical monitor once steroid dose has been tapered to an acceptable dose level of ≤10 mg prednisone daily or equivalent.
  - As needed for the prevention of emesis
  - Premedication for IV contrast allergies
  - Short-term oral or IV use in doses >10 mg/day prednisone equivalent for chronic obstructive pulmonary disease exacerbations
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
  - In addition, the following glucocorticoid use is allowed:
    - For topical use or ocular use
    - Intra-articular joint use

  - For inhalation in the management of asthma or chronic obstructive pulmonary disease

- Surgery or radiotherapy for tumor control is not permitted during the study.

COVID-19 vaccine is allowed (and if given, must be documented on the eCRF). At this time, the risks and benefits of COVID-19 vaccination in a cancer patient population are not completely understood. Generally, the benefits are felt to outweigh the risks. Guidance for administering the COVID-19 vaccine is provided below. As new data emerge, this guidance will be updated accordingly.

- When administering, follow the full prescribing information of the vaccine.
- When vaccine supplies are limited, administer to patients who are candidates for the vaccine in accordance with institutional, state, and national guidance and/or regulations.
- There are no known drug-drug interactions between COVID-19 vaccines and nemvaleukin.
- It is recommended that the vaccine is not administered within 7 days prior to or 3 days after study drug administration; however, when needed this window can be as short as ±3 days.
- Live-attenuated COVID-19 vaccine (if becomes available) should be avoided.

Medroxyprogesterone or megestrol acetate may be given to patients as an appetite stimulant, and bisphosphonates or denosumab may be administered to patients with bone metastases if started at least 60 days before each respective patient's first dose of study drug.

As nemvaleukin is a protein, there are no anticipated metabolic drug-drug interactions.

For patients being administered chemotherapy drugs (Arm 4), the relevant prescribing information should also be used for guidance on concomitant and prohibited medications.

See Section 10.1.4 for details regarding the concomitant medication review.

7.3.3. Meals and Dietary Restrictions

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

7.4. Screen Failures

Patients are screen failures if they cannot finish assessments for Screening or are ineligible based on those assessments.

7.5. Patient Discontinuation

7.5.1. Patient Discontinuation From Treatment

A patient will be discontinued from any of the study treatment at any time if the patient, Investigator, or Sponsor determines that it is not in the best interest of the patient to continue participation. Reasons for discontinuation from treatment include:

- Radiological PD outlined in Section 10.2.1
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 9.3.1
- Withdrawal by patient (Note: All reasonable efforts should be made to encourage patients to remain on study for follow-up evaluations even if they withdraw from treatment)
- Non-compliance with study schedule
- Pregnancy
- Physician decision
- Study terminated by Sponsor
- Lost to follow-up
- Extraordinary site or healthcare related issues such as site closures due to COVID-19 (See Appendix 5 for risk mitigation strategies related to the COVID-19 outbreak)

For patients on combination therapy (Arm 1): patients who discontinue either nemvaleukin or pembrolizumab (eg, due to unacceptable toxicity that cannot be managed by dose modification) must discontinue all study treatment. Note: this does not apply to the discontinuation of pembrolizumab after 35 cycles (approximately 2 years).

Patients who discontinue study treatment will be asked to continue with the EOT Visit, the 30-day Safety Follow-up, and the Survival Follow-up as outlined in the SOA (Table 2 [Arms 1 and 3], Table 3 [Arm 2], and Table 4 [Arm 4]).

7.5.2. Patient Discontinuation From Study

A patient will be discontinued from the study if any of the following occurs:

- Withdrawal of consent by patient
- Death
- Lost to follow-up
- Study terminated by Sponsor (See Appendix 5 for risk mitigation strategies related to the COVID-19 outbreak)

If a patient withdraws or is discontinued from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the Investigator, until death, or until the patient is deemed by the Investigator to be lost to follow-up. If, in the opinion of the Investigator, it is necessary to monitor a patient after the Follow-up Period has ended beyond the scheduled Survival Follow-up visits, the Follow-up Period may be extended as necessary. In such instances, the patient, Sponsor, and Investigator will agree to an acceptable follow-up schedule, while fully respecting the patient's right to withdraw from the study at any time.

In the event that a patient chooses to withdraw from the study, the Investigator should make a reasonable effort to ascertain the reason(s) for withdrawal, while fully respecting the patient's rights. Patients who choose to withdraw from the study will be asked to return to the clinic for an EOT Visit. The EOT Visit should be scheduled within 7 days from the day the decision was made to discontinue study treatment. If the patient fails or refuses to return to the study center, an attempt must be made to contact the patient by telephone to assess as many safety and efficacy parameters as possible. All data collected over the telephone must be documented (in source documentation) and entered on the appropriate eCRF.

The Investigator must maintain a record of all patients who fail to complete the study. The reason for study discontinuation will be documented and entered on the appropriate eCRF. If a patient is lost to follow-up, a reasonable attempt to contact the patient must be made and documented. If reasonable attempts to contact the patient or their family have failed, the Sponsor will request the study sites to collect survival status via available public records (Section 10.2.2).

7.5.3. Minimizing Unnecessary Withdrawal

In an effort to minimize the number of patients who are terminated from the study prior to study completion, the following procedures have been incorporated into the study design and study conduct:

- Training of study centers on the importance of continued follow-up and on informed consent processes, and ensuring patients understand the commitment they are making, including intent to complete the study
- Monitoring of data collection for adherence during the study

Please see Section 11.3.4 for statistical considerations related to missing data.

7.5.4. End of Study/Study Termination

The end of the study is defined as the date of the last patient's last visit (or, if applicable, the last phone call with the Investigator during the Follow-up Period) as indicated in the SOA.

The Sponsor may terminate the entire study or a single study center at any time for safety, administrative, or other reasons. In the event of study or site termination, patients will be required to return for a final study assessment as close as possible to the patient's last dose of study drug and will be advised by the Investigator regarding the available treatment options for the condition being studied.

Early study termination will occur if one or more of the following criteria are met:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to patients
4. Plans to modify or discontinue the development of the study drug
5. At the request of regulatory bodies (eg, IRB, FDA)

In the event of Mural's decision to no longer supply the study drug, sufficient notification will be provided so that appropriate adjustments to patient treatment can be made.

7.6. Replacement of Patients

Not applicable.

8. STUDY DESIGN

8.1. Overall Study Design

This is a Phase 3, multicenter, open-label, randomized study of nemvaleukin alfa in combination with pembrolizumab versus protocol-specific Investigator's choice chemotherapy in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.

After signing the main ICF, candidate patients will attend a Screening Visit, at which eligibility will be assessed, and demographics, medical history, prior and concomitant medications, and prior procedures will be reviewed and recorded. If tumor tissue is to be collected for central testing of PD-L1 status prior to Screening, a pre-screening ICF will be obtained. For the purposes of confirming the diagnosis of EOC and for evaluating pretreatment tumor expression of genes and/or proteins of interest (eg, PD-L1 status, TMB, and microsatellite instability), an initial tumor biopsy will be obtained prior to the start of treatment, if such tissue is not already available. Archival tissue can be used in place of pretreatment biopsy. Central testing of PD-L1 status will be required prior to randomization.

Per the original study design, patients were centrally allocated in a randomized fashion (3:1:1:3) to receive either:

- Arm 1: nemvaleukin and pembrolizumab combination therapy
- Arm 2: pembrolizumab monotherapy (closed)
- Arm 3: nemvaleukin monotherapy (closed)
- Arm 4: Investigator's choice chemotherapy. Options for protocol-specific Investigator's choice chemotherapy include one of the following: PLD, paclitaxel, topotecan, or gemcitabine. The Investigator will pre-select the Investigator's choice treatment before the randomization of each patient.

The pembrolizumab monotherapy arm (Arm 2) met its pre-specified futility criteria at the planned futility analysis and was closed to enrollment as of 31 Aug 2023, per the recommendation of the IDMC. The nemvaleukin monotherapy arm (Arm 3) did not meet its pre-specified futility criteria at the planned futility analysis and the IDMC recommended continuation. Under protocol version 4.0, the nemvaleukin monotherapy Arm 3 reached its intended enrollment and thus closed. Because no changes have been made to the objectives to Arm 3 in protocol version 5.0, the Arm 3 number of patients was not recalculated. Therefore, in protocol version 5.0, eligible patients will continue to be enrolled in the remaining 2 arms and will be centrally allocated with a randomization ratio of 1:1 to the Combination and Chemotherapy arms (Arm 1 and Arm 4, respectively).

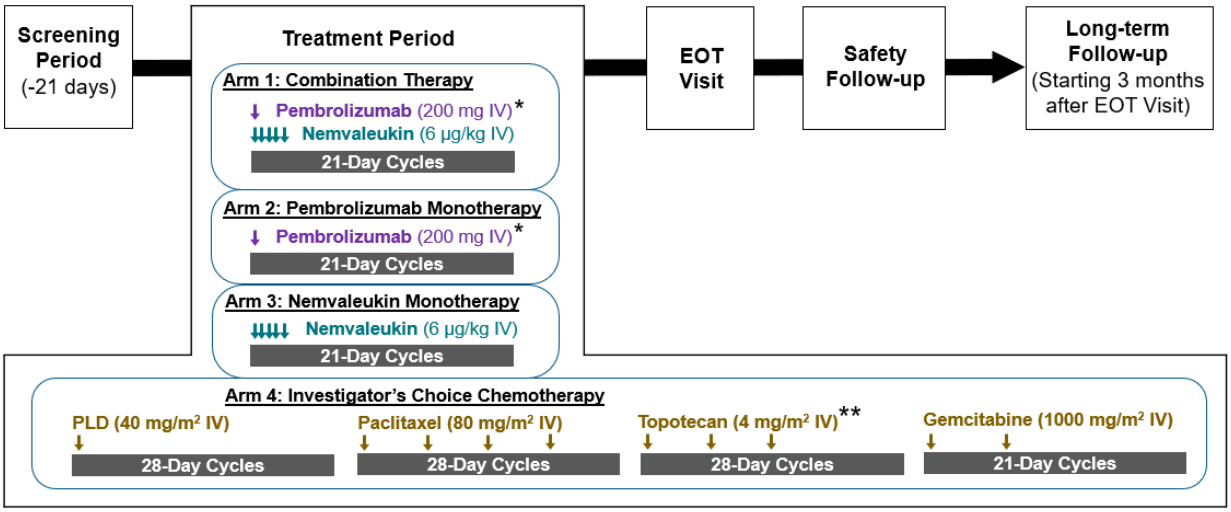
To ensure equal distribution of prognostic factors in the study arms, patients will be stratified according to the following parameters:

- PD-L1 status (IHC CPS $\geq$10 vs CPS <10)
- Histological subtype (high-grade serous vs non-high-grade serous)
- Investigator's choice chemotherapy (paclitaxel vs other chemotherapies)

Response assessments will include CT scans and/or MRI every 6 weeks (Year 1) and every 12 weeks (Year 2+), with mandatory imaging of chest, abdomen, and/or pelvis. Brain imaging at baseline (and during the study) should be performed when there is a history/suspicion of brain metastasis. Response and PFS will be evaluated per RECIST v1.1. For patients who complete treatment or discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging q6w (Year 1 from start of treatment) or q12w (Years 2+ from start of treatment) starting from the last on-treatment assessment until (1) the assessment of PD, (2) the initiation of new anticancer therapy(ies), (3) withdrawal of consent, (4) death, or (5) end of study, whichever occurs first.

A schematic of the study design is provided in Figure 1.

Figure 1: Study Design Schematic



EOT=end of treatment, IV=intravenous, PLD=pegylated liposomal doxorubicin.
Note: As of protocol version 5.0, the pembrolizumab and nemvaleukin monotherapy arms (Arm 2 and Arm 3, respectively) are closed to enrollment.
*Treatment with pembrolizumab (Arms 1 and 2) is allowed for up to a maximum of 35 cycles (approximately 2 years).
**Alternatively, topotecan may be administered at 1.25 mg/m^2 on Days 1 through 5 of 21-day cycles.

8.2. Number of Patients Planned

Approximately 376 patients were originally planned in a 3:1:1:3 ratio across 4 arms: 141 patients in Arm 1 (combination therapy), 47 patients in Arm 2 (pembrolizumab monotherapy), 47 patients in Arm 3 (nemvaleukin monotherapy), and 141 patients in Arm 4 (Investigator's choice chemotherapy).

Under protocol version 5.0, approximately 450 patients are planned, including approximately 366 patients planned across Arm 1 and Arm 4 (approximately 183 patients in each arm). Under protocol version 5.0, no additional patients will be enrolled in the pembrolizumab monotherapy or nemvaleukin monotherapy arms (Arm 2 and Arm 3, respectively).

See Section 7.6 for the replacement of patients.

8.3. Duration of Treatment and Duration of Study

Duration of treatment depends on the arm in which the patient is enrolled. Patients will receive treatment with nemvaleukin (Arms 1 and 3) for as long as they are experiencing disease control and are tolerating treatment well, or until any other criteria for treatment discontinuation are met. Treatment with pembrolizumab (Arms 1 and 2) will be allowed for up to a maximum of 35 treatments (35 cycles; approximately 2 years). Patients in the nemvaleukin and pembrolizumab combination therapy (Arm 1) may continue nemvaleukin as monotherapy without pembrolizumab beyond 35 cycles upon discussion with the Sponsor and not meeting any other criteria for treatment discontinuation.

Patients will receive chemotherapy (Arm 4) for as long as they are experiencing disease control and are tolerating treatment well, or until any other criteria for treatment discontinuation are met.

The maximum duration of individual patient participation in the study is 3 years. Patients will be followed for survival for up to 3 years after initiation of treatment or until closure of study, whichever comes first.

9. STUDY DRUGS

9.1. Administration of Study Drugs

In this study, nemvaleukin and pembrolizumab are considered investigational study drugs. The options for chemotherapy (either PLD, paclitaxel, topotecan, or gemcitabine) are considered standard of care, non-investigational reference therapy drugs. Collectively, the investigational study drugs and reference therapy drugs will be described as study drugs.

Sites must have written procedures in place detailing the healthcare personnel required to be on-site during patient dosing, the availability of equipment and medications necessary to treat an emergency (should it occur), and the process for transferring a patient to a medical facility if necessary.

Descriptions and administration of study drugs are summarized in Table 7. Note: for protocol-specific chemotherapy agents, Institutional guidelines can be followed for duration of infusion to avoid or manage hypersensitivity reactions.

Table 7: Study Drug Description and Administration

Intervention Name	Nemvaleukin alfa	Pembrolizumab	PLD	Paclitaxel	Topotecan	Gemcitabine
Relevant Study Arms	Arms 1, 3	Arms 1, 2	Arm 4	Arm 4	Arm 4	Arm 4
Type	Biologic	Biologic	Drug	Drug	Drug	Drug
Dosage Level(s)	6 µg/kg/day; Days 1 through 5 of 21-day cycles	200 mg; Day 1 of 21-day cycles	40 mg/m^2; Day 1 of 28-day cycles	80 mg/m^2; Days 1, 8, 15, and 22 of 28-day cycles	4 mg/m^2; Days 1, 8, and 15 of 28-day cycles; or 1.25 mg/m^2, Days 1 through 5 of 21-day cycles	1,000 mg/m^2; Days 1 and 8 of 21-day cycles
Route of Administration	IV infusion over 30 min	IV infusion over 30 min	IV infusion; 1 mg/min (Cycle 1); 60-min infusion (Cycles 2+)	IV infusion over 60 min	IV infusion over 30 min	IV infusion over 30 min
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided locally by the study site, subsidiary, or designee	Provided locally by the study site, subsidiary, or designee	Provided locally by the study site, subsidiary, or designee	Provided locally by the study site, subsidiary, or designee
Packaging and Labeling	Study Intervention will be provided in single-dose vials of lyophilized powder	Study Intervention will be provided in single-dose vials of either lyophilized powder or solution	NA	NA	NA	NA

IV=intravenous, NA=not applicable, PLD=pegylated liposomal doxorubicin.

Nemvaleukin drug product is supplied at a concentration of 1 mg/mL in a single-dose vial of lyophilized powder. Patients receiving nemvaleukin will be administered nemvaleukin at 6 µg/kg/day for 5 consecutive days, q21d, via a 30-minute IV infusion (refer to Pharmacy Manual). A mandatory 2-hour observation period, to commence after the completion of infusion, may be extended as recommended in Section 9.2.1.

Pembrolizumab is supplied as single-dose vials of either lyophilized powder or solution. Patients receiving pembrolizumab will be administered pembrolizumab at 200 mg q21d via a 30-minute IV infusion. Nemvaleukin and/or pembrolizumab may be infused using peripheral or central venous access per local standards of care and the treating Investigator's judgment. All patients should have adequate IV access to allow the immediate management of toxicities. Patients who do not have adequate peripheral venous access should have a central venous access device placed per local standards of care.

For patients randomized to Arm 1, nemvaleukin will be administered prior to pembrolizumab, with a 30-minute observation period between infusions. The mandatory 2-hour post-infusion observation period shall commence after the completion of pembrolizumab infusion.

Investigator's choice chemotherapy will be sourced per institution and documented accordingly in eCRF. Single-agent chemotherapy must be selected prior to randomization; choice of chemotherapy is not allowed to be changed during the course of the study.

Sites should make every effort to target infusion timing to be as close to the indicated duration as possible (ie, 30 or 60 minutes). However, given the variability of infusion pumps from site to site, a window between −5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes [−5 minutes/+10 minutes] or 60 minutes [−5 minutes/+10 minutes]).

9.2. Guidance for Study Drug Administration

9.2.1. Guidance for Nemvaleukin Administration

- Administration of antipyretics is recommended prior to nemvaleukin administration, during dosing of nemvaleukin, and subsequently as needed. Premedications such as antihistamines, nonsteroidal anti-inflammatory agents, H2-blockers, and/or other agents may also be used per the Investigator's discretion.
- Prophylactic use of systemic corticosteroids is not allowed.
- Post-administration prophylactic use of antipyretics, nonsteroidal anti-inflammatory drugs, and/or H2-blockers may be utilized per institutional guidelines and may be administered starting 4 to 6 hours following nemvaleukin administration, per the Investigator's discretion.
- All premedications and postdose medications (those prescribed prophylactically) must be captured in the appropriate eCRFs with reason for use being "prophylaxis."
- It is recommended that patients be well hydrated (orally or with IV fluids) and not fasting for long periods (>4 hours) prior to nemvaleukin administration.

- For patients who have had or are at risk of experiencing hypotension following nemvaleukin alfa administration, consider withholding antihypertensive medications 24 to 48 hours prior to the next dose of nemvaleukin, per Investigator discretion. For patients receiving nemvaleukin and who have had or are at risk of experiencing hypotension, avoid H1-blockers as premedication if possible and monitor the patient for a longer duration (recommended up to 6 hours), per the Investigator's discretion.
- Demerol (meperidine) may be administered to patients who experience intolerable chills.
- Montelukast leukotriene receptor antagonists may be administered to patients as a pre-medication to help reduce symptoms of CRS, especially for patients who have a history of sensitivity to other systemic agents.
- For patients who experience nemvaleukin-related toxicity, refer to Section 9.3.1.1 for additional guidance prior to resuming dosing.
- For the impact of the investigational drug as it relates to COVID 19, refer to Appendix 5.

9.2.2. Guidance for Pembrolizumab Administration

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator.

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the pembrolizumab dose modification guidelines in Section 9.3.1.2.

9.2.3. Guidance for Chemotherapy Administration

Hypersensitivity premedication should be administered in accordance with local standard of care in order to prevent severe hypersensitivity reactions. Institutional guidelines can be followed for duration of infusion to avoid or manage the hypersensitivity reactions.

Administration of growth factors (eg, G-CSF, erythropoietic growth factor) or blood transfusion is permitted according to approved indications and scientific recommendations. All pre-medications and postdose medications (those prescribed prophylactically) must be captured in the appropriate eCRFs with reason for use being "prophylaxis".

For all toxicities, patients should receive appropriate management and/or supportive care measures as deemed necessary by the treating Investigator. For patients who experience chemotherapy-related toxicity, refer to Section 9.3.1 for guidance prior to resuming dosing.

9.3. Study Drug Adjustments, Stopping Rules, and Dose Delays

9.3.1. Dosing Modification and Management of Toxicities

For all toxicities, optimal supportive care is recommended before considering dose modification of study drug(s). All dose reductions, interruptions (dose skipping or delay), re-challenges, and treatment discontinuations of study drug(s) due to AEs/SAEs should be discussed with the Medical Monitor and must be recorded on the eCRF with their corresponding AE/SAE following

eCRF completion guidelines. Please refer to Section 10.3.1.2 for complete clinical definitions of AESIs.

If discontinuing study drug(s) permanently, the patient should still be followed for safety and PFS/OS.

The weight measurements performed at the Day 1 Visit of each cycle should be considered for dose adjustments. The dose of nemvaleukin should be adjusted if the patient's weight changes by >10% since the last time the dose was calculated or adjusted. Weight-based dose adjustments are not applicable to pembrolizumab. Prescribing information or local institutional guidelines, if available, should be followed for weight-based dose adjustments during administration of chemotherapies.

9.3.1.1. Nemvaleukin: Dosing Modification and Management of Toxicities

There is no allowance for an extension of the 5-(consecutive) day treatment period within each cycle. If a patient misses dosing for any reason on a scheduled day within the 5-day treatment period (eg, Day 2, Day 3, or Day 4), then the patient may continue with dosing on the next scheduled day; the missed day is not to be replaced. Thus, the 5-day treatment period is unchanged. If the patient misses the fifth dosing day in a cycle, then the next scheduled dosing day will be Day 1 of the following cycle. If the patient misses dosing on the scheduled first day of dosing in a cycle, the next available dosing day will be considered Day 1. Note: for patients receiving nemvaleukin and pembrolizumab combination therapy, pembrolizumab is not to be administered if the patient misses nemvaleukin dosing on the scheduled first day of dosing in a cycle.

Dosing modifications may be required to manage toxicity. For recommendations on nemvaleukin dose modifications for the management of nemvaleukin-related toxicities, refer to Table 8 (excludes AESIs) and Table 9 (AESIs). Any laboratory value that meets any criteria for dosing modifications should be confirmed with a second test. For any asymptomatic laboratory value changes that are known to be a transient effect of IL-2 class drugs (eg, AST/ALT elevations, neutrophil count decrease), the dose modification could be delayed; refer to Table 8. Dose reductions will be allowed from 6 µg/kg/day to 3 µg/kg/day; no further dose reductions are allowed.

Patients who discontinue either nemvaleukin or pembrolizumab due to unacceptable toxicity that cannot be managed by dose modification must discontinue both study treatments. Patients who require treatment hold for either nemvaleukin or pembrolizumab due to unacceptable toxicity, based on recommendation in Table 9, may hold both study treatments. However, holding one agent is feasible if the Investigator's causality assessment clearly attributes the AE to only one of the components.

Table 8: Recommendations for Nemvaleukin Dosing Modifications for Drug-Related Toxicity (Excluding Adverse Events of Special Interest)

Toxicity	Grade	Temporarily Hold Treatment	Timing for Resuming Treatment	Dose/Schedule for Resuming Treatment	Discontinue Study Drug
Hematologic (excluding uncomplicated G3 neutropenia, lymphopenia)	3 to 4	Yes	Toxicity resolves to G1 or less	If toxicity resolves in ≤3 weeks, resume same dose and schedule If toxicity resolves in >3 to <6 weeks, or in patient with recurrent G3 to G4 events, reduce dose as follows: • reduce dose to 3 µg/kg/day	If toxicity does not resolve to lower grade in ≥6 weeks of dose hold, consider permanent discontinuation If patient experiences recurrent G3 to G4 toxicity after nemvaleukin administration (at any dose), consider permanent discontinuation
Non-Hematologic (excluding alopecia)	3	Yes	Toxicity resolves to G1 or less	If toxicity resolves in ≤3 weeks, resume same dose and schedule If toxicity resolves in >3 to <6 weeks, or in patient with recurrent G3 events, reduce dose as follows: • reduce dose to 3 µg/kg/day	If toxicity does not resolve to lower grade in ≥6 weeks of dose hold, consider permanent discontinuation If G3 toxicity recurs at reduced dose, or patient experiences recurrent G3 toxicity after nemvaleukin administration (at any dose), consider permanent discontinuation
	4[a]	Yes	Toxicity resolves to G1 or less	Consult with Medical Monitor to determine if appropriate to continue nemvaleukin with dose reduction as follows: • reduce dose to 3 µg/kg/day	Consider permanent discontinuation If patient experiences recurrent G4 toxicity, permanently discontinue

G=Grade.

[a] For sites in France only: patients should permanently discontinue nemvaleukin if a Grade 4 non-hematologic toxicity occurs.

Table 9: Recommendations for Nemvaleukin Dosing Modifications for Drug-Related Adverse Events of Special Interest

Toxicity[a]	Grade	Temporarily Hold Treatment	Timing for Resuming Treatment	Dose/Schedule for Resuming Treatment	Discontinue Study Drug
IRR/CRS	3	Yes	Toxicity resolves to G1 or less	Resume with same dose with premedications[b] in setting where emergent care is available If G3 toxicity recurs, resume with reduced dose with premedications[b] in setting where emergent care is available Dose reduction is as follows: • reduce dose to 3 µg/kg/day	If G3 toxicity recurs at reduced dose, permanently discontinue
	4	Yes	NA	NA	Permanently discontinue
CLS	2	Yes	Toxicity resolves to G1 or less	Resume with reduced dose with premedications[b] in setting where emergent care is available Dose reduction is as follows: • reduce dose to 3 µg/kg/day	Consider permanent discontinuation Consult with Medical Monitor to determine if appropriate to continue nemvaleukin with dose reduction If G2 toxicity recurs at reduced dose, permanently discontinue
	3 to 4	Yes	NA	NA	Permanently discontinue
irAE of pneumonitis, nephritis or relevant labs undergoing work-up for irAE of nephritis	2	Yes	Toxicity resolves to G1 or less	Resume with reduced dose as follows: • reduce dose to 3 µg/kg/day	If G2 toxicity recurs at reduced dose, permanently discontinue
	3 to 4	Yes	NA	NA	Permanently discontinue
irAE of colitis	2 to 3	Yes	Toxicity resolves to G1 or less	Resume with reduced dose as follows: • reduce dose to 3 µg/kg/day	If G2 to G3 toxicity recurs at reduced dose, permanently discontinue
	4	Yes	NA	NA	Permanently discontinue

Toxicity[a]	Grade	Temporarily Hold Treatment	Timing for Resuming Treatment	Dose/Schedule for Resuming Treatment	Discontinue Study Drug
irAE of endocrinopathies	3	Yes	Toxicity resolves to G1 or less and/or controlled with adequate replacement	Resume with same dose If G3 toxicity recurs, reduce dose as follows: • reduce dose to 3 µg/kg/day	If G3 toxicity recurs at reduced dose, permanently discontinue (excluding endocrinopathies that can be controlled with hormone replacement therapy)
	4	Yes	NA	NA	Permanently discontinue (excluding endocrinopathies that can be controlled with hormone replacement therapy)
irAE of hepatitis or relevant labs undergoing workup for irAE of hepatitis	2[c]	Yes	Toxicity resolves to G1 or less	If toxicity resolves to G1 in ≤2 weeks, resume at same dose If toxicity resolves in >2 weeks, discuss with Medical Monitor or designee If dose reduction is required, resume with reduced dose as follows: • reduce dose to 3µg/kg/day	If G2 toxicity recurs at reduced dose, permanently discontinue
	3[d]	Yes	After discussion with Medical Monitor	Discuss with Medical Monitor or designee	For nemvaleukin-related asymptomatic G3 lab event, discuss with Medical Monitor prior to discontinuing
	4[e]	Yes	NA	NA	Permanently discontinue
irAE of neurological toxicities	2	Yes	Toxicity resolves to G1 or less	Resume with reduced dose as follows: • reduce dose to 3 µg/kg/day	If G2 toxicity recurs at reduced dose, permanently discontinue
	3 to 4	Yes	NA	NA	Permanently discontinue
Myocarditis	2 to 4	Yes	NA	NA	Permanently discontinue
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS of any grade	Yes	Toxicity resolves to G0	Resume with reduced dose as follows: • reduce dose to 3 µg/kg/day after consultation with Medical Monitor	If toxicity recurs at reduced dose, permanently discontinue
	Confirmed SJS, TEN, or	Yes	NA	NA	Permanently discontinue

Toxicity[a]	Grade	Temporarily Hold Treatment	Timing for Resuming Treatment	Dose/Schedule for Resuming Treatment	Discontinue Study Drug
	DRESS of any grade				
All other irAE	2 (persistent)	Yes	Toxicity resolves to G1 or less	Resume with same dose If ≥G2 toxicity recurs, reduce dose as follows: • reduce dose to 3 µg/kg/day	If G2 toxicity recurs at reduced dose, permanently discontinue
	3 (recurrent), or 4 (anytime)	Yes	NA	NA	Permanently discontinue

AESI=adverse event of special interest, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CLS=capillary leak syndrome, CRS=cytokine release syndrome, DRESS=Drug Rash with Eosinophilia and Systemic Symptom, G=Grade, irAE=immune-related adverse event, IRR=infusion-related reaction, NA=not applicable, SJS=Stevens-Johnson Syndrome, TEN=Toxic Epidermal Necrolysis, ULN=upper limit of normal.

[a] Refer to Section 10.3.1.2 for complete clinical definitions of the AESIs.

[b] Refer to Section 9.2.1 for guidance on premedication for nemvaleukin.

[c] AST/ALT: >3.0 to 5.0 × ULN if baseline normal; >3.0 to 5.0 × baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 × ULN if baseline normal; >1.5 to 3.0 × baseline if baseline abnormal.

[d] AST/ALT: >5.0 to 20.0 × ULN, if baseline normal; >5.0 to 20.0 × baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 × ULN if baseline normal; >3.0 to 10.0 × baseline if baseline abnormal.

[e] AST/ALT: >20.0 × ULN, if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × baseline if baseline abnormal.

9.3.1.2. Pembrolizumab: Dosing Modification and Management of Toxicities

Dose adjustments of pembrolizumab are not allowed. The IB for pembrolizumab should be followed for toxicity management, including dosing modifications to manage pembrolizumab-related toxicities.

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks (21 days) of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the patient's study record.

Dose Modification and Toxicity Management for Immune-related AEs Associated With Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and/or skin biopsy may be included as part of the evaluation.

Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab monotherapy or immuno-oncology combination are provided in Table 10.

Table 10: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab Monotherapy or Immuno-Oncology Combinations

General instructions:

Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.

Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.

The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.

If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor patients for signs and symptoms of pneumonitis • Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor patients for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Patients with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Patients 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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Table 10: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab Monotherapy or Immuno-Oncology Combinations (Continued)

General instructions:

Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.

Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.

The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.

If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 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 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for patients with T1DM • Administer antihyperglycemic in patients with hyperglycemia	• Monitor patients 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 [d]		

Table 10: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab Monotherapy or Immuno-Oncology Combinations (Continued)

General instructions:

Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.

Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.

The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.

If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Table 10: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab Monotherapy or Immuno-Oncology Combinations (Continued)

General instructions:

Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.

Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.

The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.

If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 2, 3, or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s), ALT=alanine aminotransferase, AST=aspartate aminotransferase, CTCAE=Common Terminology Criteria for Adverse Events, DRESS=Drug Rash with Eosinophilia and Systemic Symptom, GI=gastrointestinal, IO=immuno-oncology, ir=immune-related, IV=intravenous, SJS=Stevens-Johnson Syndrome, T1DM=type 1 diabetes mellitus, TEN=Toxic Epidermal Necrolysis, ULN=upper limit of normal.

[a] AST/ALT: >3.0 to 5.0 × ULN if baseline normal; >3.0 to 5.0 × baseline, if baseline abnormal; bilirubin: >1.5 to 3.0 × ULN if baseline normal; >1.5 to 3.0 × baseline if baseline abnormal.

[b] AST/ALT: >5.0 to 20.0 × ULN, if baseline normal; >5.0 to 20.0 × baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 × ULN if baseline normal; >3.0 to 10.0 × baseline if baseline abnormal.

[c] AST/ALT: >20.0 × ULN, if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × baseline if baseline abnormal.

[d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the Investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in the Pembrolizumab IB.

9.3.1.3. PLD: Dosing Modification and Management of Toxicities

Up to 2 dose reductions are acceptable for PLD (Table 11). Guidance for PLD dosing modifications is provided in Table 12 and Table 13. The study site can apply institutional guidance if available.

Table 11: Dose Reduction Levels of Pegylated Liposomal Doxorubicin

Initial Dose	First Dose Reduction	Second Dose Reduction
40 mg/m^2	30 mg/m^2	20 mg/m^2

Table 12: Guidance for Pegylated Liposomal Doxorubicin Dosing Modifications

Toxicity	Temporarily Hold Treatment	Timing for Resuming Treatment	Dose/ Schedule for Next Treatment	Discontinue Study Drug
Hematologic				
Grade 4 neutropenia ≥7 days, or All other Grade 4 hematological toxicity, or febrile neutropenia, or cycle delay for hematological toxicity or thrombocytopenic bleeding	Yes	ANC ≥1.5 × 10^9/L and platelet ≥100 × 10^9/L	If toxicity resolves in <6 weeks, decrease dose by 1 level, or continue with the same dose as previously administered with G-CSF support	-If toxicity does not resolve to lower grade in ≥6 weeks of dose hold, consider permanent discontinuation -If Grade 3 to 4 events recur at lowest reduced dose, consider permanent discontinuation
15% change from baseline in LVEF, or below normal	NA	NA	NA	Permanently discontinue
Non-Hematologic				
All major organ Grade 3 toxicity that is not disease-related (excluding alopecia, nausea, or vomiting) at start of next cycle For mucositis & cutaneous toxicity, see Table 13	Yes	When the toxicity is no longer clinically significant per Investigator's discretion	If resolve to lower grade in <6 weeks, decease dose by 1 level	-If toxicity does not resolve to lower grade in ≥6 weeks of dose hold, consider permanent discontinuation. -If Grade 3 events recur at lowest reduced dose, consider permanent discontinuation.
All major organ Grade 4 toxicity that is not disease-related (excluding mucositis & cutaneous toxicity) For mucositis & cutaneous toxicity, see Table 13	NA	NA	NA	Permanently discontinue
Hypersensitivity reaction to PLD, all grades	Stop infusion immediately; symptomatic therapy should be initiated	Once reaction is completely resolved	For Grade 1 to 2 hypersensitivity reactions, consider rechallenge with premedications and at a reduced rate	-If Grade 3 to 4 hypersensitivity reactions occur, permanently discontinue; the patient should not be re-challenged. -If Grade 1 to 2 reactions occurring with premedications and at lowest reduced dose, consider permanent discontinuation

ANC=absolute neutrophil count, G-CSF=granulocyte colony-stimulating factor, LVEF=left ventricular ejection fraction, NA=not applicable, PLD=pegylated liposomal doxorubicin.

Table 13: Summary of Pegylated Liposomal Doxorubicin Dose Reductions in Case of Mucositis and Cutaneous Toxicity

Grade	Mucositis	Cutaneous	Situation at Day 28	Situation at Day 35	Situation at Day 42
1	Painless ulcers, erythema, or mild soreness	Mild erythema, swelling, or desquamation not interfering with daily activities	Wait an additional week and re-dose at full dose unless patient had experienced a Grade >2 toxicity in which case reduce dose by 1 level	Wait an additional week and reduce dose by 1 level	Permanently discontinue PLD
2	Painful erythema, edema, or ulcers, but can eat	Erythema, desquamation, or swelling interfering with but not precluding normal activities; can wear regular cloth	Wait an additional week and reduce dose by 1 level	Wait an additional week and reduce dose by 1 level in case of first occurrence, or permanently discontinue PLD	Permanently discontinue PLD
3	Painful erythema, edema, or ulcers, and cannot eat	Blisters, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular cloth	Wait an additional week and reduce dose by 1 level in case of first occurrence or Discontinue PLD	Discontinue PLD	Permanently discontinue PLD
4	Requires parenteral or enteral support	Diffuse or local process causing infectious complications, or a bedridden state or hospitalization	Discontinue PLD	Discontinue PLD	Permanently discontinue PLD

NA=not applicable, PLD=pegylated liposomal doxorubicin.

9.3.1.4. Paclitaxel: Dosing Modification and Management of Toxicities

Up to 2 dose reductions are acceptable for paclitaxel (Table 14). If dose is reduced to 70 mg/m^2 and followed by an omission of the next dose within a treatment cycle, 70 mg/m^2 can be maintained in lieu of a second dose reduction. Guidance for paclitaxel dosing modifications is provided in Table 15. The study site can apply institutional guidance if available.

Table 14: Dose Reduction Levels of Paclitaxel

Initial Dose	First Dose Reduction	Second Dose Reduction
80 mg/m^2	70 mg/m^2	60 mg/m^2

Table 15: Guidance for Paclitaxel Dosing Modifications

Toxicity	Temporarily Hold Treatment	Timing for Resuming Treatment	Dose/Schedule for Next Treatment	Discontinue Study Drug
Hematologic				
ANC $<1.5 \times 10^9$/L and/or platelets $<100 \times 10^9$/L at start of each cycle	Yes	ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L within 6 weeks of last dose[a]	No change. Consider prophylactic G-CSF support	-If toxicity does not resolve to lower grade in ≥6 weeks of dose hold, consider permanent discontinuation -For recurrent Grade 3 to 4 events, consider permanent discontinuation
ANC $\leq 0.5 \times 10^9$/L and/or platelets $\leq 75 \times 10^9$/L	Yes	ANC $\geq 1.5 \times 10^9$/L and platelet $\geq 100 \times 10^9$/L within 6 weeks of last dose[a]	Decease dose by 1 level. Consider prophylactic G-CSF support	-If toxicity does not resolve to lower grade in ≥6 weeks of dose hold, consider permanent discontinuation -For recurrent Grade 3 to 4 events, consider permanent discontinuation
Non-Hematologic				
All major organ Grade 3 toxicity that is not disease-related, excluding alopecia, nausea, or vomiting	Yes	When the toxicity is no longer clinically significant per Investigator's discretion within 6 weeks of last dose	Decrease dose by 1 level	-If toxicity does not resolve to lower grade in ≥6 weeks of dose hold, consider permanent discontinuation -If Grade 3 event recurs at lowest reduce dose, consider permanent discontinuation
All major organ Grade 4 toxicity that is not disease-related	NA	NA	NA	Permanently discontinue
Hypersensitivity reaction	Stop infusion immediately; symptomatic therapy should be initiated	When the toxicity is no longer clinically significant per Investigator's discretion	For Grades 1 to 2 hypersensitivity reactions, consider rechallenge with premedications and at a reduced rate	-If Grade 3 to 4 hypersensitivity reactions occur, permanently discontinue; the patient should not be re-challenged -For recurrent Grade 1 to 2 reactions occurring with premedications, consider permanent discontinuation

ANC=absolute neutrophil count, G-CSF=granulocyte colony-stimulating factor, NA=not applicable.

[a] For patients who do not achieve hematological recovery on scheduled day of the course, complete blood counts should be performed twice weekly until the above defined limits are achieved.

9.3.1.5. Topotecan: Dosing Modification and Management of Toxicities

Up to 2 dose reductions are acceptable for topotecan weekly dosing (Table 16). Dose escalation is not permitted. Guidance for topotecan dosing modifications is provided in Table 17. The study site can apply institutional guidance if available.

Table 16: Dose Reduction Levels of Topotecan

Dosing Schedule	Initial Dose	First Dose Reduction	Second Dose Reduction
Weekly Dosing	4 mg/m^2	3.5 mg/m^2	3 mg/m^2
5-day Dosing	1.25 mg/m^2	1.0 mg/m^2	0.75 mg/m^2

Table 17: Guidance for Topotecan Dosing Modifications (Weekly and 5-Day Dosing Schedules)

Toxicity	Temporarily Hold Treatment	Timing for Resuming Treatment	Dose/ Schedule for Next Treatment	Discontinue Study Drug
Hematologic				
Grade 4 neutropenia ≥7 days, or All other Grade 4 hematological toxicity, or febrile neutropenia, or Cycle delay for hematological toxicity, or Thrombocytopenic bleeding	Yes	When neutrophils ≥1,000/µL, Hb ≥9 g/dL, and platelets ≥80,000/µL (weekly dosing) or platelets ≥100,000/µL (5-day dosing)	If toxicity resolves in <6 weeks, decrease dose by 1 level or continue with the same dose as previously administered with G-CSF support If toxicity recurs with prophylactic G-CSF support, reduce 1 dose level For Grade 4 thrombocytopenia, reduce 1 dose level	-If toxicity does not resolve to lower grade in ≥6 weeks of dose hold, consider permanent discontinuation -If Grade 3 to 4 events recur at lowest reduced dose, consider permanent discontinuation
Non-Hematologic				
Grade 2 neurotoxicity, or All major organ Grade 3 toxicity that is not disease-related (excluding alopecia, nausea, or vomiting)	Yes	When the toxicity is no longer clinically significant per Investigator's discretion	If toxicity resolves in <6 weeks, decease dose by 1 level	-If toxicity does not resolve to lower grade in ≥6 weeks of dose hold, consider permanent discontinuation -If Grade 3 events recur at lowest reduced dose, consider permanent discontinuation
All major organ Grade 4 toxicity that is not disease-related, or Pneumonitis (confirmed) of any grade	NA	NA	NA	Permanently discontinue

G-CSF=granulocyte colony-stimulating factor, Hb=hemoglobin, NA=not applicable.

9.3.1.6. Gemcitabine: Dosing Modification and Management of Toxicities

Up to 2 dose reductions are acceptable for gemcitabine (Table 18). Guidance for gemcitabine dosing modifications is provided in Table 19. The study site can apply institutional guidance if available.

Table 18: Dose Reduction Levels of Gemcitabine

Initial Dose	First Dose Reduction	Second Dose Reduction
1,000 mg/m^2	750 mg/m^2	500 mg/m^2

Table 19: Guidance for Gemcitabine Dosing Modifications

Toxicity	Temporarily Hold Treatment	Timing for Resuming Treatment	Dose/Schedule for Next Treatment	Discontinue Study Drug
Hematologic				
ANC $<1.5 \times 10^9$/L, platelets $<100 \times 10^9$/L, or febrile neutropenia, or thrombocytopenic bleeding	Yes	ANC $\geq 1.5 \times 10^9$/L and platelet $\geq 100 \times 10^9$/L	If toxicity resolves to a lower grade within <6 weeks of dose hold, restart treatment with dose reduced by 1 level; or continue with the same dose as previously administered, with G-CSF support	-If toxicity does not resolve to lower grade within ≥6 weeks of dose hold, consider permanent discontinuation -If Grade 3 to 4 events recur at lowest reduced dose, consider permanent discontinuation
Non-Hematologic				
All major organ Grade 3 to 4 toxicity that is not disease-related (excluding alopecia, nausea, or vomiting)	Yes	When the toxicity is no longer clinically significant per Investigator's discretion	If toxicity resolves to a lower grade within <6 weeks of dose hold, restart treatment with dose reduced by 2 levels	-If toxicity does not resolve to lower grade within ≥6 weeks of dose hold, consider permanent discontinuation -If Grade 3 to 4 events recur at lowest reduced dose, consider permanent discontinuation
Pneumonitis, HUS, SJS, TEN, CLS, PRES of all grades	NA	NA	NA	Permanently discontinue

ANC=absolute neutrophil, CLS=capillary leak syndrome, G-CSF=granulocyte colony-stimulating factor, HUS=hemolytic uremic syndrome, NA=not applicable, PRES=posterior reversible encephalopathy syndrome, SJS=Stevens-Johnson syndrome, TEN=toxic epidermal necrolysis.

9.3.2. Delay of Cycles for Other Reasons

Once the patient has started study treatment (ie, after C1D1), study drugs may be interrupted or cycles may be delayed for up to 2 weeks for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention (eg, a holiday, anticipated study site closure, or other personal event). In addition, study drug may be interrupted for treatment-related AE not mentioned in Section 9.3.1 but requiring treatment hold for clinical reasons. However, study intervention is to be restarted within 3 weeks (21 days) for treatments with 21 days/cycle (nemvaleukin and/or pembrolizumab, gemcitabine, or 5-day dosing of topotecan) or 4 weeks (28 days) for treatments with 28 days/cycle (PLD, paclitaxel, or weekly dosing of topotecan) of the originally scheduled dose, unless discussed otherwise with the Sponsor. The reason for study intervention interruption is to be documented in the patient's study record.

9.4. Treatment Adherence

All study drugs will be administered at a medical facility or study site by study staff. The clinical research associates will confirm that the study drugs were administered and documented in the patient's eCRFs during site visits.

9.5. Storage, Handling, Accountability, and Disposal of Study Drugs

The Nemvaleukin Alfa Directions for Use and/or Pharmacy Manual will be distributed to the study sites and will provide in-use storage conditions and duration of time within which it should be used. Details on preparation and administration of pembrolizumab are provided in the pembrolizumab Pharmacy Manual.

Parenteral drug products should be inspected visually for particulate matter and discoloration after reconstitution and prior to administration. Discard the drug product vial if visible particles are observed.

The study site is required to maintain current drug dispensation and accountability logs throughout the study. All unused supplies will be checked against the drug movement records during the study and/or at the end of the study.

Following completion and verification of accountability logs, all unused and used packages must be destroyed. Packages may be destroyed on-site according to GCP and site practice. Alternatively, the Sponsor may arrange for destruction with a third-party vendor operating in accordance with GCP and/or Good Manufacturing Practice, as applicable.

Investigators choice chemotherapy (PLD, paclitaxel, topotecan, gemcitabine) is locally sourced and should be handled and stored accordingly.

10. STUDY PROCEDURES AND ASSESSMENTS

10.1. Study Procedures Descriptions

Details of the study procedures are described below. The overall SOA is described in Table 2 (Arms 1 and 3), Table 3 (Arm 2), and Table 4 (Arm 4).

There may be rare circumstances beyond the patient's or site's control in which patients are not able to come to the site for protocol-specified site visits. These would include states of emergency, including natural disasters, public health mandates, etc. (See Appendix 5 for risk mitigation strategies related to the COVID-19 outbreak.) If this occurs, sites, in consultation with Mural and the IRB/EC, should evaluate whether alternative methods for safety assessments (eg, phone contact, virtual visit/telemedicine, alternative location for assessment, including local labs or imaging centers) can be implemented when necessary and feasible. Sites, in consultation with the Sponsor and the IRB/EC, should also evaluate whether these alternative methods would be sufficient to assure the safety of patients. The implementation of alternative processes should be consistent with the protocol to the greatest extent possible. Investigators should document the alteration of any study conduct and the reason for any contingency measures implemented in source documents and in the EDC system.

See Appendix 6 for details on data quality assurance.

10.1.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the patient by the Investigator or designated study personnel as outlined in Section 13.6.3.

Prior to the administration of any study-specific procedures, authorized study personnel will obtain written informed consent from each potential patient. If tumor tissue is to be collected for central IHC testing of PD-L1 status prior to Screening, a pre-screening ICF will be obtained.

10.1.2. Eligibility Review

An eligibility review will be conducted by the Investigator during Screening using the patient inclusion criteria in Section 7.1 and exclusion criteria in Section 7.2. The site will share the screening checklist with the Sponsor and await Sponsor's review prior to enrollment of patients according to operational plan. The most recent laboratory results before C1D1, including repeated assessments during the Screening Period or on C1D1 (prior to randomization and predose), should be used to assess eligibility. C1 must be scheduled within the 21-day screening window.

10.1.3. Demographics and Medical History

Patient's demographic data and medical history will be reviewed and documented at pre-specified time point(s).

10.1.4. Prior and Concomitant Medication Review

At pre-specified time point(s), prospective patients will be asked for a history of anticancer medications and a history of all the medications they have taken in the last 30 days, including

prescription and nonprescription medications, vitamins and supplements including herbal supplements, and recreational drug use.

10.1.4.1. Prior and Concomitant Medication

The name, dose, regimen, route of administration, start and stop dates, and the indication for use of all medications will be recorded. Medications will be categorized using the World Health Organization-Anatomical Therapeutic Chemical classification system.

10.1.4.2. Anticancer Medication

Information collected on prior anticancer medications as well as subsequent anticancer medications will be collected to the greatest degree of detail possible and will include the following information on all previous and subsequent anticancer treatments (including systemic therapy, local therapy, topical therapy, and/or hormonal therapy):

- Medicinal agents used (approved and/or investigational)
- Start and stop dates
- Best response by line of therapy
- Reason for discontinuation (ie, AE, progression, etc)

10.1.5. Randomization

The pembrolizumab monotherapy arm (Arm 2) met its pre-specified futility criteria at the planned futility analysis and was closed to enrollment as of 31 Aug 2023, per the recommendation of the IDMC. The nemvaleukin monotherapy arm (Arm 3) did not meet its pre-specified futility criteria at the planned futility analysis and the IDMC recommended continuation. Under protocol version 4.0, the nemvaleukin monotherapy arm (Arm 3) reached its intended enrollment and thus closed. Because no changes have been made to the objectives related to Arm 3 in protocol version 5.0, the Arm 3 number of patients was not recalculated. Therefore, in protocol version 5.0, eligible patients will continue to be enrolled in the remaining 2 arms and will be centrally allocated with a randomization ratio of 1:1 to the Combination and Chemotherapy arms (Arm 1 and Arm 4, respectively):

- Arm 1: nemvaleukin and pembrolizumab combination therapy
- Arm 2: pembrolizumab monotherapy (closed)
- Arm 3: nemvaleukin monotherapy (closed)
- Arm 4: Investigator's choice chemotherapy. Options for protocol-specific Investigator's choice include one of the following: PLD, paclitaxel, topotecan, or gemcitabine. The Investigator will pre-select the Investigator's choice treatment before the randomization of each patient.

To ensure equal distribution of prognostic factors and selection of chemotherapy in the study arms, patients will be stratified according to the following parameters:

- PD-L1 status (CPS ≥10 vs CPS <10)
- Histological subtype (high-grade serous vs non-high-grade serous)

- Investigator's choice chemotherapy (paclitaxel vs other chemotherapies)

Patients should begin C1D1 within 7 days following randomization.

10.2. Efficacy Assessments

10.2.1. Tumor Assessment

Tumor assessment is to be performed using tumor imaging. In addition, histology, cytology, and/or ultrasound may be used for disease assessment.

- CT scans and/or MRI are mandatory for the extent of disease assessment.
  - Conventional or, preferably, spiral CT scans with (and possibly without) IV contrast and possibly oral and/or rectal contrast (at the discretion of the attending radiologist) should be performed with contiguous cuts of ≤5 mm thickness and appropriate reconstructions in multiple dimensions.
  - MRI with and/or without gadolinium (at the discretion of the attending radiologist) should be performed with contiguous cuts of ≤5 mm thickness and appropriate reconstructions in multiple dimensions.
  - For both of the above modalities, anatomic/organ specific protocols should be followed, as appropriate, at the discretion of the attending radiologist and consistent with individual institutional standards. For each patient, consistency in the choice of imaging modality(ies) and protocol(s) should be maintained to the greatest extent possible throughout the study, except when this is deemed by the attending radiologist and/or Investigator to be unsafe, inadequate, or not in the best interest of the patient (eg, on study development of a CT contrast allergy).
- Positron emission tomography scan alone will not be considered adequate for assessment of disease. Complementary CT scans and, when applicable, cytologic or histologic evaluation should be performed, as appropriate.
- Histology and/or cytology could be considered during the study to confirm if new lesions is malignant (eg, new pleural effusion, etc), except for CNS metastases.
- Although CT scan/MRI is the preferred method to assess all lesions throughout the study, the dimensions of superficial lesions (typically cutaneous or SC) may be documented by photographs with measuring tape and/or calipers in place in order to collect lesion measurements, whenever feasible. If superficial lesions are identified as target or nontarget lesion, the photograph must be taken in duplicate, and 1 copy must be sent for blinded independent central review. The superficial lesion must be followed throughout the study using the same method.
- Deep SC lesions and other amenable lesions (eg, lymph nodes) may be measured and documented by ultrasound (in addition to the requisite CT and/or MRI examinations), and ultrasound guided tissue sampling should be attempted per institutional standards when deemed safe and feasible by the attending radiologist.

It is requested that the method used for baseline disease assessment is maintained throughout the study. Tumor assessment should include all appropriate procedures to document the full extent of

the patient's neoplastic disease (eg, relevant imaging of chest, abdomen, and/or pelvis) according to RECIST v1.1. Scans used for screening disease assessment that were performed previously as part of routine clinical management are acceptable to use if they are of diagnostic quality, have anatomic extent to cover the entirety of disease involvement, were performed within 28 days prior to C1D1, and the method used for the scan can be maintained throughout the study.

Assessments will be based on Investigator review (including centralized review for sensitivity analysis) of the radiographic or photographic images as defined by RECIST v1.1; tumors are assessed as CR, PR, SD, or PD (Eisenhauer et al, 2009). Tumor images will be collected, stored, and reviewed centrally for blinded independent central review in addition to the Investigator review. A manual will be provided to sites with instructions on how to collect and transmit tumor images to the central imaging vendor.

Patients with history of brain metastases or a suspicion of brain metastases must have a brain MRI at baseline. In these patients, brain MRI does not need to be performed at baseline if appropriate CNS imaging confirming absence of metastatic disease has been performed within 28 days prior to the first dose of study drug and is available for review by the respective investigational site.

For patients being administered investigational study drugs (ie, Arms 1, 2, 3), it is recommended that disease progression be confirmed 4-6 weeks later prior to discontinuation of treatment. For all patients, a confirmatory scan is required for the first demonstration of a PR or better and should be performed at no sooner than 4 weeks and no later than 6 weeks after the demonstration of a PR or better.

10.2.2. Survival Status

Patients will be followed for survival every 3 months (±15 days) or more frequently to assess for survival status starting from the EOT Visit, for up to 3 years from first dose of study drug. These assessments can be done in person or by phone. If a patient withdraws consent from the study treatment and does not consent to continued follow-up or is lost to follow-up, the Investigator or site study team may consult public records (eg, obituary, etc) to collect patient's survival status.

10.3. Safety Assessments

10.3.1. Adverse Event Monitoring

AE data collection will begin after a patient signs the ICF. During pre-screening period, AEs resulting from the protocol-specified procedure must be reported if the event is considered related to study procedure.

For all arms, all AEs (including SAEs) from the time of randomization until completion of the 30-day Safety Follow-up Visit must be reported by the Investigator; AE (including SAE) collection will stop if new anticancer therapy is initiated. However, SAEs will be collected for patients in Arms 1 and 2 through 90 days after the EOT or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier. For all arms, any SAE brought to the attention of an Investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

All AEs (including SAEs) will be followed by the Investigator until resolution, return to the baseline level, deemed stable by the Investigator, until the patient is deemed by the Investigator to be formally lost to follow up, or until death of the patient.

The Investigator, Medical Monitor, and Sponsor will review the collected data regularly for identification/verification of AEs. All patients will be assessed routinely for AEs as outlined in the SOA. All AEs observed will be graded using NCI CTCAE version 5.0 (sites will receive notification when a higher version of NCI CTCAE becomes available and has been approved by the Sponsor for implementation). Refer to the NCI CTCAE website for descriptions of Grades 1 through 5 for AEs.

Patients will be instructed by the Investigator or designee to report the occurrence of any AE. All volunteered, elicited, and observed AEs are to be recorded on the AE eCRFs.

AEs and SAEs are defined in Section 10.3.1.1 and Section 10.3.1.3, respectively. Section 10.3.1.5 provides guidance on the monitoring and recording requirements for AEs. Section 10.3.1.6 provides guidance on the reporting requirements for SAEs and pregnancy. For dose interruptions and discontinuation rules based on AEs, see Section 9.3.1.

10.3.1.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient who has been administered a pharmaceutical product. The occurrence, which may or may not have a causal relationship with the investigational treatment, may include any clinical or laboratory change that does not commonly occur in that patient and is considered clinically significant.

Illnesses presenting prior to the patient signing the ICF are considered to be pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study will be considered AEs and will be entered on the AE eCRF.

All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the Investigator. An abnormal laboratory value, in and of itself, may not be an AE. An abnormal laboratory value may be considered an AE under any of the following conditions:

- It is clinically significant
- It is an SAE (eg, it requires hospitalization)
- It requires medical intervention (eg, blood transfusion)
- It requires a change or delay in the administration of study drug(s) or permanent discontinuation of study drug(s)

Clinically significant laboratory values will be considered AEs and recorded as such on the eCRFs. Laboratory values that do not meet one of the above criteria are not required to be reported as AEs.

Pregnancy is not considered an AE, although a patient will be discontinued from treatment if a pregnancy occurs. As described in Section 10.3.1.6, the pregnancy must be reported to the Sponsor, and additional follow-up may be required.

10.3.1.2. Definition of Nemvaleukin Adverse Events of Special Interest (AESIs)

AESIs are known or potential risks following nemvaleukin administration for which additional guidance is provided. These include IRR/CRS, CLS, and irAEs that may occur following administration of nemvaleukin. Investigators should use their medical judgment to determine if AEs meet the definition of an AESI as described below. All AESIs should be entered in the appropriate eCRF. All ≥Grade 3 AESIs should be entered in the appropriate eCRF within 1 business day of discovery. (Note: Any AESI that meets the definition of an SAE as described in Section 10.3.1.3 must be reported as described in Section 10.3.1.6). All medications used to manage these AESIs should be captured in appropriate eCRF forms. All complications resulting from an AESI, such as acute kidney injury or cardiac dysfunction, should be captured separately in the appropriate eCRF forms. Additional information may need to be collected in the supplemental AESI eCRF.

IRR/CRS: IRR/CRS can occur following nemvaleukin administration. The disorders are characterized by the occurrence of at least 2 of the following events: fever, tachypnea, headache, chills, shakes, itching, tachycardia, hypotension, rash, and/or hypoxia (Shimabukuro-Vornhagen et al, 2018). For more details refer to the IB. More severe forms of IRR/CRS may be associated with myalgia, change in mental status, pulmonary infiltrates, metabolic acidosis, hypotension requiring vasopressors, hypoxia requiring supplemental oxygen (FiO_2 ≥40%) and/or acute kidney injury. When IRR/CRS is suspected, collection of trypase laboratory tests is recommended to aid diagnosis. As sepsis/septic shock can also present with fever, chills, and/or hypotension, it is important to rule out any infections.

IRR/CRS reactions are different from allergic/hypersensitivity reactions, which are believed to be due to IgE-mediated mechanisms. Development of anti-drug antibodies, especially IgE antibodies, can cause allergic reactions. However, typically the onset of anti-drug antibodies occurs after 7 to 11 days and following repeated dosing. While many symptoms of allergic/hypersensitivity reaction are like IRR/CRSs, allergic/hypersensitivity reactions generally present with bronchospasm, urticaria, wheezing, angioedema, and anaphylactic symptoms.

For management of IRR/CRS refer to Section 9.3.1.

CLS: CLS is a disorder characterized by loss of vascular tone and release of plasma proteins and fluid into the extracellular space (Siddall et al, 2017). This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. Typical clinical presentation includes a **triad** of hypotension, edema, and hypoalbuminemia. Hemoconcentration (high hematocrit) and reduced urine output is commonly observed. Severe forms of CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, generalized edema, mental status changes, multi-organ failure, and death.

For management of CLS, refer to Section 9.3.1.

irAEs: An irAE is a side effect associated with the increased activity of the immune system that affects one or more organs of the body such as the skin (eg, Stevens-Johnson syndrome and toxic epidermal necrolysis), gastrointestinal tract (colitis), endocrine system (endocrinopathies such as hypothyroidism), liver (hepatitis), kidney (nephritis), musculoskeletal system (arthritis), and lungs (pneumonitis). Early recognition and initiation of treatment is critical to reduce

complications. Diagnostic work-up is dependent on the organ system involvement and may include biopsy to verify the clinical diagnosis, per Investigator discretion.

irAEs occurring in any treatment arm must be reported with appropriate relationship to study drug.

For management of irAEs, refer to Section 9.3.1.

10.3.1.3. Definition of Serious Adverse Event

An SAE is any AE, occurring at any dose and regardless of causality, which meets one or more of the following criteria:

- Results in death
- Is life-threatening. The patient is at immediate risk of death from the reaction as it occurs. This does not include a reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (eg, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they jeopardize the patient and/or require intervention to prevent one of the other outcomes listed above.

Progression of underlying malignancy is not considered an AE or an SAE. Death that is secondary to disease progression will not be reported as an SAE. However, disease progression and outcome, as assessed by the Investigator, will be recorded on the eCRF.

Hospitalization for up to 24 hours to facilitate protocol-mandated procedures or IV administration of fluids or drugs does not require an SAE report. Planned hospital admission for protocol-related biopsy collection or hospitalization in an inpatient unit for a nonmedical reason (ie, social stay admission) during the study in the absence of untoward medical occurrence will not be considered an SAE. Overnight stay for observation, stay at emergency room for less than 24 hours, or treatment on an out-patient basis do not constitute a hospitalization. However, medical judgement must always be exercised, and when in doubt, the case should be considered serious (ie, if case fulfills the criteria for a medically important event).

10.3.1.4. Relationship to Study Drug or Procedure

The assessment of individual study drug relationships to each AE will be reported on the appropriate source document (and SAE form, in the event of an SAE) by the Investigator (or designated Sub-Investigator) according to his or her best clinical judgment. The criteria listed in Table 20 should be used to guide this assessment. Please note that not all criteria must be present to be indicative of the drug relationship. All study drugs are considered "test drugs" for the purposes of the definitions listed in the table.

For patients receiving both nemvaleukin and pembrolizumab (Arm 1), assessment of relationship should be assigned for each drug where possible.

Table 20: Adverse Event Causality Guidelines

Relationship	Criteria for Assessment
Related	There is evidence of exposure to study drug(s). The temporal sequence of the AE onset relative to the administration of the study drug(s) is reasonable. The AE is more likely explained by the study drug(s) than by another cause.
Not related	Patient did not receive the study drug(s) OR temporal sequence of the AE onset relative to administration of the study drug(s) is not reasonable OR there is another obvious cause of the AE.

AE=adverse event.

10.3.1.5. Monitoring and Recording of Adverse Events

All patients will be assessed routinely for AEs as outlined in the SOA. All AEs observed will be graded using NCI CTCAE version 5.0 (sites will receive notification when a higher version of NCI CTCAE becomes available and has been approved by the Sponsor for implementation). Refer to the NCI CTCAE website for descriptions of Grades 1 through 5 for AEs. For AEs that are not specified in the NCI CTCAE, the following criteria should be used to guide the assessment of intensity (severity grade):

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2**: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (Note: Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc)
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Note: Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)
- **Grade 4**: Life-threatening consequences; urgent intervention indicated
- **Grade 5**: Death related to AE

Patients will be instructed by the Investigator or designee to report the occurrence of any AE. All volunteered, elicited, and observed AEs are to be recorded on the AE eCRFs.

The Investigator will evaluate all AEs regarding any causal relationship to the study drug(s) (see Section 10.3.1.4), the intensity (severity grade) of the event, action taken, and patient outcome.

For clinical study safety reporting purposes, the reference safety information approved for nemvaleukin and pembrolizumab will be based on the IB version at the time of the event occurrence. The reference safety information for all other chemotherapy drugs will be their relevant prescribing information.

10.3.1.6. Reporting of Serious Adverse Events and Pregnancy

All SAEs and pregnancies must be reported within 24 hours of discovery, by emailing or faxing the report to the following:

Attention: PPD Safety

Toll Free Fax: +1 (888) 488-9697

Direct Dial Fax: +1 (919) 654-3849

Email: WILSafety@ppd.com

A written report for all SAEs should be submitted on the SAE form provided for this purpose. The SAE report must include the Investigator's opinion as to whether the event is related to study drug. If there is a reasonable possibility the event is related to study drug(s), evidence to support this assessment must also be provided.

10.3.2. Physical Examination

Physical examinations will be performed at pre-specified time points. A focused physical examination shall address anatomic sites and organ systems at which signs and symptoms are present and/or that are known or suspected to be involved with the patient's underlying malignancy, following institutional standards of care.

Physical examinations will be performed at pre-specified time points. A full physical exam at baseline will be needed to assess whether all body systems are normal, abnormal but clinically not significant, or abnormal and clinically significant. This full physical examination will serve as a baseline physical exam.

A focused/directed physical examination shall address anatomic sites and organ systems at which signs and symptoms are present and/or that are known or suspected to be involved with the patient's underlying malignancy, following institutional standards of care. Focused physical exams will collect information on whether the relevant body system(s) are abnormal but clinically not significant, or abnormal and clinically significant findings. New clinically significant findings from focused examination should be recorded as AEs.

10.3.3. Vital Signs, Electrocardiograms, and Left Ventricular Ejection Fraction

Vital signs (eg, blood pressure, pulse, respiratory rate, and body temperature), height, and weight will be assessed at pre-specified time point(s). Blood pressure, pulse, and respiratory rate will be measured after the patient has been resting in a seated or supine position for at least 5 minutes.

A 12-lead ECG will be conducted at pre-specified time point(s). ECGs should be performed in singlet.

Baseline LVEF is collected if PLD is selected as Investigator's choice chemotherapy. On-treatment LVEF assessments only apply to patients receiving PLD. The same assessment technique (multiple gated acquisition or echocardiogram) should be conducted throughout treatment. If patient LVEF drops below normal or by at least 15% from baseline, treatment with PLD should be discontinued.

10.3.4. Laboratory Assessments

10.3.4.1. Hematology, Biochemistry, Urinalysis, and Coagulation

Blood and urine samples for clinical laboratory assessments will be collected at pre-specified time points. Specific hematology, biochemistry, urinalysis, and coagulation assessments are listed in Appendix 3. A Laboratory Manual is to be provided to the site by the central laboratory with details regarding the collection, handling, and shipping of samples for clinical laboratory assessments. Fasting is not required prior to sample collection for clinical laboratory assessments.

Study sites may also utilize their local laboratory for dosing decisions and to ensure safety-related results are available for review prior to dosing.

10.3.4.2. Pregnancy Testing

A serum or urine pregnancy test, performed by local laboratory, will be administered to all WOCBP at pre-specified time points. At the Screening Visit, results must be negative for the patient to be eligible for the study. WOCBP must have a negative pregnancy test (serum or urine) within 3 days (72 hours) before the first dose of study drug is administered in every cycle. If pregnancy testing is performed within 3 days (72 hours) of dosing, sampling does not need to be repeated on the day of dosing.

- For sites in France and Norway only: after treatment discontinuation, pregnancy testing in heterosexually active WOCBP must continue to be assessed monthly for 30 days in Arm 3, for 120 days in Arm 1 and Arm 2, and for the recommended duration of the contraception in the approved label and/or institutional guidelines for the specific Investigator's choice chemotherapy in Arm 4.

Section 10.3.1.6 provides guidance on the reporting requirements for pregnancies.

10.3.5. Eastern Cooperative Oncology Group Status

The ECOG status is used to evaluate the patients' activity status and will be evaluated at pre-specified time points. Possible scores are from 0 to 5. Descriptions of activity status are presented in Appendix 4.

10.4. Assessment of Pharmacokinetics, Pharmacodynamics, and Immunogenicity

Samples for PK, pharmacodynamics, and immunogenicity testing will be obtained at pre-specified time points.

The PK, pharmacodynamic, and immunogenicity sample analyses will be conducted by a central laboratory identified by the Sponsor. A Laboratory Manual is to be provided to the site by the central laboratory with details regarding the collection, handling, and shipping of samples for PK, pharmacodynamic, and immunogenicity testing. Samples will be collected in accordance with the site's usual procedures.

10.4.1. Pharmacokinetics

Serum samples for evaluation of nemvaleukin PK and/or pembrolizumab PK will be obtained from each patient at pre-specified time points. A validated electrochemiluminescence method will be used for the quantitation of nemvaleukin in human serum. Serum samples for evaluation of pembrolizumab PK will be stored for potential analysis.

10.4.2. Pharmacodynamics and Biomarkers

The pharmacodynamic response of various biomarkers will be assessed in blood and serum samples collected from all patients in the study. Plasma samples will also be collected for isolation of circulating tumor DNA from patients at pre-specified time points. Additional biomarker analyses may be performed on tumor tissue samples.

10.4.2.1. Blood-Based Biomarkers

The pharmacodynamic effect of nemvaleukin will be assessed by measuring circulating CD8+ T cells, T_{regs}, and NK cells in peripheral blood from each patient at pre-specified time points. Expression of IL-2Rs on immune cells and T cell receptor clonality may also be assessed.

In addition, serum samples will be obtained from each patient at pre-specified time points. Concentration of multiple pro-inflammatory cytokines including interferon-γ, tumor necrosis factor-α, IL-1β, IL-6, and IL-10, and other soluble proteins will be determined using validated assay kits.

Circulating tumor DNA may be isolated from plasma collected at pre-specified time points and may be subject to genetic and epigenetic analyses.

10.4.2.2. Tumor Tissue Assessment

Guidance on collection of tumor biopsies and archival tumor tissue is provided below. Tumor biopsies and archival tumor tissues may be used for analyzing tumor cells and tumor-infiltrating immune cells by methods such as IHC and/or immunofluorescence. They may also be used for gene expression analysis using methods such as RNA sequencing or NanoString. In addition, they may be used for obtaining mutation status of tumors including mutation burden of tumors by DNA sequencing analysis. Note: if surgery is planned during the study, collection of tissue and blood samples is recommended with appropriately documented consent under the optional biopsy collection procedures.

Archived Tumor

Patient must provide tumor tissue collected from prior cytoreductive surgery or any archival tumor tissue collected after diagnosis of EOC or fresh biopsy (newly obtained tissue at Screening). Fresh biopsy is preferred and highly recommended. Collection of tumor tissue samples from both prior cytoreductive/debulking surgery and fresh biopsy are recommended (when possible) to understand changes in the tumor microenvironment during treatment. The tumor tissue sample should be made available for central testing of PD-L1 status prior to randomization. In cases when archival tissue has been taken from a target lesion(s), baseline imaging used to document initial extent of disease must have been performed after sampling of archival tissue. Archival tissue may provide useful information about the pretreatment state of immune activation in the respective patient's tumor(s).

If the tumor tissue is to be collected for central testing of PD-L1 status prior to Screening, a pre-screening ICF will be obtained. A patient can be pre-screened while on current therapy if the patient is interested in participating in the study in case of disease progression (the full ICF still needs to be obtained and the patient needs to meet the remaining eligibility criteria at the time of Screening for participation in the study). The pre-screening window of Day −90 to −22 allows additional time for collection and processing the tissue for PD-L1 status, which may require more than the 21 days of the Screening Period. The pre-screening ICF does not need to be used if the site does not anticipate a requirement for additional time for tumor tissue collection and processing.

Central PD-L1 results are required for randomization. Under extreme circumstances the medical monitor may pre-approve the use of local PD-L1 result for randomization if:

- Tissue was submitted for central assessment, and the laboratory was given at least 10 business days to run the assay, but the results did not become available in the expected timeframe for randomization; **and**
- The local assessment was performed using DAKO 22C3 assay and the result allows PD-L1 status categorization (CPS ≥10 vs CPS <10).

See Lab Manual for details on collecting archival tumor tissue.

Tumor Biopsies

If archival tissue is not available at baseline, patients must undergo a biopsy during Screening. The tumor tissue specimen provided at Screening will be archived and will serve as the baseline sample.

In patients with accessible lesions, an additional tumor biopsy is to be taken on-treatment as indicated in the SOA. This additional tumor biopsy is optional for patients but strongly encouraged. If patient undergoes biopsy or tissue collection any other time on study (ie, at progression), it is encouraged that this be utilized as the optional tumor biopsy. Only patients providing this optional informed consent will have the optional tumor biopsy performed.

Neither baseline nor on-treatment biopsies shall be performed on target lesions. The on-treatment biopsy should be taken at the same anatomic site as the baseline biopsy, if feasible.

Refer to the Laboratory Manual for tumor sample handling and processing information.

10.4.3. Immunogenicity

Serum samples for detection of anti-nemvaleukin antibodies and anti-pembrolizumab antibodies will be obtained from each patient at pre-specified time points. A validated electrochemiluminescence method will be used for the detection of anti-nemvaleukin antibodies. Additional immunogenicity characterization (eg, detection of neutralizing anti-nemvaleukin antibodies) may be performed as deemed appropriate. Serum samples for detection of anti-pembrolizumab antibodies will be stored for potential future analysis.

11. STATISTICS

11.1. Sample Size Considerations

The Chemotherapy Arm is considered the comparator arm in this study; the antitumor activity of nemvaleukin in combination with pembrolizumab as compared to that of Investigator's choice chemotherapy in patients with PROC will be evaluated.

The primary endpoint was changed from PFS to OS in protocol version 5.0; therefore, the sample size was recalculated based on OS assumptions.

Approximately 366 patients are planned to be randomized in a 1:1 ratio into the Combination and the Chemotherapy arms (Arm 1 and Arm 4, respectively). It is expected that approximately 286 deaths will have been observed between the Combination and the Chemotherapy arms at the final OS analysis. The study has an approximate 85% power to detect an OS HR of 0.7 (the Combination arm versus the Chemotherapy arm at an alpha level of 2.5% (1-sided).

The sample size calculation is based on the following assumptions:

1. 2.5% alpha is allocated to the OS endpoint
2. OS follows an exponential distribution with a median of 10 months and 14.3 months in the Chemotherapy arm and Combination arm, respectively
3. the HR is 0.7, corresponding to a 4.3 month increase in the median OS
4. an enrollment period of 25 months; and
5. a yearly dropout rate of 5%

Under protocol version 5.0, approximately 450 patients are planned, including approximately 366 patients planned across Arm 1 and Arm 4 (approximately 183 patients in each arm). Under protocol version 5.0, no additional patients will be enrolled in the pembrolizumab monotherapy or nemvaleukin monotherapy arms (Arm 2 and Arm 3, respectively).

In order to reach 286 death events, patients may be followed longer.

One planned efficacy interim analysis of OS will be performed when approximately 215 death events (approximately 75% information fraction) are observed in the 2 arms (the Combination and the Chemotherapy arms). The Lan-DeMets O'Brien-Fleming alpha-spending function is constructed to implement group sequential boundaries to control the type I error rate.

The sample size and power calculations were performed in the software R (package "gsDesign").

The monotherapy arms (either pembrolizumab alone or nemvaleukin alone) are included for reference only to examine component effect, and no statistical comparison or testing will be conducted against or between these arms.

11.2. Analysis Populations

- ITT Population: The ITT Population will include all randomized patients regardless of the study drug received.

- Safety Population: The Safety Population will include all randomized patients who received any exposure to nemvaleukin, pembrolizumab, or Investigator's choice chemotherapy.
- Pharmacodynamic Population: The Pharmacodynamic Population will consist of all patients who received at least 1 dose of nemvaleukin, pembrolizumab, or Investigator's choice chemotherapy and have at least 1 available post-baseline pharmacodynamic measurement.
- Pharmacokinetic Population: The PK Population will consist of all patients who received at least 1 dose of nemvaleukin or pembrolizumab and have at least 1 measurable serum concentration of nemvaleukin or pembrolizumab at any scheduled PK time point.

11.3. Statistical Methodology

In general, summary statistics (n, mean, standard deviation, median, minimum, and maximum values for continuous variables and number and percentage of patients in each category for categorical variables) will be provided for evaluated variables by treatment arms. Study drug is defined as nemvaleukin and/or pembrolizumab, or Investigator's choice chemotherapy.

All individual patient-level data will be presented as data listings. Missing data will not be imputed.

Baseline is defined as the last non-missing value prior to each respective patient's first dose of study drug.

Multiplicity adjustment will not be applied to sensitivity analyses. Details can be found in the SAP. The Chemotherapy Arm consists of multiple agents depending on the Investigator's choice; all these agents together will be considered as one Chemotherapy Arm. The statistical comparison or testing will only be conducted between the Combination Arm and the Chemotherapy Arm. No statistical comparison or testing will be conducted against or between the monotherapy arms.

11.3.1. Demographics and Baseline Characteristics

Patient disease and baseline characteristics will be summarized by treatment arms using frequency distribution or descriptive statistics, as appropriate.

Demographics and baseline characteristics such as age, race, weight, ECOG status, prior line(s) of therapy, vital signs, and clinical laboratory data will be summarized with descriptive statistics.

Medical history information will be coded and summarized by treatment arms for the ITT Population using the most recent version of Medical Dictionary for Regulatory Activities. Cancer disease history data will be summarized.

11.3.2. Patient Disposition

The number of patients in the ITT Population and the reasons for discontinuation from either treatment or from study will be summarized separately.

11.3.3. Drug Administration and Compliance

The treatment exposure of study drug (eg, treatment duration, number of treatment cycles, number of infusions for each cycle, and cumulative dose received) and duration of study follow-up time will be summarized.

Duration of exposure to study drug is defined for each patient as duration from C1D1 to the end of last cycle.

The major protocol deviations will be summarized, and all the protocol deviations will be provided in the listing.

11.3.4. Handling of Missing Data

The missing data including antitumor and safety endpoints will not be imputed.

11.3.5. Multiplicity Adjustments

The overall type I error for this study is controlled at 2.5% (1-sided), fully allocated to OS. The statistical comparison is only performed between the Combination and Chemotherapy arms (Arm 1 and Arm 4, respectively).

The Lan-DeMets O'Brien-Fleming alpha-spending function is constructed to implement group sequential boundaries for OS hypothesis testing to control the type I error.

Efficacy boundaries are based on the assigned type I error rate and the projected number of events at study milestones. The actual boundaries will be determined from the actual number of events at the time of the specified interim analysis using the alpha-spending function.

There will be no type I error rate adjustment for the interim futility analysis performed for each of the monotherapy arms since the monotherapy arms are not included for any statistical comparisons.

11.3.6. Concomitant Medications

Prior and concomitant medications will be summarized for the ITT Population using the World Health Organization-Anatomical Therapeutic Chemical classification system.

11.3.7. Efficacy Analyses

Antitumor activity analyses will be based on the ITT Population unless otherwise specified.

Antitumor activity and efficacy data (including ORR, DCR, DOR, PFS, TTR, and OS) will be summarized.

The monotherapy arms (either nemvaleukin alone or pembrolizumab alone) are included in the study for reference only and descriptive estimates of efficacy will be provided for those arms.

Details of the analyses will be specified in the SAP.

11.3.7.1. Primary Efficacy Analyses

The primary efficacy endpoint is OS. The primary endpoint was changed from PFS to OS in protocol version 5.0 because it is considered the most appropriate primary endpoint to objectively demonstrate clinical benefit in the target population (El Bairi et al, 2023).

OS is defined as the time from randomization to death due to any cause. For patients without documentation of death, patients will be censored at the last known contact date or the date of study cut-off, whichever comes earlier.

OS will be calculated as duration from date of randomization to the date of death or censoring.

Survival information may be collected from publicly available sources (eg, public health registries or databases) for patients that have died after discontinuation from the study.

The statistical hypothesis test, where HR is:

H_0 (Null Hypothesis): HR (combination/chemotherapy) = 1

H_a (Alternative Hypothesis): HR (combination/chemotherapy) <1

The treatment difference in survival will be assessed by the stratified log-rank test, and p-value will be reported. A stratified Cox proportional hazard model will be used for modeling the treatment effect between the Combination and the Chemotherapy arms (Arm 1 and Arm 4, respectively). The Efron method will be used for handling the ties. The HR and its associated 95% CI will be reported.

OS will be displayed by Kaplan-Meier curves. Median OS and its 95% CI will be provided. The 1-year and 2-year OS rate will be estimated using the Kaplan-Meier method.

The censoring rule for OS is summarized in Table 21.

Table 21: Censoring Rule for Overall Survival Analysis

Situation	Date of Death or Censoring	Outcome
Death during study	Date of death	Death
Patient alive at data cut-off/ death occurred after data cut-off	Date of cut-off	Censored
Patient lost to follow-up before data cut-off	Date last known to be alive	Censored

Sensitivity analyses of OS:

- OS will be compared between the Combination and the Chemotherapy arms (Arm 1 and Arm 4, respectively) using the unstratified log-rank test based on the ITT Population, and p-value will be reported. The unstratified Cox proportional hazard model will be used to assess the treatment effect between the Combination and the Chemotherapy arms (Arm 1 and Arm 4, respectively) based on the ITT Population. The Efron method will be used for the handling of ties. The HR will be reported with 95% CI.
- To account for the potential non-proportional hazards effect associated with immunotherapies, OS will be compared between the Combination and the Chemotherapy arms (Arm 1 and Arm 4, respectively) using the Fleming and Harrington weighted log-rank test with parameter (rho=0, gamma=1) stratified by factors used for randomization based on the ITT Population. The p-value will be reported.

- To address the possible violation of the proportional hazard assumption, a restricted mean survival time with the ITT Population based on the AUC for survival will be implemented using different truncation points (eg, 12 months and 18 months). The estimated restricted mean survival time difference in OS between the Combination and the Chemotherapy arms (Arm 1 and Arm 4, respectively) will be reported with 95% CIs. The SAS procedure such as RMSTREG will be used with a linear link function, and the model will adjust for the stratification factors.
- Additional analyses of OS adjusting for the effect of subsequent treatment may be performed based on recognized methods [eg, the Rank Preserving Structural Failure Time model (Robins and Tsiatis 1991)], if a sufficient proportion of participants switch. The choice of the method will be based on an examination of the appropriateness of the data to the assumptions required by the method.

11.3.7.2. Secondary Efficacy Analyses

Progression-Free Survival

PFS is defined as the time from randomization to the first documentation of objective tumor progression (by RECIST v1.1) or death due to any cause.

For patients who have PD while on study treatment, the date of disease progression will be the date of the first assessment at which PD is objectively documented per RECIST v1.1 by the Investigator. If the patient discontinues study treatment for reasons other than documented PD per RECIST v1.1, then the date of disease progression will be the date of the first assessment at which PD is objectively documented per RECIST v1.1 by the Investigator during the Follow-Up Period and prior to start of new anticancer treatment. Death is considered as a confirmed PD event. In case PD or death are observed immediately after 2 or more missed consecutive tumor assessments, PFS will be censored at the date of the last tumor assessment immediately before 2 or more missed consecutive tumor assessments. All remaining patients will be censored at the last known date at which the patient was considered progression-free.

PFS will be calculated from the date of randomization to the date of PD or death, whichever occurs first.

A stratified Cox proportional hazard model will be used for modeling the treatment effect between the Combination and the Chemotherapy arms (Arm 1 and Arm 4, respectively). The Efron method will be used for handling the ties. The HR and its associated 95% CI will be reported.

The median PFS will be provided along with the 95% CI. In addition, Kaplan-Meier curves will be provided. The 6-month, 9-month, or 1-year PFS rate will be estimated using the Kaplan-Meier method.

The censoring rules for PFS are summarized in Table 22.

Table 22: Censoring Rule for Progression-Free Survival

Cases	Analysis
Patients received a new anticancer treatment that started before PD per RECIST v1.1 or death	Censored at the last assessment where the patient was documented as progression-free prior to the intervention
PD per RECIST v1.1 or death at the next tumor assessment immediately after 2 or more missed consecutive tumor assessments	Censored at the date of the last tumor assessment immediately before 2 or more missed consecutive tumor assessments

PD=progressive disease, RECIST= Response Evaluation Criteria in Solid Tumors

PFS2 (delayed PFS) analysis: PFS2 is defined as the time from randomization to subsequent disease progression after initiation of new anticancer therapy, or death from any cause, whichever occurs first. If progression after next-line therapy cannot be measured, a PFS event is defined as end or discontinuation of next-line treatment or death from any cause, whichever occurs first. Patients alive and for whom a PFS event has not been observed should be censored at the last time known to be alive and without second disease progression. The same statistical model for PFS will be used for the PFS2 analysis.

Objective Response Rate

ORR is defined as the proportion of patients in the analysis population who have a CR or PR.

The best overall response is the best response recorded after initiation of study treatment until initial documented disease progression or start of a new anticancer treatment, whichever occurs first, taking into account the requirements for confirmation of CR or PR, unless otherwise specified.

The analysis of ORR between the Combination and the Chemotherapy arms (Arm 1 and Arm 4, respectively) will be conducted by the CMH test based on randomization stratification factors. The ORR difference and its associated 95% CI will be reported.

Duration of Response:

DOR is defined as the time from the first documentation of CR or PR to the first documentation of objective tumor progression or death due to any cause. Patients who never achieve CR or PR prior to starting any new anticancer treatment will be excluded from the analysis. DOR is based on a non-randomized subset of patients (specifically, patients who achieve an objective response). Therefore, a formal hypothesis testing will not be performed for this endpoint.

DOR will be calculated as follows (in weeks):

(date of disease progression/death – date of first response (CR or PR) + 1) / 7

The distribution of DOR will be estimated using the Kaplan-Meier method. The median estimate of DOR will be provided along with 95% CI. Kaplan-Meier curves will also be provided.

The censoring rule for DOR is the same as that of PFS.

Disease Control Rate:

DCR is defined as the proportion of patients with objective evidence of CR, PR, or SD. For SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

The DCR will be analyzed using the CMH test based on randomization stratification factors. The difference and its associated 95% CI will be reported.

Time to Response:

TTR is defined as the time from randomization to the first documentation of CR or PR. Patients who never achieve CR or PR prior to starting any new anticancer treatment will be excluded from the analysis. No censoring observation will occur by definition. TTR is based on a non-randomized subset of patients (specifically, patients who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes.

The TTR will be calculated as follows (in weeks):

(date of first response [Complete or Partial] – date of randomization + 1) / 7

Cancer Antigen 125 Response

CA-125 response is defined as at least a 50% reduction in CA-125 levels from baseline and the response must be confirmed and maintained for at least 28 days. The number of responders will be analyzed using the CMH test based on randomization stratification factors. The response difference and its associated 95% CI will be reported.

In addition, the change from baseline value in CA-125 will be summarized with descriptive statistics.

11.3.8. Pharmacokinetic, Pharmacodynamic, and Immunogenicity Analyses

11.3.8.1. Pharmacokinetic Analyses

A patient listing of individual serum concentrations of nemvaleukin (and pembrolizumab as appropriate) will be provided. Concentration data will be summarized descriptively according to nominal (protocol-specified) sampling times. PK concentration data from this study may be used in a subsequent population PK analysis or other post-hoc analyses conducted outside of this study.

11.3.8.2. Pharmacodynamic Analyses

Blood Pharmacodynamic Analyses

Pharmacodynamic data will be summarized descriptively, including absolute cell counts or proportion and concentrations at nominal (protocol-specified) time points, as well as fold change from baseline for circulating leukocytes (including T and NK cells) and cytokines (including interferon-γ, and IL6). Additional analyses may be conducted as deemed necessary upon exploration of data.

A patient listing of individual pharmacodynamic data will be provided.

Tumor Tissue Pharmacodynamic Analyses

Tumor biopsy samples from patients will be processed and may be analyzed by IHC and/or immunofluorescence for tumor-infiltrating immune cells. The baseline (pretreatment) values, post-treatment values, and the changes from baseline in density of immune cells in tumor tissues may be summarized descriptively in tables.

Relevant markers for disease (eg, BRCA status and homologous recombination deficiency status; TMB scores; and PD-L1 expression) may be summarized descriptively. Additional analyses may be conducted as deemed necessary upon exploration of data.

11.3.8.3. Immunogenicity Analyses

A patient listing of individual immunogenicity data for nemvaleukin (and pembrolizumab as appropriate) will be provided.

Immunogenicity endpoints include the following:

- Presence of anti-drug antibodies
- Titer of anti-drug antibodies
- Frequency of the presence of anti-drug antibodies by relevant treatment arms

Time of onset of immunogenicity and time of resolution of immunogenicity will be calculated and summarized. (Time of onset is defined as the first time point with a positive result for ADA; time of resolution is defined as the first time point when the previously observed positive for ADA returns to negative for ADA.)

Additional immunogenicity characterization (eg, presence of neutralizing ADAs) may be summarized as deemed appropriate.

11.3.9. Safety Analyses

11.3.9.1. General Considerations

All safety endpoints will be summarized for the Safety Population. Safety evaluations will be based on AEs, vital signs, weight, clinical laboratory tests, and ECGs.

11.3.9.2. Adverse Events

AEs will be coded using the most recent version of MedDRA. TEAEs are defined as AEs that that have an onset on or after the day of the first dose of study drug or increases in severity after the first dose of study drug. Disease progression will not be captured as an AE or SAE. Death due to disease progression will not be captured as an SAE.

Analyses of AEs will include TEAEs that were collected during the safety reporting period as defined in Section 10.3.1.5. Events where the onset date was the same as the study drug start date will be assumed to be treatment-emergent, unless the study drug start time and the AE start time are collected, and the AE start time is prior to the study drug start time. Handling of missing or incomplete onset dates will be described in the SAP.

TEAEs will be summarized by PT and by SOC. Patients reporting more than one AE within a SOC will be counted only once for that SOC. Patients reporting the same AE more than once will be counted only once for that PT.

The severity of TEAEs will be assessed by NCI CTCAE. For TEAEs that are not specified in the NCI CTCAE, severity grade is assigned by the criteria in Section 10.3.1.5. If a patient has the same AE on multiple occasions, the highest severity recorded for the event will be presented in the AEs by severity table.

An overview table, including the number of patients with any TEAEs, SAEs, TEAEs related to study drug, TEAEs by severity, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to dose interruption, and TEAEs leading to death will be summarized.

In addition, the TEAEs will be summarized by treatment arm for the following:

- TEAEs and related TEAEs by SOC and PT
- TEAEs and related TEAEs by SOC, PT, and grade
- Grade 3-4 TEAEs by SOC and PT
- Grade 3-4 related TEAEs by SOC and PT
- SAEs and related SAEs by SOC and PT
- TEAEs and related TEAEs by PT by decreasing order of frequency
- TEAEs and related TEAEs leading to dose reduction by SOC and PT
- TEAEs and related TEAEs leading to dose interruption by SOC and PT
- TEAEs and related TEAEs leading to treatment discontinuation by SOC and PT
- TEAEs and related TEAEs leading to death
- AESIs and related AESI

Listings will be provided for all AEs, SAEs, AESI, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to dose interruption, and TEAEs leading to death.

11.3.9.3. Clinical Laboratory Parameters

Laboratory parameters will be presented in conventional (ie, US) units. Only scheduled laboratory parameters will be included in the laboratory results summaries, unless specified otherwise. All laboratory data, including those collected at unscheduled visits, will be included in the listings.

Results of clinical laboratory tests will be summarized for pre-specified visits by treatment arm for the actual values and for change from baseline. Data collected at the EOT Visit will be included as one time point.

In addition, where applicable, hematology and chemistry laboratory determinations will be categorized according to NCI CTCAE grades and shifts from baseline NCI CTCAE grades to maximum and final post-baseline grades will be summarized. The baseline and final grades will

be defined respectively as the grade of the last measurement collected prior to the first dose of study drug, and as the last post-baseline measurement collected no more than 30 days after the last dose of study drug.

The maximum NCI CTCAE toxicity grade value will be the value with the highest NCI CTCAE toxicity grade collected after the first dose of study drug and within 30 days following study drug discontinuation. In cases where multiple values are collected on the same day, the maximum grade value will be selected as the value for that day.

Detailed listings of data for patients experiencing NCI CTCAE grade ≥3 hematology and chemistry values will be provided. All measurements collected after the first dose of study drug and within 30 days following study drug discontinuation will be included in these listings.

The number of patients who meet the following criteria will be summarized and corresponding listing will be presented:

An elevated AST or ALT laboratory value that is ≥3 × ULN, an elevated total bilirubin laboratory value that is ≥2 × ULN, and an ALK-P laboratory value that is <2 × ULN.

11.3.9.4. Vital Signs and ECG

Vital Signs

Descriptive statistics for vital signs and changes from baseline values after the first dose of study drug will be presented for pre-specified visits. Tables will also present the shifts from baseline. All vital sign data will be presented in the patient data listings. In addition, a detailed data listing for patients experiencing potentially clinically significant events will be provided.

Electrocardiograms

Data for patients experiencing clinically significant ECG changes will be provided.

11.3.9.5. ECOG Status

The ECOG status assesses the patients' activity status (Appendix 4). Descriptions of activity status are presented as possible scores from 0 to 5. The number and percentage of patients with baseline score versus post-baseline scores will be summarized by treatment arm in a shift table.

11.3.10. Patient-Reported Outcomes: Health-Related Quality of Life

FACT-O

The FACT-O is a 39-item questionnaire about the past 7 days using a 5-point Likert-type scale. It includes 5 subscale domains (physical well-being, social/family well-being, emotional well-being, functional well-being, and ovarian subscale). The scoring guideline is summarized in the SAP.

EQ-5D-5L

The EQ-5D-5L is a validated quality of life questionnaire developed by the EuroQol Group in order to provide a simple, generic utility measure for characterizing current health states of patients. The EQ-5D-5L is designed for self-completion by patients. It consists of 2 parts – the EQ-5D-5L descriptive system and the VAS.

The EQ-5D-5L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels.

The 5-dimensional, 5-level systems are converted into an index value. Values for theoretically possible health states are calculated using a regression model and weighted according to the social preferences of the US population (Van Hout et al, 2012).

The VAS records the respondent's self-rated health on a vertical VAS. The VAS "thermometer" has 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom. This information can be used as a quantitative measure of health outcomes as judged by the individual respondents. The EQ-5D-5L self-reported VAS data generates information on the self-perceived overall HRQoL. During the Long-term Follow-up Period, only the VAS will be administered to patients in all treatment arms.

The HRQoL endpoints will be analyzed based on the ITT Population who have the baseline and at least one post-baseline score. The absolute values and changes from baseline at each administration time point in total score and subscale domain scores for the FACT-O and EQ-5D-5L index and VAS scores will be descriptively summarized. The statistical comparison between the Combination and Chemotherapy arms will be conducted for selected items, domain, or total score as described in the SAP.

11.4. Randomization/Method of Assigning Patients to Treatment

Per the original study design, patients were centrally allocated in a randomized fashion (3:1:1:3) to receive either:

- Arm 1: nemvaleukin and pembrolizumab combination therapy
- Arm 2: pembrolizumab monotherapy (closed)
- Arm 3: nemvaleukin monotherapy (closed)
- Arm 4: Investigator's choice chemotherapy. Options for protocol-specific Investigator's choice include one of the following: PLD, paclitaxel, topotecan, or gemcitabine. The Investigator will pre-select the Investigator's choice treatment before the randomization of each patient.

The pembrolizumab monotherapy arm (Arm 2) met its pre-specified futility criteria at the planned futility analysis and was closed to enrollment as of 31 Aug 2023, per the recommendation of the IDMC. The nemvaleukin monotherapy arm (Arm 3) did not meet its pre-specified futility criteria at the planned futility analysis and the IDMC recommended continuation. Under protocol version 4.0, the nemvaleukin monotherapy arm (Arm 3) reached its intended enrollment and thus closed. Because no changes have been made to the objectives related to Arm 3 in protocol version 5.0, the Arm 3 number of patients was not recalculated. Therefore, in protocol version 5.0, eligible patients will continue to be enrolled in the remaining 2 arms and will be centrally allocated with a randomization ratio of 1:1 to the Combination and Chemotherapy arms (Arm 1 and Arm 4, respectively).

To ensure equal distribution of prognostic factors and chemotherapy partners in the study arms, patients will be stratified according to the following parameters:

- PD-L1 status (CPS ≥10 vs CPS <10)

- Histological subtype (high-grade serous vs non-high-grade serous)
- Investigator's choice chemotherapy (paclitaxel vs other chemotherapies)

11.5. Blinding and Independent Data Monitoring Committee

An IDMC will be established by the Sponsor to analyze and interpret the data for the interim analysis. Members will include experts in oncology and biostatistics who are not participating in this study at any capacity and do not have any external conflict of interest for the study. The IDMC members and specific duties will be fully described in an IDMC charter.

The Sponsor's study team members will remain blinded for any aggregate antitumor efficacy data or efficacy results by assigned treatment group during the study conduct.

11.6. Interim Analyses

The interim analyses planned in this study are described below. All the analyses will be conducted by an independent statistician under the guidance of IDMC. The Sponsor's study team members will be blinded for any aggregate antitumor efficacy data or results by assigned treatment group during the study conduct. More details can be found in the IDMC charter.

Interim Futility Analysis of ORR in Each Monotherapy Arm

The monotherapy arms (either nemvaleukin alone or pembrolizumab alone) are included in the study as reference arms to isolate the component effect; thus, no statistical comparison or testing will be conducted against or between the monotherapy arms.

Interim analyses will be conducted separately when the 24th patient enrolls into the nemvaleukin monotherapy arm and the 12th patient enrolls into the pembrolizumab monotherapy arm; these analyses will be conducted by an independent statistician. The interim analysis on the ORR will provide a statistical recommendation for early stopping due to futility. The pembrolizumab monotherapy arm (Arm 2) met its pre-specified futility criteria at the planned futility analysis and was closed to enrollment as of 31 Aug 2023, per the recommendation of the IDMC.

The stopping boundary is summarized in Table 23.

Table 23: Stopping Boundary for Interim Futility Analysis of Objective Response Rate in Monotherapy Arms

Monotherapy Arm:	Interim Analysis at:	Recommend Stopping Enrollment if:
Pembrolizumab Monotherapy Arm (closed as of 31 Aug 2023)	First 12 dosed patients	0 or 1 response (confirmed PR or CR)
Nemvaleukin Monotherapy Arm	First 24 dosed patients	0 response (confirmed or unconfirmed PR or CR or durable SD lasting for ≥3 months)

CR=complete response, PR=partial response, SD=stable disease.

If the futility criteria are met, further enrollment into the arm will stop; patients in the arm receiving benefit (SD or better) may remain on study until progression. Crossover to another

treatment arm is not allowed. (Note: all patients who progress at any time will be immediately discontinued from treatment; Section 7.5.1).

There will be no type I error rate adjustment caused by this futility analysis, as the monotherapy arms are not included for any statistical comparisons.

Interim Analysis of OS

One planned efficacy interim analysis of OS will be performed when approximately 215 death events (at approximately 75% information fraction) are observed in the 2 arms (the Combination and the Chemotherapy arms). The Lan-DeMets O'Brien-Fleming alpha-spending function is constructed to implement group sequential boundaries to control the type I error rate.

Table 24 summarizes the analysis strategies. If the actual number of OS events at the interim and final analyses differs from those specified in the table, the boundaries will be adjusted using the Lan-DeMets O'Brien-Fleming alpha-spending function accordingly.

Table 24: Summary of Number of Events and Decision Guidance at the Planned Overall Survival Analyses

Analysis	Expected Number of Events at the Time of Analysis	Efficacy Boundary	
		p-value[a]	HR
OS IA	~215 OS events in the Combination and the Chemotherapy arms	0.0096	0.7265
OS FA	~286 OS events in the Combination and the Chemotherapy arms	0.0221	0.7882

Abbreviations: FA=final analysis, HR=hazard ratio, IA=interim analysis, OS=overall survival

[a] p-value (1-sided) is the nominal significance level for testing and will be used to claim crossing of a boundary.

11.7. Subgroup Analysis

Subgroup analyses relevant to baseline characteristics and disease will be performed (eg, prior treatments, ECOG status, biomarkers, stratification factors, age, region, race, disease stage, and number of prior lines of therapy). Details of these analyses and additional subgroup analyses will be described in the SAP.

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13. APPENDICES

13.1. Appendix 1: Contraception Definitions

Woman of Childbearing Potential

A woman is considered a WOCBP, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. (Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.)

- WOCBP using highly effective methods of contraception are eligible to participate in this study.
- WOCBP using unacceptable methods of contraception or effective methods of contraception are not eligible to participate in the study unless they switch to a highly effective method of contraception prior to their participation in the study.

Postmenopausal Female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle stimulation hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one follicle stimulating hormone measurement (>40 IU/L or mIU/mL) is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Sterilized Female

Sterilized females are those who have undergone total hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy.

Highly Effective Methods of Contraception

- Intrauterine device
- Bilateral tubal occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the study patient and that the vasectomized partner has received medical assessment of the surgical success)
- Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug
  - Oral
  - Intravaginal

  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug
  - Oral
  - Injectable
  - Implantable
- Sexual abstinence: sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.

Effective Methods of Contraception

If genotoxicity/teratogenicity/embryotoxicity is unlikely to be caused by the investigational drug, comparator, background therapy, or standard of care medications, effective methods of contraception (there may be a higher than 1% failure rate) are:

- Double-barrier method (combination of male condom with either cap, diaphragm or sponge with spermicide)
- Male or female condom, with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action

Unacceptable methods of contraception are:

- Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods)
- Spermicides only
- Withdrawal (coitus interruptus)
- Lactational amenorrhea method
- Use of female and male condoms together
- Cap/diaphragm/sponge without spermicide and without condom

13.2. Appendix 2: New York Heart Association Heart Disease Classifications

Table 25: New York Heart Association Heart Disease Classifications

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, and/or dyspnea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, and/or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; 01 Mar 1994.

13.3. Appendix 3: Clinical Laboratory Assessments

Table 26: Clinical Laboratory Assessments

Hematology	Biochemistry		Urinalysis	Coagulation
• Hematocrit • Hemoglobin • Red blood cell count • Total and differential (absolute) white blood cell count • Note: absolute counts for neutrophils, lymphocytes, monocytes, and eosinophils • Platelet count • C-reactive protein	<u>General Chemistry</u> • Albumin • Bicarbonate • Calcium • Chloride • CPK • Glucose • Magnesium • Phosphorus • Potassium • Sodium • Total protein • Uric acid • Amylase • Lipase <u>Renal Function Tests</u> • BUN • Creatinine	<u>Liver Function Tests</u> • ALT • ALK-P • AST • LDH • Total bilirubin <u>Endocrine Tests</u>[a] • Thyroid-stimulating hormone (TSH)[b] • ACTH • Total cortisol • Free T4 • Total or free T3	• Color and appearance • pH • Specific gravity • Ketones • Protein • Glucose • Bilirubin • Nitrites • Urobilinogen • Leukocytes • Leukocyte esterase • Occult blood • Microscopic examination of sediment, *only if urinalysis dipstick results for blood, leukocytes or protein are abnormal* (ie, 2+ or higher)	• INR • aPTT

ACTH=adrenocorticotropic hormone, ALK-P=alkaline phosphatase, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CPK=creatine phosphokinase, INR=international normalized ratio, LDG=lactate dehydrogenase, T3=triidothyronine, T4=thyroxine

[a] Endocrine tests will be performed for all patients at Screening. On-treatment endocrine tests are only applicable to Arm 1, 2, and 3.

[b] If TSH result is abnormal, collect total T3 or free T3 and Free T4.

13.4. Appendix 4: Eastern Cooperative Oncology Group Status

Table 27: Eastern Cooperative Oncology Group Status

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 or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: (Oken et al, 1982)

13.5. Appendix 5: COVID-19 Structured Risk Analysis

13.5.1. COVID-19 Related Risks

The objective of this appendix is to outline the protocol procedures that can be considered during the COVID-19 pandemic.

In response to COVID-19, the FDA, the EMA, and local authorities have issued guidance to assist Sponsors during the pandemic. Compliance with the study protocol should be ensured to such an extent that an ongoing benefit-risk assessment for the clinical study and its participants is not compromised.

The goal is to have the protocol followed in full and to minimize missing data, but where this is not possible due to COVID-19 (or another catastrophe), the site, in consultation with Mural and the IRB/EC, should assess alternative protocol procedures in a risk and benefit manner, leading with patient safety, personnel safety, study objectives, and considering local and regional requirements.

The current COVID-19 pandemic can pose a challenge to the continuity of studies, the protection of study patients' rights, and the safety and well-being of study staff. Such situations may necessitate, for example, quarantines (patient-imposed, institution-imposed, or government-imposed), site closures, travel restrictions, interruptions to the supply chain for study materials, or other considerations for the protection of clinical study patients and/or site personnel. Related challenges may lead to difficulties in performing protocol-specified procedures, administration of study drug(s), as well as adherence to site visits, laboratory/diagnostic testing, and/or disease assessment scheduling.

Therefore, risk mitigation strategies will be evaluated on an ongoing basis for the duration of this study, or until there is a consensus that the period of the COVID-19 outbreak has been brought under control. Ongoing monitoring of the study will be performed in accordance with the Monitoring Plan, using risk-based monitoring and/or remote monitoring methods when needed in lieu of on-site monitoring. If the dynamics of the COVID-19 outbreak change in such a way that the safety of the study patients and study staff, or the integrity of the data collected during this study cannot be guaranteed, a temporary study hold may be implemented.

13.5.2. Risk for Patients and Study Staff

The risks of COVID-19 have not been fully established and there may be comorbidities, other than cancer itself that can put patients at higher risk. Investigators should use their medical judgement and current evidence and consult with Mural and their local IRB/EC at any time point, in order to determine the risks and benefits for each study patient to continue in the study as more information becomes known regarding the potential impact COVID-19 may have on study patients.

Sites are recommended to follow institutional guidelines to prevent COVID-19 infections among study patients.

In order to mitigate the possible increased risk associated with study participation during the COVID-19 pandemic, investigators should evaluate whether alternative methods for assessments (eg, phone contact, virtual visit/telemedicine, extension of visit windows, alternative location for

assessment, including local labs) can be implemented when necessary and feasible, in consultation with Mural and the IRB/EC to ensure patient safety.

In the event of disruption to the conduct of the study during a pandemic/epidemic, the following alternative methods are available for study-related patient management; and where appropriate, protocol deviation will be documented and communicated to Mural and the IRB/EC according to local requirements:

1. If at any time a patient is considered to be at risk, appropriate modification to the patient's study schedule should be made. If needed, study treatment may be delayed, and re-treatment guidance should be followed as described in the protocol. If deemed necessary, study treatment should be discontinued, and study follow-up assessments should be conducted.
2. If a scheduled visit cannot be conducted in person at the study site, it should be performed remotely/virtually or delayed until such time that on-site visits may be safely resumed. Upon remote contact, patients should be interviewed to collect clinical safety data. Patients should also be questioned regarding their general health status to fulfill physical examination requirements to the extent possible.
3. Every effort should be made to adhere to protocol-specified laboratory and/or diagnostic assessments, including follow-up assessments. Safety laboratory assessments may be performed at a local laboratory closer to the patient, if needed.
4. Sites are expected to comply with (S)AE reporting requirements as described in the protocol. (S)AEs as a result of, eg, COVID-19 infection while on study should be reported accordingly, and the event should be recorded as a separate AE.
5. Key disease status and efficacy endpoint assessments should be performed if required and feasible.
6. Study site representatives should inform the Sponsor regarding any locally imposed COVID-19 mitigations as soon as possible.
7. If necessary, protocol deviations should be specified as being due to the pandemic/epidemic.
8. Changes to study procedures, including missed study visits or a decision to discontinue study participation, should be documented in source notes and in the eCRF as advised by the Sponsor.

Patients who volunteer to participate in this clinical study have a life-threatening disease and it is expected that this specific population may be offered the COVID-19 vaccine before or while being treated with study drug. Live vaccines are prohibited, and sites should follow the guidance provided in study entry-criteria, including prohibited and concomitant medication section of the protocol.

If a patient is offered a COVID-19 vaccine during participation in the clinical study, the following advice is offered to minimize unanticipated interactions with the study treatment (since it is unknown whether investigational product will affect the efficacy of the vaccine), as well as facilitate the ability to distinguish side effects potentially attributable to the vaccine vs those attributable to the study treatment:

- It is recommended that the vaccine is not administered within 7 days prior to or 3 days after study drug administration; however, when needed this window can be as short as ±3 days ie, for weekly dosing schedule for study treatment is applied.

Regulatory guidance requires the Sponsor to continuously monitor for overall COVID-19 impact on achieving the objectives of the study and any changes (eg, interruption or discontinuation in patient recruitment, site monitoring, and audits) will be communicated to sites and to relevant health authorities according to local guidance. Modifications made to study conduct as a result of disruption(s) related to the COVID-19 pandemic/epidemic will be summarized in the Clinical Trial Report.

This guidance is not intended to supersede any local or government requirements or the clinical judgement of the Investigator to protect the health and well-being of clinical study patients and site personnel.

13.5.3. Impact of the Investigational Drug on COVID-19

The impact of the study drug (nemvaleukin) on the susceptibility of study patients to the SARS-CoV-2 virus infection, effect on signs, symptoms, or complications are unknown at this time. Sites and patients will be made aware as further information becomes available.

13.6. Appendix 6: Regulatory, Ethical, and Study Oversight Considerations

13.6.1. Regulatory and Ethical Considerations

This study will be conducted under ICH E6 GCP and all applicable regulatory requirements. To ensure data accuracy, completeness, and compliance, the study site should have processes in place for data review and quality control. Mural may also conduct monitoring and quality assurance audits. Please see Section 13.6.6.2 for details regarding the audit process.

This study will be conducted in accordance with the IRB/EC-approved protocol, protocol amendments, ICF, IB, other relevant documents (eg, advertisements), and with the following applicable regulatory requirements to ensure data accuracy, completeness, and compliance:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines and US CFR applicable to clinical studies
- Applicable state, local, and federal laws and regulatory requirements

Each clinical site's IRB/EC must meet all relevant regulatory requirements. The study protocol, ICF, recruitment materials, and all patient materials will be submitted to the IRB/EC for review and approval. Written approval from the committee must be received by Mural before study drug(s) will be released to the Investigator. Approval of both the protocol and the consent form must be obtained before any patient is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. In addition, all changes to the consent form will be IRB/EC-approved; a determination will be made regarding whether a new consent needs to be obtained from patients who provided consent, using a previously approved consent form.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Submitting all protocol changes, deviations, and SAE reports to the IRB/EC according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, and all other applicable local regulations.
- Forwarding all relevant correspondence from the IRB/EC to the Sponsor in a timely fashion.

13.6.2. Financial Disclosure

Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

13.6.3. Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. A prospective patient is defined as a patient who have indicated in advance (before receiving the ICF) a wish to receive information about a possible participation in the study. Each prospective patient will receive an IRB/EC -approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. The Investigator (or authorized designee) at each study center will ensure that the patient (or the patient's legal representative as applicable per regional requirements) is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study, and answer all questions regarding the study. The ICF will include information, as it becomes available, related to the use of nemvaleukin in relation to the SARS-CoV-2 virus (see Appendix 5 for further details). All information is to be provided in a language understandable to the patient and must not include any language that waives the patient's legal rights. Prospective patients must be informed that their participation is voluntary and must also be informed of their right to withdraw consent without prejudice at any time during the study. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If the patient chooses to participate, he or she must sign the ICF before any study-specific procedures are conducted.

- Patients or their legally authorized representative will be required to sign an ICF that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/EC or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. The time that informed consent is obtained must be documented. The Investigator must maintain the original signed ICF in the patient's source documents.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative (as applicable per regional requirements).
- Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and approved by the IRB/EC, and then signed by all applicable study patients. Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

- A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 14 days from the previous ICF signature date.

All candidate patients will be informed of their rights to privacy and will be made aware that the study data will be submitted to Mural, the IRB/EC, the CRO, if applicable, and to regulatory authorities for review and evaluation for the duration of the study and until the project has been approved for marketing or is withdrawn from investigation. They will also be informed that the study monitors may inspect their medical records to verify the accuracy and completeness of the study records and results.

If circumstances occur that are beyond the control of patients or sites (ie, states of emergency including natural disasters, public health mandates, etc), and the resultant changes to study processes require written informed consent from patients, alternative informed consent processes can be considered, in consultation with the sites' IRB/EC.

13.6.4. Confidentiality of Data

By signing this protocol, the Investigator affirms to Mural that he or she will maintain in confidence information furnished to him or her by Mural and will divulge such information to his or her respective IRB/EC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of Mural. Please refer to the CSA for details.

Data generated in this study are proprietary information that are the sole property of Mural. Results of the study are to be held in confidence by both the Investigators and the Sponsor.

Retention and storage of all essential clinical study documents shall be governed by the terms and conditions of the site's CSA and in accordance with ICH guidelines/local regulatory requirements as follows:

- Essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by the terms of the CSA. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. No records may be transferred to another location or party without written notification to the Sponsor.
- Patients' medical files should be retained in accordance with the applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice.

Please refer to the CSA for details on the procedures for publishing and presenting data.

13.6.5. Committees Structure

The Investigator must obtain IRB/EC approval for the investigation. Initial IRB/EC approval, as well as all materials approved by the IRB/EC for this study, including the ICF and recruitment materials, must be maintained by the Investigator and made available for inspection.

13.6.6. Data Quality Assurance

13.6.6.1. Study Monitoring

Mural or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the Monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct.

The investigational site will provide direct access to all study-related sites, source data/documents, and reports for the purpose of study-related monitoring, audits, and IRB/EC review by the Sponsor, and inspection by local and regulatory authorities.

Monitoring of the study site (including, but not limited to, reviewing eCRFs for accuracy and completeness) will be performed by a Mural Monitor or designee.

Clinical site monitoring is conducted to ensure that the rights and well-being of study patients are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirements. Monitoring of this study will be performed by a Mural Monitor and according to the Study Clinical Monitoring Plan. The Clinical Monitoring Plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

13.6.6.2. Audits and Inspections

Independent audits will be conducted by the Sponsor to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the Clinical Monitoring Plan.

By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of Mural, a regulatory authority, and/or an IRB/EC may visit the site to perform audits or inspections, including all study-related sites (ie, the drug storage area, study drug stocks, drug accountability records, patient charts and source documents, and other records relative to study conduct). The purpose of a Mural audit or inspection is to systematically and independently examine all study-related activities and documents (eg, laboratory reports, x-rays, workbooks, patients' medical records) to determine whether these activities were conducted, and data recorded, analyzed, and accurately reported, according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The auditor should verify that source documents and study records are accurate, complete, timely, and maintained.

The Investigator should contact Mural immediately if contacted by a regulatory agency regarding an inspection.

13.6.7. Source Documents

An overview of study data handling and recordkeeping procedures and restrictions is provided here; please refer to the CSA for further details.

This study will use eCRFs for capturing data. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The EDC system maintains a full audit trail.

A paper copy of all laboratory reports will remain with the source documents at the study site. All electronic source data collected outside of the eCRF, such as central laboratory data, will be transferred directly to EDC or directly to Mural for incorporation into the final datasets.

All eCRF data must be based on source documents or approved to be the original data (ie, data directly reported on the eCRF). All eCRFs will be completed by the clinic staff prior to review by the Mural Monitor or designated representative.

The Mural Monitor or designated representative will review all source records on-site and compare them to the data collected on the eCRF.

Changes to study visit schedules, missed visits, treatment discontinuations, or patient discontinuations from study due to rare circumstances beyond the patient's or site's control (ie, states of emergency including natural disasters, public health mandates, etc) should be captured in the eCRF, to explain the reason for the missing data.

13.6.8. Study and Site Closure

The Sponsor may terminate the entire study or a single study center at any time for safety, administrative reasons, or other reasons.

13.6.9. Use of Information and Publication Policy

Data generated in this study are proprietary information that are the sole property of Mural. Results of the study are to be held in confidence by both the Investigators and the Sponsor.

Please refer to the CSA for details on the procedures for publishing and presenting data.

13.6.10. Major Protocol Deviations

Sites will report protocol deviations to the Sponsor and to the IRB/EC per IRB/EC reporting requirements. During data cleaning and during review of data listings, CRO and Sponsor representatives (from data management, drug safety, statistical programming, biostatistics, translational medicine, and/or the Medical Monitor) may identify additional deviations from the protocol. Deviations may also be identified through auditing or risk monitoring activities. All deviations will be collected in a deviation log.

Deviations will be reviewed by Sponsor representatives in order to identify (1) any trends with site compliance, quality of data, and/or patient safety issues, (2) promptly assess areas of correction, re-training, and re-evaluation at the site and/or to the program, (3) identify the major protocol deviations, and (4) assess the need for protocol improvements and/or site training for the current or future studies.

Deviations will be categorized and characterized as major or minor in accord with a protocol deviation plan. Major deviations will be reported to IRB/EC and to the Sponsor's Biostatistics and Medical Writing groups for analysis and reporting in the clinical study report.

Major deviations include, but are not limited to, those that involve fraud or misconduct, affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data

generated, or confound interpretation of the primary study assessment. Any decision by the Sponsor to close a site due to non-compliance will also be reported to the applicable regulatory authorities.