CLINICAL PROTOCOL

A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY OF AVELUMAB* (MSB0010718C) ALONE OR IN COMBINATION WITH PEGYLATED LIPOSOMAL DOXORUBICIN VERSUS PEGYLATED LIPOSOMAL DOXORUBICIN ALONE IN PATIENTS WITH PLATINUM-RESISTANT/REFRACTORY OVARIAN CANCER

JAVELIN OVARIAN 200

Compound:	MSB0010718C
Compound Name:	avelumab
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2015-003091-77
Protocol Number:	B9991009
Phase:	Phase 3

[redacted]

* Avelumab is the proposed International Nonproprietary Name (INN) for the anti-PD-L1 monoclonal antibody (MSB0010718C).

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PROTOCOL SUMMARY

Background and Rationale:

Ovarian cancer is the leading cause of death from gynecologic cancer and the fifth most common cause of cancer mortality in women. The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life. The median age at the time of diagnosis is 63 years, and 70% of patients present with advanced disease.[3] Although expectations for long-term survival can be very high if the cancer is identified and treated early, the women diagnosed with advanced ovarian cancer continue to have less than 30% 5-year survival.

Patients are considered to have platinum-sensitive disease if they respond to first-line platinum therapy and experience a relapse-free period of greater than 6 months following the last dose of platinum therapy. Platinum-resistant disease is defined by relapse between 0 to 6 months after the last platinum dose. Platinum-refractory disease is defined by lack of response to platinum-based chemotherapy or recurrence prior to completion of platinum-based therapy.[46]

There are no highly effective therapies in the platinum-resistant/refractory population, although non-platinum-related agents have demonstrated modest antitumor efficacy in a subset of these patients.

Programmed death ligand 1 (PD-L1, also called B7-H1 or CD274) and its receptor, PD-1, have a known role in the suppression of T-cell responses. The PD-1 receptor is expressed on activated CD4+ and CD8+ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals to inhibit T-cell function.[7,8,9]

Avelumab[*] (MSB0010718C), a fully human antibody of the immunoglobulin G1 (IgG1) isotype, specifically targets and blocks PD-L1, the ligand for PD-1 receptor. In preclinical studies, combination of avelumab with chemotherapies showed improved anti-tumor activity.[1] Prelimenary data from the ongoing ovarian cancer Study EMR 100070-001, which is being conducted by Merck KGaA/EMD Serono (EudraCT number 2013-002834-19, NCT01772004) showed an Objective Response Rate (ORR) of 10.7% (8/75) and stable disease in an additional 44% (33/75) of patients with advanced ovarian cancer.

Certain chemotherapy agents, including doxorubicin, have been shown to have immunostimulatory properties.[52] Preclinical evaluation of breast tumor and sarcoma responses to anthracyclines suggested that immune mechanisms contribute to tumor growth inhibition.[50]

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[*] Avelumab is the proposed International Nonproprietary Name (INN) for the anti-PD-L1 monoclonal antibody (MSB0010718C)

In addition, expression of genes such as CD8α, CD8β, and IFN-γ correlated with response to anthracycline chemotherapy in breast cancer patients.[50] Enhanced exposure of tumor antigens as a result of tumor cell kill may enhance the activity of immune checkpoint blockade.[47] In preclinical studies, combination of avelumab with chemotherapies showed improved anti-tumor activity of chemotherapy (gemcitabine, oxaliplatin, 5FU).[1]

Taken together, these observations suggest that combination of anthracyclines with avelumab may provide added clinical benefit relative to either agent alone.[51]

Study Objectives

Primary Objectives

- To demonstrate that avelumab given alone or in combination with Pegylated liposomal doxorubicin (PLD) is superior to (PLD) alone in prolonging Overall Survival (OS) in patients with platinum -resistant/platinum-refractory ovarian cancer.

- To demonstrate that avelumab given alone or in combination with PLD is superior to PLD alone in prolonging PFS in patients with platinum-resistant/platinum-refractory ovarian cancer.

Secondary Objectives

- To evaluate anti-tumor activity of avelumab given alone or in combination with PLD versus PLD alone in ovarian cancer patients.

- To evaluate the overall safety profile of avelumab alone or in combination with PLD versus PLD alone in ovarian cancer patients.

- To characterize the Pharmacokinetics (PK) of doxorubicin (PLD samples) and avelumab when administered in combination, and to assess the effect of avelumab on the PK of doxorubicin (PLD samples) and the effect of PLD on PK of avelumab.

- To assess the immunogenicity of avelumab.

- To evaluate candidate predictive biomarkers of sensitivity or resistance to avelumab alone or PLD in combination with avelumab in pre-treatment tumor tissue, that may aid in the identification of patient subpopulations most likely to benefit from treatment.

- To compare the effect of avelumab alone or in combination with PLD versus PLD alone on patient-reported outcomes (PRO) in patients with ovarian cancer.

Exploratory Objectives

CCI

[redacted]

Study Endpoints

Primary Endpoints

- Overall Survival (OS).
- PFS as determined by blinded independent central review (BICR) according to RECIST version 1.1.

Secondary Endpoints

- Efficacy: Objective response, Duration of Response (DR), and Disease Control (DC) as determined by Blinded Independent Central Review (BICR) and Investigator [as assessed by RECIST version 1.1]. (Appendix 3).
- PFS as determined by Investigator according to RECIST version 1.1.
- Safety: Adverse Events (AEs) (as graded by NCI CTCAE v.4.03); laboratory abnormalities (as graded by NCI CTCAE v.4.03); vital signs (blood pressure, pulse rate); electrocardiograms (ECGs), Echocardiogram (ECHO) or multiple gated acquisition (MUGA) scans.
- Pharmacokinetics: PK parameters, including C_{trough} and C_{max} for avelumab: C_{max}, volume of distribution (V_d), clearance (CL), area under the concentration-time curve (AUC) for doxorubicin (PLD samples).
- Immunogenicity: Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against avelumab.
- Candidate predictive biomarkers in tumor tissue (including, but not limited to, PD-L1 expression and tumor infiltrating CD8+ T lymphocytes as assessed by immunohistochemistry (IHC)).
- Patient-Reported Outcomes: EORTC QLQ-C30, EORTC QLQ-OV28, and EQ-5D-5L.

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Exploratory Endpoints

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- CA-125 levels, CCI [redacted]

Study Design

This is a Phase 3, multicenter, randomized, open-label, parallel 3-arm study in which approximately 550 patients will be randomized in a 1:1:1 ratio to receive avelumab alone, avelumab in combination with PLD, or PLD alone, as follows:

- Arm A: avelumab alone;
- Arm B: avelumab plus PLD;
- Arm C: PLD alone.
- Patients will be stratified according to platinum-refractory or platinum-resistant status, number of prior regimens (1 vs 2 or 3), and bulky disease (defined as presence of a tumor ≥5 cm) vs not.

Study Treatments

Avelumab (Arm A, Arm B) 10 mg/kg will be given as a 1-hour intravenous infusion (IV) every 2 weeks (Q2W) in 4-week cycles.

PLD (Arm B, Arm C) 40 mg/m^2 will be given as a 1-hour IV infusion every 4 weeks (Q4W) in 4-week cycles.

In all patients, study treatment may continue until PD as assessed by BICR, unacceptable toxicity, patient refusal, patient loss to follow up, or termination of the study by the Sponsor, whichever comes first (see Section 6.5 Withdrawal). Avelumab may be continued beyond disease progression. PLD will not be continued beyond confirmed disease progression. Cross-over will not be permitted.

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Statistical Methods

Sample Size Determination

The primary objectives of this study are to demonstrate that avelumab given alone or in combination with PLD is superior to PLD alone in prolonging OS or PFS in patients with platinum-resistant/refractory ovarian cancer. The study is designed to test in parallel four hypotheses.

- The first null hypothesis is that the true OS hazard rates for PLD alone and avelumab alone arms are the same (([HR]=1) versus the alternative hypothesis that the true hazard rate is smaller in the avelumab alone arm than in the PLD alone arm (HR<1).

- The second null hypothesis is that the true OS hazard rates for PLD alone and avelumab in combination with PLD arms are the same (HR=1) versus the alternative hypothesis that the true hazard rate is smaller in the avelumab in combination with PLD arm than in the PLD-alone arm (HR<1).

- The third null hypothesis is that the true PFS hazard rate for PLD alone and avelumab alone arms are the same (HR=1) versus the alternative hypothesis that the true hazard rate is smaller in the avelumab alone arm than in the PLD alone arm (HR<1).

- The fourth null hypothesis is that the true PFS hazard rate for PLD alone and avelumab in combination with PLD arms are the same (HR=1) versus the alternative hypothesis that the true hazard rate is smaller in the avelumab in combination with PLD arm than in the PLD alone arm (HR<1).

Approximately 550 patients will be randomized using a 1:1:1 randomization, stratified by platinum-refractory or platinum-resistant status, number of prior regimens (1 vs 2 or 3), and bulky disease (defined as presence of a tumor ≥5 cm) vs not.

The sample size is determined based on the following assumptions for OS and PFS.

- OS

It is assumed that the median OS for patients receiving PLD is 12 months[24] and that treatment with avelumab alone or avelumab in combination with PLD is expected to increased the median to 20 months, corresponding to a hazard ratio (HR) of 0.6 under the exponential model. The sample size further assumes a 5% drop-out rate within each arm, a non-uniform patient accrual over a 19-month period and a minimum follow-up of 12 months after the last patient is randomized.

If the true HR is 0.6 under the alternative hypothesis, 196 OS events within each comparison will be required to have 90% power to detect a HR of 0.6 using a one-sided log rank test at a significance level of 0.0115 (overall significance level in the study one-sided 0.025), and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to

determine the efficacy boundary and a Gamma Family (-10) β-spending function to determine the non-binding futility boundary.

- PFS

It is assumed that the median PFS for patients receiving PLD is 3.5 months[24] and that treatment with avelumab alone or avelumab in combination with PLD is expected to increase the median PFS to 5.8 months, corresponding to a HR of 0.6 under the exponential model assumption. The sample size further assumes a 15% drop-out rate within each arm, a non-uniform patient accrual over a 19-month period and minimum follow-up of 12 months after the last patient is randomized.

If the true HR is 0.6 under the alternative hypothesis, 325 PFS events by BICR assessment within each comparison will provide 93% power to detect a HR of 0.6 using a one-sided logrank test at a significance level of 0.001 (overall significance level in the study one-sided 0.025), and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-10) β-spending function to determine the non-binding futility boundary.

OS time will be summarized using the Kaplan-Meier method and displayed graphically by treatment arm. Confidence intervals (CIs) for the 25th, 50th and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratios for OS and the corresponding 95% CI. A stratified log-rank test (one-sided) stratified by randomization stratification factors will be used within each comparison at the interim and/or final analyses with the overall significance level preserved at 0.0115 (one-sided).

PFS time by BICR assessment will be summarized using the Kaplan-Meier method and displayed graphically by treatment arm. CIs for the 25th, 50th and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratios for PFS and the corresponding 95% CI. A stratified log-rank test (one-sided) stratified by randomization stratification factors will be used within each comparison at the interim and/or final analyses with the overall significance level preserved at 0.001 (one-sided).

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SCHEDULE OF ACTIVITIES

The Schedule of Activities (SOA) table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Activities table, in order to conduct evaluations or assessments required to protect the well-being of the patient.

Protocol Activities[1]	Screening[2] (≤28 Days Prior to Randomization)	Cycle 1		Cycle 2		Cycle 3		Cycles ≥4		End of Treatment/ Withdrawal Visit[4]	Safety Follow-up (Day 30, Day 60 , Day 90[5]	Follow-up[6]
		1 cycle = 4 weeks[3]										
		Day1	Day 15	Day1	Day15	Day1	Day15	Day1	Day15			
Visit Time Window		-2	±2	±2	±2	±2	±2	±2	±2	±3	±3	±7
Informed Consent[7]	X											
Tumor History[8]	X											
Medical History	X											
Physical Examination[9]	X	X	X	X	X	X		X		X		
Baseline Signs and Symptoms[10]	X											
Height	X											
Vital Signs[11]	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status[12]	X	X		X		X		X		X		
Contraception Check[13]		X		X		X		X		X		
Hematology[14]	X	X	X	X	X	X	X	X	X	X		
Blood Chemistry[15]	X	X	X	X	X	X	X	X	X	X		
Coagulation[16]	X	X	X	X	X	X	X	X	X	X		
ACTH, Free T4, TSH[17]	X	X				X				X	X	
HBV, HCV[18]	X											
CA-125[19]	X	X		X		X		X		X		
BRCA 1/2 Mutation Status[20]	X											
Urinalysis[21]	X	X										
Pregnancy Test[22]	X	X		X		X		X		X		
Triplicate (12-lead) ECG[23]	X	X	X	X		X						
Single 12-lead ECG[23]								X		X		
LVEF (by MUGA or ECHO) (time window ±5 days)[24]	X					X (every 2 cycles)				X		
PK Sampling for avelumab (Arms A and B only)[25]		X	X	X	X	X	X	X	X Cycle 4 only[25]	X	X Day 30 visit only	
PK Sampling for doxorubicin (PLD samples) Arm B and C only (18 patients in each arm)[26]				X	X							
Anti-Drug Antibody (ADA)[27] (Arms A and B only)		X		X		X		X[27]		X	X	

Protocol Activities[1]	Screening[2] (≤28 Days Prior to Randomization)	Cycle 1		Cycle 2		Cycle 3		Cycles ≥4		End of Treatment/ Withdrawal Visit[4]	Safety Follow-up (Day 30, Day 60 , Day 90[5]	Follow-up[6]
		1 cycle = 4 weeks[3]										
		Day1	Day 15	Day1	Day15	Day1	Day15	Day1	Day15			
Visit Time Window		-2	±2	±2	±2	±2	±2	±2	±2	±3	±3	±7
Registration and Treatment												
Randomization[28]	X											
Study treatment[29]												
Avelumab (Arms A and B)		X	X	X	X	X	X	X	X			
PLD (Arm B and Arm C)		X		X		X		X				
Premedications[30]		X	X	X	X	X	X	X	X			
Tumor Assessments												
CT or MRI Scan[31]	X			X every 8 weeks						X		X
Other Clinical Assessments												
Patient Reported Outcomes Questionnaire[32]		X		X		X		X		X	X (required at all 3 visits)[32]	
Adverse Events[33]		→	→	→	→	→	→	→	→	X	X	
Concomitant Treatments[34]		→	→	→	→	→	→	→	→	X	X	
Patient Status Follow-up[4,6]										X		X
Other Patient Samples												
Mandatory Archival FFPE Tumor Tissue Block[35]	X											
De Novo Tumor Biopsy[36]	X									X		
Banked Biospecimens[37]	X	X	X	X		X				X		

[redacted]

Footnotes

1. **Protocol Activities:** All assessments should be performed prior to dosing with study medication unless otherwise specified. There is no need to repeat activity at Day 1 if it was done during the screening timeframe of 28 days unless otherwise specified.
2. **Screening**: To be performed within 28 days prior to randomization.
3. **Study Cycle:** Cycle length is 4 weeks for each treatment arm.
4. **End of Treatment/Withdrawal**: Obtain these assessments if not completed within the prior week, except for tumor assessments, which need not be repeated if performed within the prior 4 weeks.
5. **Safety Follow-up:** All patient safety follow-up visits are scheduled monthly for 90 days after the last dose of study treatment (Day 30 ±3, Day 60 ±3, Day 90 ±3). Final visit is scheduled to occur at least 90 days, and no more than 93 days, after the last dose of study treatment. PK sample collection is only required at the first followup visit (Day 30).
6. **Follow-up for PFS and OS:** Patients without evidence of disease progression at the time of treatment discontinuation should remain on the study and continue to have tumor assessment radiological scans every 8 weeks until documented progressive disease. Patients who have discontinued study treatment due to progressive disease should be followed for survival every 12 weeks via telephone call until study end. Additionally, subsequent anti-cancer therapies, surgery, and date of initiation and discontinuation of each anti-cancer drug will be recorded in the CRF.
7. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.
8. **Tumor History**: Includes collection of tumor history, prior antitumor regimen(s), including treatment duration and best response observed.
9. **Physical Examination:** Includes an examination of major body systems, and weight (height included at screening only). Abnormal findings identified prior to first dose of study treatment should be documented in medical history.
10. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study enrollment. Baseline signs and symptoms will be recorded on the Medical History case report form (CRF) page.
11. **Vital Signs:** Blood pressure (BP) and pulse rate should be taken before any other assessments (eg, PK, laboratory blood draws) with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.
12. **ECOG Performance status:** Use Eastern Cooperative Oncology Group (ECOG) – see Appendix 2.
13. **Contraception Check:** Patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient.
14. **Hematology:** No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. Required tests are listed in Table 12 and will be performed every 2 weeks and the results should be available for review prior to infusion of treatment.
15. **Blood Chemistry:** No need to repeat on C1D1 if screening assessment performed within 7 days prior to that date. Full chemistry panel (required tests are listed in Table 12) is required at screening and Day 1 of each cycle and at End of Treatment/Withdrawal. Core chemistry panel (required tests are listed in Table 12) is required on Days 1 and 15 of each cycle. If full and core chemistry panels are scheduled at the same visit, only the full chemistry will be performed. **The results should be available for review prior to infusion of study treatment.**
16. **Coagulation:** No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. Required tests are listed in Table 12.
17. **ACTH and Thyroid Function Tests:** ACTH, Free T4 and TSH will be measured prior to trial treatment, every 8 weeks for 2 additional measurements, then every 12 weeks thereafter while on treatment, End of Treatment, at the 30-, 60-, 90-day post-treatment visits,and as clinically indicated.
18. **HBV serology, and HCV serology**: measured prior to study study enrollment and then as clinically indicated.
19. **CA-125:** Will be assessed locally according to the schedule in the table.

20. **BRCA status.** If BRCA1/2 mutation status is known or becomes known for a patient during the study, this information will be recorded in the CRF either at screening or at later visits. No BRCA1/2 testing is required for this study.

21. **Urinalysis:** Dipstick is acceptable. Microscopic analyses must be performed if dipstick is abnormal.

22. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a urine or serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy, once at the start of screening and once at the baseline visit, immediately before study treatment administration. Urine pregnancy tests will also be routinely repeated at every treatment cycle during the active treatment period, at the end of study therapy and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations. See Section 4.3.1 for contraception guidelines.

23. **12-Lead ECGs:** All patients require a triplicate ECG measurement at screening. On-treatment ECGs will be performed on Day 1 of Cycles 1, 2, and 3 pre-infusion and Day 15 of Cycle 1. At each time point, three (3) consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart (within 10 minutes) to determine mean QTc (average of triplicates). In Cycle 4 and subsequent cycles, a single ECG should be taken pre-dose on Day 1. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. It is recommended that ECGs are performed prior to any blood collection or other invasive procedures. If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.

24. **ECHO/MUGA for LVEF (**multiple gated acquisition (MUGA) or echocardiogram (ECHO)**:** An ECHO/MUGA must be performed for all patients during screening. The same assessment technique should be performed throughout the study.

25. **PK Sampling for avelumab (all patients in Arm A and Arm B):** Blood samples (3.5 mL) for avelumab PK will be collected in all patients: pre-dose and at the end of infusion (immediately before the end of avelumab infusion) on Days 1 and 15 of Cycles 1 to 4. Pre-dose samples should be collected on Days 1 of Cycles 5, 6, 9, 12, 15, 18, 21 24; at the End of Treatment and at Day 30 Safety Follow-up visit Do not collect blood from the same arm being infused. See Section 7.3.

26. **PK Sampling for doxorubicin (PLD samples) (18 patients each, Arm B and Arm C only):** Serial blood samples (3 mL) for PLD PK will be collected in 18 patients in each arm, pre-dose, immediately prior to end of infusion, and at 2, 6, 24, and 336 hours (Day 15) post start-infusion of PLD on Day 1 of Cycle 2. Do not collect blood from the same arm being infused. See Section 7.3.

27. Blood for Avelumab Immunogenicity Testing (anti-avelumab antibodies (ADA); neutralizing antibodies (NaB) (Arm A and Arm B only): All ADA samples (3.5 mL) should be drawn within 2 hours before the start of the avelumab infusion on Day 1 of Cycles 1-4. Thereafter, a sample will be collected on Day 1 prior to avelumab infusion in Cycles 5, 6, 9, 12, 15, 18, 21 24 and at the End of Treatment. An additional sample for ADA must be collected at 30 days after the last dose of avelumab. Samples positive for ADA may be analyzed for neutralizing antibody (Nab). Do not collect blood from the same arm being infused.

28. **Randomization:** Patient number allocation via interactive response technology (IRT) operated by Pfizer Inc. Following informed consent, patients who complete baseline studies and are eligible for randomization should start study treatment within 3 days of randomization.

29. **Study Treatment**: Described in the Study Treatments section. Arm A: Avelumab will be given as a 1-hour intravenous infusion every 2 weeks. In the PLD + avelumab arm (Arm B), PLD will be administered on Day 1 of each cycle and on that day it will be administered first before the avelumab infusion. Also in Arm B avelumab will be given on Day 15 of each cycle. Arm C: PLD will be given on Day 1 of each cycle. Weight should be collected prior to each infusion, assessed and documented in the CRF. There is a plus or minus 3 day window for PLD and avelumab administration but for avelumab there should not be less than 10 days between doses. See Section 5.2.3.

30. **Premedications:** For additional information about premedications for PLD and avelumab, see Section 5.2.3.1 and Section 5.2.3.3.

31. **Tumor Assessments***:* Tumor assessments will include all known or suspected disease sites. Tumor assessments must include chest, abdomen and pelvis CT or MRI scans and will be conducted every 8 weeks until documented disease progression as assessed by BICR regardless of subsequent anti-cancer therapy. Brain scans will be performed at baseline only if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases. A bone scan (bone scintigraphy) or ^{18}FDG-PET/CT is required at baseline only if disease is suspected and then every 16 weeks only if bone metastases are present at baseline. Otherwise, bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of CR confirmation for patients who have bone metastases. MRI is acceptable for bone imaging if consistent with local practice. CT or MRI scans to be done every 2 cycles (every 8 weeks) (window of 5 days prior to dosing is allowed) throughout the study. In case partial response (PR), complete response (CR) or Progressive Disease (PD) is observed according to RECIST v.1.1 (Appendix 3) CCI [redacted] confirmation CT or MRI should be performed no sooner than 4 weeks after the first documentation of response. Tumor assessment should be repeated at the End of Study visit if more than 4 weeks have passed since the last evaluation. All radiographic images will be collected and will be objectively verified by a BICR independent third-party core imaging laboratory as described in Study Manual. See Section 7.6 for additional information.

32. **Patient-Reported Outcome Questionnaire:** EORTC QLQ-C30, EORTC QLQ-OV28, and EQ-5D-5L are to be administered on Day 1 of Cycle 1, Day 1 of each subsequent cycle, End of Treatment/Withdrawal Visit and the 30, 60 and 90 day Safety Follow-up visits prior to any study or medical procedure. See Appendix 6.

33. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded in the CRF. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version (v) 4.03 will be used. (Appendix 5) See Section 8.2 for Reporting Period details.

34. **Concomitant Treatments:** All concomitant medications and Non-Drug Supportive Interventions should be recorded in the CRF. See Section 5.4 for additional information.

35. **Mandatory FFPE Tumor Tissue:** A mandatory archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue block must be provided that is of sufficient size to allow for sectioning of ten (10) 5-micron tissue sections. If an FFPE tumor tissue block cannot be provided, sites should provide, preferably, fifteen (15), but a minimum of ten (10), unstained slides each containing a 5-micron tissue section cut serially from the same FFPE block. If tissue from multiple surgeries is available, the most recent specimen should be submitted. If archived FFPE tissue is not available, a de novo (ie, fresh) tumor sample **must** be obtained in accord with local institutional practice for tumor biopsies. Archived or de novo tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) is not adequate and should not be submitted. See Sections 6.1.1 and Section 7.4.

36. **De Novo Tumor Tissue:** In addition to the archival specimen a de novo (ie, fresh biopsy) tumor sample must be collected prior to enrollment unless clinically contraindicated. An optional de novo tumor sample is encouraged to be collected at End of Treatment if a patient discontinues due to disease progression. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. See Section 6.1.1 and Section 7.4.1.

37. **Banked Blood Biospecimens:** Blood biospecimens will be collected from patients at Screening (4 mL) and 20.5 mL will be collected before the start of the first infusion on Cycle 1, Day 1 and Day 15; Cycle 2, Day 1; Cycle 3, Day 1; and at End of Treatment. The biospecimens will be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. Patients also have the choice to allow these specimens to be used in research on additional topics. See Sections 7.5.1 and 7.5.2.

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1. INTRODUCTION

1.1. Indication

Avelumab* is a fully human monoclonal antibody of the immunoglobulin (Ig) G1 isotype that is currently being investigated in patients with Platinum-resistant/refractory epithelial ovarian, fallopian tube, or primary peritoneal cancer.

1.2. Background and Rationale

1.2.1. Ovarian Cancer

Ovarian cancer is the leading cause of death from gynecologic cancer and the fifth most common cause of cancer mortality in women. The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life. The median age at the time of diagnosis is 63 years, and 70% of patients present with advanced disease.[3] Although expectations for long-term survival can be very high if the cancer is identified and treated early, the women diagnosed with advanced ovarian cancer continue to have less than 30% 5-year survival.[54]

Ovarian neoplasms consist of several histopathological entities. Epithelial ovarian cancer (EOC) comprises the majority of malignant ovarian neoplasms (about 80%);[4] however, other less common pathologic subtypes must be considered in treatment recommendations. Fallopian tube cancer and primary peritoneal cancer are managed in a similar manner to epithelial ovarian cancer.

Patients are considered to have platinum-sensitive disease if they respond to first-line platinum therapy and experience a relapse-free period of greater than 6 months following the last dose of platinum therapy. Platinum-resistant disease is defined by relapse between 0 to 6 months after the last platinum dose. Platinum-refractory disease is defined by lack of response to platinum-based chemotherapy or recurrence prior to completion of platinum-based therapy.[46]

There are no highly effective therapies in the platinum-resistant/refractory population, although non-platinum-related agents have demonstrated modest antitumor efficacy in a subset of these patients. Frequently, these patients have declining performance status and bowel dysfunction. Drugs that have demonstrated activity in ovarian cancer include taxanes (paclitaxel, docetaxel, nab-paclitaxel), topoisomerase 1 and 2 inhibitors (topotecan, liposomal doxorubicin, and etoposide), epothilones (ixabepilone and ZK-EPO), alkylators (hexamethymelamine and ifosfamide), and antimetabolites (pemetrexed and gemcitabine). For management of resistant disease, these drugs are used as single agents in sequence and have demonstrated response rates in the range of 10% to 20% with median times to progression of 3 to 4 months.[46] In 2014, bevacizumab plus chemotherapy was approved in

* Avelumab is the proposed International Nonproprietary Name (INN) for the anti-PD-L1 monoclonal antibody (MSB0010718C)

European Union (EU) and US in combination with paclitaxel, pegylated liposomal doxorubicin (PLD), or topotecan, for the treatment of patients with platinum-resistant recurrent ovarian cancer. This approval was based on results of the AURELIA study, which randomized patients to physician's choice of chemotherapy (PLD, paclitaxel, or topotecan) with or without bevacizumab, and included patients with more than one prior line of platinum based chemotherapy. This study demonstrated improvement in median progression-free survival (PFS) from 3.4 months to 6.7 months (HR=0.48, 95 % CI: 0.38 to 0.60, p<0.001). No statistically significant improvement in OS was seen.[5] In 2014, olaparib, a (Poly ADP ribose polymerase) PARP inhibitor, was approved for the treatment of patients with advanced Breast Cancer Angtigen (BRCA)-mutated ovarian cancer by European Medical Authority (EMA) and Federal Drug Administration (FDA).[6]

Single-agent PLD has been extensively studied in platinum-resistant ovarian cancer, with response rates of 10-20%, median PFS times of 2.1-3.7 months, and median OS ranging from 8.4 to 16.8 months.[20,21,22,23,24,25] The approved dose of PLD in the US and EU is 50 mg/m^2 intravenously every 4 weeks; however, 40 mg/m^2 every 4 weeks is commonly used in clinical practice and in clinical trials including the AURELIA study.[25]

1.2.2. Pharmaceutical and Therapeutic Background

1.2.2.1. Avelumab (MSB0010718C)

The investigational product in the present clinical trial is avelumab (MSB0010718C), a fully human monoclonal antibody of the immunoglobulin (Ig) G1 isotype.

Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-1. Compared with anti-PD-1 antibodies, that target T cells, avelumab targets tumor cells and therefore, is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the PD-L2/PD-1 pathway intact to promote peripheral self-tolerance.[2] For complete details of the in vitro and nonclinical studies, refer to avelumab Investigator's Brochure (IB).[1]

Avelumab is currently in clinical development with 2 ongoing Phase 1 studies in patients with solid tumors and a Phase 2 study in patients with Merkel cell carcinoma.

Trial EMR100070-001(conducted by Merck KGaA/EMD Serono (EudraCT number 2013-002834-19, NCT01772004)) is a Phase 1, open-label, multiple-ascending-dose trial to investigate the safety, tolerability, pharmacokinetics, biological, and clinical activity of avelumab in patients with locally advanced or metastatic solid tumors. This trial consisted of 2 parts, a dose-escalation phase and a dose-expansion phase, which is performed in selected tumor indications. Avelumab was administered intravenously at the assigned dose level as a 1-hour intravenous (IV) infusion once every 2 weeks. The following dose levels were investigated: 1.0 mg/kg, 3.0 mg/kg, 10.0 mg/kg, and 20.0 mg/kg.

As of 05 November 2014, a total of 50 patients were treated in the dose-escalation phase of the trial, with 4 patients being treated with 1 mg/kg avelumab, 13 patients being treated with 3 mg/kg avelumab, 13 patients being treated with 10 mg/kg avelumab, and 20 patients being treated with 20 mg/kg avelumab. None of the patients treated with doses up to 10 mg/kg experienced a dose-limiting toxicity (DLT), and the 10 mg/kg dose of avelumab was thus considered a safe and well-tolerated dose for further investigation in the dose-expansion cohorts. One DLT (Grade 3 AE) was observed in 1 patient at a dose of 20 mg/kg. This was an immune-related AE with creatine kinase increased, myositis, and myocarditis.

Eleven (11) expansion cohorts are ongoing, including an expansion cohort in EOC (see below). Four hundred and eighty (480) patients have been enrolled and treated as of the data cutoff date, 05 November 2014, with the recommended dose of 10 mg/kg avelumab once every 2 weeks.

1.2.2.2. Safety

Of the 480 patients treated in the pooled expansion cohort, 218 (45.4%) experienced at least 1 Grade ≥3 Treatment Emergent Adverse Event (TEAE), and 330 (68.8%) had treatment-related TEAEs, of whom 59 (12.3%) had Grade ≥3 treatment-related TEAEs.

The most frequently reported (incidence ≥5% in the pooled expansion cohort) treatment-related TEAEs (any grade) in the pooled expansion cohort are summarized in Table 1. The most frequently reported (occurring in at least 2 patients in the pooled extension cohort) Grade ≥3 treatment-related TEAEs in the pooled expansion cohort are presented in Table 2.

Table 1. Most Frequently Reported (Incidence ≥5% in the Pooled Expansion Cohort) Treatment-Related Treatment-Emergent Adverse Events (TEAEs) in the Pooled Expansion Cohort (Any Grade)

MedDRA PT	Pooled Expansion Cohort Patients (n=480) n (%)
Number of patients with at least 1 TEAE	330 (68.8%)
Fatigue	97 (20.2%)
Nausea	62 (12.9%)
Infusion related reaction	47 (9.8%)
Chills	33 (6.9%)
Diarrhea	33 (6.9%)
Decreased appetite	30 (6.3%)
Pyrexia	27 (5.6%)
Influenza like illness	25 (5.2%)
Arthralgia	24 (5.0%)

Table 2. Most Frequently Reported (in ≥2 Patients in the Pooled Expansion Cohort) Grade ≥3 Treatment-Related TEAEs in the Pooled Expansion Cohort

MedDRA PT	Pooled Expansion Cohort Patients (n=480) n (%)
Number of patients with at least 1 TEAE	59 (12.3%)
Anemia	5 (1.0%)
Fatigue	5 (1.0%)
Gamma-glutamyltransferase increased	4 (0.8%)
Infusion related reaction	4 (0.8%)
Lipase increased	4 (0.8%)
Lymphocyte count decreased	3 (0.6%)
Autoimmune hepatitis	2 (0.4%)
Constipation	2 (0.4%)
Dyspnea	2 (0.4%)
Hypertension	2 (0.4%)
Hypokalemia	2 (0.4%)
Hypoxia	2 (0.4%)
Pneumonitis	2 (0.4%)
Vomiting	2 (0.4%)

Overall, 176 of the 480 patients (36.7%) treated in the dose expansion cohorts had serious TEAEs. Of these, 22 (4.6%) patients experienced dyspnea, 19 patients (4.0%) disease progression, 12 patients (2.5%) pleural effusion, 11 patients (2.3%) pneumonia, 8 patients respiratory failure (1.7%) and 7 patients (1.5%) anemia. All other serious TEAEs were each reported in less than 1.5% of patients. Of the serious TEAEs considered treatment-related by the Investigator (31 patients; 6.5%), the following were reported for 2 or more patients: infusion-related reaction (4 patients, 0.8%), pneumonitis (3 patients, 0.6%), and disease progression, dyspnea, and hypercalcemia (2 patients each, 0.4%).

As of 05 November 2014, 134 patients (27.9%) treated in the dose expansion cohorts died, mostly due to disease progression (101 deaths; 21.0%). In 4 patients (0.8%), the primary cause of death was attributed to an AE related to study treatment and in 8 patients (1.7%) to an AE unrelated to study treatment. The reason for 13 (2.7%) deaths was "unknown" and for 8 (1.7%) was "other." Of the 134 patients who died, 53 patients (11.0%) died within 30 days following the last administration of trial treatment. Overall there were (14%) patients who experienced treatment related AEs with fatal outcome; in 4 patients the treatment-related AE was reported as the primary cause of death as noted above. These 7 cases with AEs related to study treatment included: pneumonitis radiation induced and dyspnea; acute liver failure associated with autoimmune hepatitis (no biopsy/autopsy performed); disease progression; fatal anoxic brain injury after cardiac arrest; autoimmune hepatitis with hepatic failure and fatigue (no biopsy/autopsy performed); respiratory distress and sepsis; and acute respiratory failure, acute exacerbation chronic obstructive pulmonary disease (COPD), and leukocytosis (occurred after the end of the on-treatment period).

Eighty (80) patients (16.7%) treated in the dose expansion cohorts withdrew permanently from trial treatment due to one or more TEAE. In 34 (7.1%) of these patients, the TEAEs leading to treatment discontinuation were considered related to trial treatment by the Investigator. These TEAEs were infusion-related reaction (8 withdrawals; 1.7%), Gamma

glutamyl transferase (GGT) increased and rash (3 withdrawals each, 0.6%), and aspartate aminotransferase increased, blood creatine phosphokinase increased, and disease progression (2 patients each, 0.4%); or other events led a single patient to discontinue trial treatment.

Immune-related Adverse Events: As of 05 November 2014, a cumulative review revealed 56 patients of potential immune-related AEs in the 480 patients (11.7%) treated in the dose expansion part of trial EMR 100070-001, and 4 of 50 patients (8.0%) treated in the dose escalation part of trial EMR 100070-001, for a total of 69 events. Of these 69 events, 46 events (67%) were assessed as treatment-related by the Investigator and 23 events (33.3%) were assessed as not treatment-related by the Investigator. Twenty-six (26) events were assessed as Grade 1, 29 events as Grade 2, 11 events as Grade 3, 2 events as Grade 4, and 1 event had fatal outcome (radiation pneumonitis) (note: 2 events of suspicion of autoimmune hepatitis, not confirmed by biopsy, assessed as Grade 3 had a fatal outcome).

Infusion-Related Reactions: Two unexpected serious adverse reactions (SUSARs; anaphylactic reaction and infusion-related reaction) involving 2 patients were reported in December 2013 and triggered a cumulative review of serious and non-serious cases of infusion-related reactions/hypersensitivity across the avelumab program. Following evaluation of safety signals, infusion-related reactions/hypersensitivity have been classified as a newly identified risk (previously classified as a potential risk) and a mandatory premedication regimen of a histamine H1 receptor (H1) blocker plus acetaminophen was implemented for all trial patients starting 29 January 2014.

As of 05 November 2014, 49 (10.2%) of the 480 patients in the expansion cohort experienced at least 1 episode of an infusion-related reaction when receiving avelumab monotherapy. Most of the events were Grade 1 (8 patients, 1.7%) or Grade 2 (36 patients, 7.5%) in intensity, and Grade 3 (3 patients, 0.6%) or Grade 4 events (2 patients, 0.4%) were less frequent. No Grade 5 events were reported from the infusion-related reactions. Most of the infusion-related reaction events had an onset after the first (30 patients, 6.3%) or second (16 patients, 3.3%) avelumab infusion. In 8 patients (1.7%), avelumab treatment was discontinued because of infusion-related reaction events. In addition, 1 patient (2.0%) in the dose escalation cohort reported an infusion-related reaction event (Grade 2).

Starting from 29 January 2014, a mandatory premedication with H1 blockers plus acetaminophen was implemented for all patients who are to receive avelumab. This premedication procedure was applied to 28/50 patients in the dose escalation phase and to 440/480 patients in the pooled treatment expansion cohort. Under this premedication procedure, 33 of 440 patients (7.5%) in the expansion cohort experienced infusion-related reaction events, with 6 patients (1.4%) having Grade 1, 26 patients (5.9%) having Grade 2, and 1 patient (0.2%) having Grade 3 events. No infusion-related reaction events were reported in the 28 patients in the dose escalation cohort.

In addition to the aforementioned patients, one case of Grade 4 cardiac arrest occurred 1.5 hours after the third infusion of avelumab (10 mg/kg). The patient died due to an anoxic brain injury 7 days later; no autopsy was performed.

Guidelines for the management of infusion-related reactions and severe hypersensitivity reaction are found in Section 5.2.7.2. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) and can be found at https://www.resus.org.uk/pages/reaction.pdfhttps://www.resus.org.uk/pages/reaction.pdfhttps://www.resus.org.uk/pages/reaction.pdf.

1.2.2.3. Pharmacokinetics

Pharmacokinetics following the first 1-hour infusion and dose proportionality of avelumab have been characterized in 57 Caucasian patients treated in the dose escalation and expansion cohort of Study EMR 100070-001 by standard non-compartmental analysis. This analysis revealed that the exposure parameters of C_{max} and AUC_{τ} increased in a dose proportionate fashion across the 1, 3, 10 and 20 mg/kg doses. Apparent half-life tended to increase with dose, likely due to target mediated disposition at lower doses, but terminal half-life of 10 and 20 mg/kg doses were similar (106-134 hours). This likely indicates that target mediated elimination does not increase at these two doses and target occupancy is very high.

Target occupancy on peripheral blood CD3+ T cells was investigated in human blood in vitro by flow cytometry after spiking of whole blood samples from eight healthy volunteers with avelumab over a concentration of 0.003-10 μg/mL. Fifty percent (50%) receptor occupancy was observed at a drug concentration of 0.122 μg/mL ±0.042 μg/mL with a plateau indicating at least a (95% receptor occupancy reached in all blood samples at 1 μg/mL. PK profiles obtained from the dose escalation phase of Trial EMR 100070-001 found all patients at 10 mg/kg dose reached or exceeded the serum level (median C_{trough} 20-37 ug/mL) of avelumab required for >95% TO. For patients treated with 3 mg/kg of avelumab, 10 of 13 patients reached the required serum level (3.7- 8.3 ug/mL).

1.2.2.4. Efficacy and Safety in Patients with Ovarian Cancer

Single-agent avelumab activity at 10 mg/kg Q2W was evaluated in heavily pretreated epithelial ovarian cancer (EOC) patients in an ovarian-specific expansion cohort in Study EMR100070-001. Patients with ovarian cancer whose disease progressed on standard therapy were eligible. 75 patients were enrolled from Nov 2013 to Nov 2014. Median age was 62 years (range 38-84 years); ECOG performance status was 0 (41%) or 1 (59%); median number of prior therapies for locally advanced or metastatic disease (excluding adjuvant treatment) was 4 (range, 0-10). At the data cutoff of February 13, 2015, median duration of treatment with avelumab was 12 weeks (range 2-54 weeks), and 8 patients remained on treatment. Eight patients (10.7%, 95% CI, 4.7%, 19.9%) achieved an unconfirmed best objective response (BOR) of partial response (PR). Five out of 8 responses were ongoing at the time of data cutoff. Thirty-three (44%) patients had stable disease. Two additional patients had partial response by immune-related response criteria. Median progression-free survival was 11.4 weeks.

Avelumab was well-tolerated in the ovarian cancer expansion cohort (n=75). Table 3 demonstrates treatment-related adverse events observed in ≥5% of patients. The following Grade 3 avelumab-related adverse events were observed in a total of 6 patients (8.0%): one event each of peripheral edema, localized edema, increased lipase, increased blood creatine phosphokinase, arthritis, myositis, hyperglycemia, anemia, tumor pain. There were no Grade 4 or 5 AEs related to avelumab reported in this cohort. Related serious TEAEs were observed in 3 patients (4.0%): Dyspnea (1), pyrexia (1), non-cardiac chest pain (1), flushing (1), localized edema (1), and peripheral edema (1). Immune-related TEAEs were seen in 8 patients (10.7%) and included hypothyroidism (5; 6.7%), arthritis (2; 2.7%), and myositis (1; 1.3%). No drug-related intestinal obstruction or perforations occurred. Discontinuation related to treatment with avelumab was reported in 9 patients (12.0%) [Pfizer/Merck KGaA data on file, cutoff 13 February 2015].[45]

Table 3. Avelumab Treatment Related Adverse Events (Incidence ≥5%) in the Ovarian Cancer Cohort

Events (n=75)	Treatment-Related AEs, all grades*, n (%)
Any event	52 (69.3)
Fatigue	12 (16.0)
Chills	9 (12.0)
Nausea	8 (10.7)
Diarrhea	8 (10.7)
Infusion-related reaction	6 (8.0)
Rash	6 (8.0)
Vomiting	4 (5.3)
Constipation	4 (5.3)
Hypothyroidism	4 (5.3)

Source: Table 15.3.1.5C.

Complete information for avelumab may be found in the single reference safety document (SRSD), which for this study is the avelumab Investigator's Brochure.[1]

1.2.2.5. Peglyated Liposomal Doxorubicin

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from Streptomyces peucetius var. caesius which has been available since the 1960s. Its main mode of action is to bind with topoisomerase II and DNA, forming a complex which results in lethal double-stranded DNA breaks.[25] Pegylated liposomal doxorubicin (PLD) (trade names Doxil®, Caelyx®) is a formulation of liposomal doxorubicin coated in polyethylene glycol (PEG). This hydrophilic coating protects the liposomes from detection by the body's reticular endothelial system, reducing the rate at which the active substance is broken down, and increasing its circulating half-life compared with conventional doxorubicin.[25]

PLD displayed linear pharmacokinetics over the range of 10 to 20 mg/m^2. Relative to PLD doses at or below 20 mg/m^2, the pharmacokinetics of total PLD following a 50 mg/m^2 PLD dose are nonlinear. At this dose, the elimination half-life of PLD is longer and the clearance lower compared to a 20 mg/m^2 dose. Converse to the pharmacokinetics of doxorubicin, which displays a large volume of distribution (700-1100 L/m^2), the steady-state volume of distribution of PLD is restricted to the vascular fluid volume. The major metabolite of

doxorubicin, doxorubicinol, was detected at negiligible levels in patients who received 10 or 20 mg/m^2 PLD.[16]

The most common toxicities of PLD (>20%) are asthenia, fatigue, fever, anorexia, nausea, vomiting, stomatitis, diarrhea, constipation, hand-foot syndrome, rash, neutropenia, and anemia.[16] Acute Infusion-Related Reactions occur occurred in 11% of patients with solid tumors. Serious, life-threatening, and fatal infusion reactions have been reported. PLD can cause myocardial damage, including congestive heart failure. The risk of cardiotoxicity is 11% when the lifetime cumulative anthracycline dose (not limited to PLD) approaches 450-550 mg/m^2.

Single-agent PLD has been extensively studied in platinum-resistant ovarian cancer, demonstrating an objective response rate (ORR) of 10-20%, median PFS of 2.1-3.7 months, and OS ranging from 8.4 to16.8 months.[20,21,22,23,24,25]

Complete information for PLD may be found in the single reference safety document (SRSD), which for this study is the Caelyx SmPC.

1.2.3. Study Rationale

Programmed death ligand 1 (PD-L1 also called B7-H1 or CD274) and its receptor, PD-1, have a known role in the suppression of T-cell responses. The PD-1 receptor is expressed on activated CD4+ and CD8+ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals to inhibit T-cell function.[7,8,9]

Tumors including ovarian cancer present with various rates of somatic (or genetic) mutations.[11,12] These genetic alterations result in expression of proteins that are “different from self” on cancer cells which may act as antigens enhancing the ability of the host immune system to recognize tumor cells as foreign and stimulate T cell response.[13] However, tumors elude immune surveillance through the expression of PD-L1 in the tumor microenvironment.[17] Several antibodies blocking PD-1 and PD-L1 demonstrated significant and durable response in patients with cancer.[51]

Clinical activity of nivolumab, a PD-1 antibody, was observed in a Phase 2 study in patients with advanced or relapsed, platinum–resistant ovarian cancer. In heavily pretreated patients (median number of prior therapies was >4), an ORR of 17% (3 of 18 patients) was observed.[15]

Avelumab (MSB0010718C), a fully human antibody of the immunoglobulin G1 (IgG1) isotype, specifically targets and blocks PD-L1, the ligand for PD-1 receptor. In preclinical studies, combination of avelumab with chemotherapies showed improved anti-tumor activity.[1] Preliminary data from the ongoing ovarian cancer Study EMR 100070-001, which is being conducted by Merck KGaA/EMD Serono (EudraCT number 2013-002834-19, NCT01772004) showed an ORR of 10.7% (8/75) and stable disease in an additional 44% (33/75) of patients with advanced ovarian cancer.

Certain chemotherapy agents, including doxorubicin, have been shown to have immunostimulatory properties.[52] Preclinical evaluation of breast tumor and sarcoma responses to anthrcyclines suggested that immune mechanisms contribute to tumor growth inhibition.[50] In addition, expression of genes such as CD8α, CD8β, and IFN-γ correlated with response to anthracycline chemotherapy in breast cancer patients.[50] Enhanced exposure of tumor antigens as a result of tumor cell kill may enhance the activity of immune checkpoint blockade.[47] In preclinical studies, combination of avelumab with chemotherapies showed improved anti-tumor activity of chemotherapy (gemcitabine, oxaliplatin, 5FU).[1]

Taken together, these observations suggest that combination of anthracyclines with avelumab may provide added clinical benefit relative to either agent alone.[51] PLD has proven activity in platinum resistant/refractory ovarian cancer,[20,25] and is therefore appropriate to combine with avelumab in ovarian cancer patients.

1.2.4. Rationale for Starting Doses of Avelumab and PLD

1.2.4.1. Avelumab Starting Dose and Regimen

In this clinical trial, the avelumab dose will be 10 mg/kg administered as 1-hour intravenous infusions every 2 weeks (Q2W). This dose is the recommended Phase 2 dose based on experience from 480 patients in the ongoing dose-expansion phase of Study EMR 100070-001 (see Section 1.2.2.1 for details). This dose is well tolerated, and signs of antitumor activity, including durable responses, have been observed across various solid tumors, including ovarian cancer. See Section 5.2.3.3 for premedication details.

1.2.4.2. PLD Starting Dosing Regimen

The approved dose of PLD in the US and EU is 50 mg/m^2 intravenously 4 weeks; however, 40 mg/m^2 every 4 weeks is commonly used in clinical practice and in clinical trials.[25] This latter dose is associated with significantly reduced frequencies of adverse events, particularly hand-foot syndrome, and a lower frequency of dose reductions with a similar objective response rate.[46,53] The dose of 40 mg/m^2 was used in the AURELIA study which formed the basis of approval of bevacizumab in platinum-resistant ovarian cancer.

In this clinical trial, the PLD dose will be 40 mg/m^2 every 4 weeks. The first infusion will be administered at 1 mg/min to minimize the risk of infusion reactions. If no infusion-related reaction is observed, subsequent PLD infusions may be administered over a 60-minute period. See Section 5.2.3.1 for premedication details.

1.3. Summary of Benefit/Risk Assessment

An evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of Directive 2001/20/EC (cf. Article 6(3)(b) of Directive 2001/20/EC) has been conducted.

Available adverse event and laboratory abnormality data from patients with advanced solid tumors treated with single-agent avelumab suggest an acceptable safety profile of the compound. Most of the observed events were either in line with those expected in patients with advanced solid tumors or with similar class effects of monoclonal antibodies blocking the PD-1/PD-L1 axis. Infusion-related reactions including hypersensitivity and immune

related Adverse Events (irAEs)/autoimmune disorders have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this clinical trial protocol. These include a treatment algorithm and guidelines for treatment interruption and discontinuation in case of irAEs, as well as mandatory pre-treatment with a histamine H1 receptor (H1) blocker and acetaminophen. Avelumab demonstrated clinical activity in heavily pretreated ovarian cancer patients in an expansion cohort of an ongoing Phase 1study.

Chemotherapy including doxorubicin has recently been shown to have immunostimulatory properties.[52] In preclinical studies, combination of avelumab with chemotherapies showed improved anti-tumor activity of chemotherapy (gemcitabine, oxaliplatin, 5FU).[1]

PLD is approved multinationally for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy. PLD is generally well-tolerated with a well-characterized toxicity profile. Currently there are no published reports of doxorubicin combined with immune checkpoint inhibitors. The literature suggests a low possibility of overlapping toxicities for avelumab and PLD. Close safety monitoring will be performed throughout the study as outlined in Section 3.1.

Thus, the projected benefit/risk of avelumab given in combination with PLD is anticipated to be favorable for investigation in this advanced cancer patient population.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objectives

- To demonstrate that avelumab given alone or in combination with PLD is superior to PLD alone in prolonging OS in patients with platinum -resistant/platinum-refractory ovarian cancer.

- To demonstrate that avelumab given alone or in combination with PLD is superior to PLD alone in prolonging Progression Free Survival (PFS) in patients with platinum-resistant/platinum-refractory ovarian cancer.

Secondary Objectives

- To evaluate anti-tumor activity of avelumab given alone or in combination with PLD versus PLD alone in ovarian cancer patients.

- To evaluate the overall safety profile of avelumab alone or in combination with PLD versus PLD alone in ovarian cancer patients.

- To characterize the PK of doxorubicin (PLD samples) and avelumab when administered in combination, and to assess the effect of avelumab on the PK of doxorubicin (PLD sample) and the effect of PLD on PK of avelumab.

- To assess the immunogenicity of avelumab.
- To evaluate candidate predictive biomarkers of sensitivity or resistance to avelumab or PLD in combination with avelumab in pre-treatment tumor tissue, that may aid in the identification of patient subpopulations most likely to benefit from treatment.
- To compare the effect of avelumab alone or in combination with PLD versus PLD alone on patient-reported outcomes (PRO) in patients with ovarian cancer.

Exploratory Objectives

CCI

[redacted]

2.2. Endpoints

Primary Endpoints

- Overall survival (OS).
- Progression Free Survival as determined by Blinded Independent Central Review according to RECIST version 1.1.

Secondary Endpoints

- Efficacy: Objective response (OR), Duration of Response (DR), and Disease Control (DC) as determined by Blinded Independent Central Review (BICR) and Investigator [As assessed by RECIST version 1.1]. (Appendix 3).
- PFS as determined by Investigator according to RECIST version 1.1.
- Safety: AEs (as graded by NCI CTCAE v.4.03); laboratory abnormalities (as graded by NCI CTCAE v.4.03); vital signs (blood pressure, pulse rate); electrocardiograms (ECGs), ECHO or MUGA scans.
- Pharmacokinetics: PK parameters, including C_{trough} and C_{max} for avelumab, C_{max}, volume of distribution (V_d), clearance (CL), area under the concentration-time curve (AUC) for doxorubicin (PLD samples).

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- Immunogenicity: Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against avelumab.

- Candidate predictive biomarkers in tumor tissue including, but not limited to, PD-L1 expression and tumor infiltrating CD8+ T lymphocytes as assessed by immunohistochemistry (IHC).

- Patient-Reported Outcomes: EORTC QLQ-C30, EORTC QLQ-OV28, and EQ-5D-5L. (Appendix 6).

Exploratory Endpoints

CCI [redacted]

- CA-125 levels.

CCI [redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 3, multicenter, randomized, open-label, parallel 3-arm study in which approximately 550 patients will be randomized in a 1:1:1 ratio to receive avelumab alone, avelumab in combination with PLD, or PLD alone, as follows:

- Arm A: avelumab alone;

- Arm B: avelumab plus PLD;

- Arm C: PLD alone.

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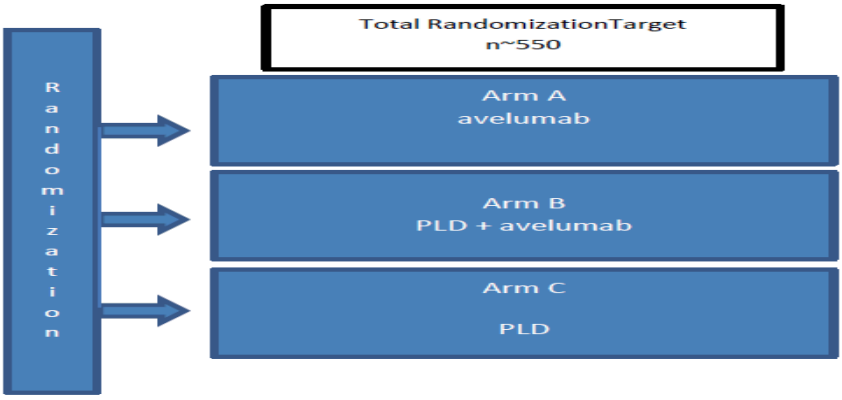
Figure 1. Study Randomization Design



Patients will be stratified by platinum-refractory or platinum-resistant status, number of prior regimens (1 vs 2 or 3), and bulky disease (defined as presence of a tumor ≥5 cm) vs not. Cross-over will not be permitted.

3.1.1. Safety Monitoring

An evaluation of the safety of the avelumab plus PLD arm will be performed during the study as follows:

Randomization to all three arms will begin at the start of the study. When six patients are randomized to the combination arm, enrollment in all arms will be held. After each patient in the combination arm has completed a minimum observation period of 4 weeks, the external data monitoring committe (DMC) will evaluate all available safety data. If there are no safety concerns precluding continuation of the study, enrollment will proceed. Other options may include termination of the combination arm, or enrollment of 6 more patients with an enrollment hold. These decisison will be at discretion of the DMC.

A second safety evaluation will be performed by the external DMC after a total of 20 patients are enrolled on the combination arm and followed for at least 4 weeks, without an enrollment hold. The frequency of subsequent DMC meetings will be determined by the external DMC at the time of the second safety evaluation.

3.1.2. Study Treatment

Avelumab (Arm A, Arm B) 10 mg/kg will be given as a 1-hour intravenous infusion (IV) every 2 weeks (Q2W) in 4-week cycles.

PLD (Arm B, Arm C) 40 mg/m^2 will be given as a 1-hour IV infusion every 4 weeks (Q4W) in 4-week cycles.

In Arm B, on the days that the patient receives both infusions, PLD should be administered prior to avelumab. See Section 5.2.3.3.

In all patients, study treatment may continue until PD as assessed by BICR, unacceptable toxicity, patient refusal, patient loss to follow up, or termination of the study by the Sponsor, whichever comes first (see Section 6.5 Patient Withdrawal). Avelumab may be continued beyond disease progression. PLD will not be continued beyond confirmed disease progression. See Section 5.2.4.

For administration information, see Section 5.2.3. Patients should be monitored closely for toxicity and infusion related reactions. For the management of infusion-related reactions and other toxicities, see Section 5.2.6.

Patients on Arm B who discontinue one study drug (avelumab or PLD) for reasons other than confirmed disease progression may continue the other study drug until withdrawal criteria are met. For details, see Section 5.2.4.

Patients without evidence of disease progression at the time of study treatment discontinuation should contine to undergo tumor assessment every 8 weeks until documented radiographic progressive disease, irrespective of the start of any new anticancer treatment. See Schedule of Activites (SOA) for details.

Patients who discontinue study treatment due to disease progression will be followed every 12 weeks for subsequent anti-cancer therapies and survival status until death or until study end. Additionally the following data will be collected: surgery, new anti cancer therapies including the date of initiation and discontinuation of each drug. These will be recorded in the case report form (CRF) until death, withdrawal of consent, or study end, whichever comes first.

3.1.3. Tumor Assessments

Tumor Assessment: Anti-tumor activity will be assessed by radiological tumor assessments at 8-week intervals until documented disease progression as assessed by BICR, using RECIST version 1.1, [redacted] CCI [redacted]. See Appendix 3, CCI [redacted] and Schedule of Activies (SOA) table.

For all patients radiologic tumor assessments must include chest, abdomen, and pelvis.

Complete responses, partial responses and progressive disease must be confirmed on repeated imaging at least 4 weeks after initial documentation. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not done in the previous 4 weeks). Brain CT or MRI scans are required at baseline **only** when there is a suspected brain metastasis. A bone scan (bone scintigraphy) or ^{18}FDG-PET/CT is required at baseline only if bone metastases are suspected, then every 16 weeks **only** if bone metastases are present at baseline. Otherwise, bone imaging is required only if new bone mestastases are suspected. Bone imaging is also required at the time of CR confirmation for patients who have bone metastases. MRI is acceptable for bone imaging if consistent with local practice.

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CA-125 will be assessed in a local lab every 4 weeks.

All patients' files and radiologic images will be collected for BICR assessment which will be the basis of the primary analysis for the primary endpoint (PFS).

3.1.4. Safety Assessments

Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits as described in the SOA table.

3.1.5. Biomarker Assessments

A key objective of the biomarker analyses that will be performed in this study is to investigate biomarkers that are potentially predictive of treatment benefit with avelumab or the combination of avelumab and PLD. In addition, biomarker studies of tumor and blood biospecimens will be carried out to help further understand the mechanism of action of the PLD plus avelumab combination, as well as potential mechanisms of resistance. See Section 7.4 for details.

3.1.6. Pharmacokinetics

Plasma/serum samples will be obtained from patients for PK analysis of doxorubicin (PLD samples) and avelumab. Sparse PK samples for avelumab PK will be collected from all patients treated with avelumab in the study (Arms A and B). Serial PK samples for PLD will be collected from 18 patients each in Arms B and C. Refer to the SOA and Section 7.3 for more information. Samples should be obtained from the opposite arm to the one being used for each drug IV infusion.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Histologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer, including malignant mixed Müllerian tumors with highgrade serous component.

2. Platinum-resistant/refractory disease, defined as disease progression within 180 days following the last administered dose of platinum therapy (resistant), or lack of response or disease progression while receiving the most recent platinum-based therapy (refractory), respectively.

3. Received up to 3 lines of systemic anticancer therapy for platinum-sensitive disease, most recently platinum-containing, and no prior systemic therapy for platinum-resistant disease.

4. Measurable disease by investigator assessment with at least 1 unidimensional measurable lesion by RECIST v.1.1 that has not previously been irradiated.

5. At least 18 years of age (≥20 years of age in Japan).

6. ECOG performance status (PS) 0 to 1.

7. Estimated life expectancy of at least 3 months.

8. Mandatory tumor biopsy must be performed prior to enrollment for all patients (unless there is a documented clinical contraindication). In addition, availability of archived FFPE tumor tissue should be confirmed. If a patient underwent tumor tissue collection within 3 months prior to enrollment with no intervening treatment, and the sample is provided, then a new *de novo* tumor biopsy is not required.

9. Adequate bone marrow function, including:

   a. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L;

   b. Platelet count ≥100 x 10^9/L;

   c. Hemoglobin ≥9 g/dL (may have been blood transfused).

10. Adequate liver function, including:

    a. Total bilirubin level ≤1.5 × the upper limit of normal (ULN).

    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN.

11. Adequate renal function as evidenced by:

    a. Creatinine clearance ≥50 mL/min as calculated using the Cockcroft-Gault equation.

12. Serum/urine pregnancy test (for females of childbearing potential) negative at screening.

13. Female patients, of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and after the last dose of assigned treatment for the following lengths of time.

    a. Patients who receive avelumab only: for at least 60 days after the last avelumab dose.

    b. Patients who receive PLD (alone or in combination with avelumab): for at least 6 months after the last PLD dose.

14. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

15. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Non-epithelial tumor, or ovarian tumors with low malignant potential (ie, borderline tumors).

2. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA 4) antibody (including ipilimumab, tremelimumab or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways).

3. Patients with PLD-resistant EOC, as evidenced by lack of response or progression within 6 months of the last dose of PLD.

4. Known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks prior to study entry and are neurologically stable.

5. Concurrent anticancer treatment within 28 days prior to study entry, eg, cytoreductive therapy, radiotherapy [with the exception of palliative radiotherapy], immunotherapy, or cytokine therapy (except for erythropoietin); major surgery within 28 days prior to study entry (excluding diagnostic biopsy); use of hormonal agents within 7 days prior to study entry; or use of any investigational drug within 28 days prior to study entry. Note: patients receiving bisphosphonate or denosumab are eligible provided treatment was initiated at least 14 days prior to study entry.

6. Diagnosis of any other malignancy within 5 years prior to registration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix.

7. Any one of the following currently or in the previous 6 months: myocardial infarction, congenital long QT syndrome, Torsades de Pointes, arrhythmias (including sustained ventricular tachyarrhythmia and ventricular fibrillation, bradycardia defined as <50 bpm), right bundle branch block and left anterior hemiblock (bifascicular block), unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF New York Heart Association Class III or IV), cerebrovascular accident, transient ischemic attack or symptomatic pulmonary embolism.

8. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥3, atrial fibrillation of any grade, or QTcF interval >470 msec at screening (average of triplicate ECG).

9. Left ventricular ejection fraction (LVEF) <50% by MUGA or echocardiography.

10. Prior anthracycline-related cardiotoxicity or prior anthracycline exposure approaching the lifetime limit.

11. Prior organ transplantation including allogeneic stem-cell transplantation.

12. Known history of a positive test for human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness.

13. Active infection requiring systemic therapy.

14. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).

15. Administration of a live vaccine within 30 days prior to study entry.

16. Current or prior use of immunosuppressive medication within 7 days prior to randomization. The following are exceptions to this exclusion criterion:

    a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);

    b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent;

    c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

17. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agents. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

18. Known severe hypersensitivity reactions to monoclonal antibodies or liposomal preparations. Known hypersensitivity to any component of the Investigational Products.

19. Persisting Grade ≥2 toxicity related to prior therapy; however, Grade 2 sensory neuropathy or alopecia is acceptable.

20. Severe gastrointestinal conditions such as clinical or radiological evidence of bowel obstruction within 4 weeks prior to study entry, uncontrolled diarrhea in the last 4 weeks prior to enrollment, or history of inflammatory bowel disease.

21. Other severe acute or chronic medical condition including pneumonitis, or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or

study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

22. Known current alcohol or drug abuse at the time of screening.

23. Pregnant or breastfeeding patients.

24. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

25. Current use or anticipated need for treatment with drugs or foods that are known strong CYP3A4 inhibitors, (eg, grapefruit juice or grapefruit/grapefruit-related citrus fruits (eg, Seville oranges, pomelos), ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan) or inducers (eg, rifampin, St. John's Wort, phenobarbital, and phenytoin) including their administration within 10 days prior to patient registration. The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

26. Current use or anticipated need for drugs that are known strong CYP2D6 inducers (eg, rifampin) or inhibitors (eg, bupropion, cinacalcet, fluoxetine, paroxetine and quinidine.and PgP inducers and inhibitors, including their administration with 10 days prior to patient registration.

4.3. Lifestyle Guidelines

4.3.1. Contraception

In this study, patients of child bearing potential will receive either avelumab, PLD or both. The effect of avelumab on reproduction is unknown. PLD can cause fetal harm when administered to pregnant women.

Patients of childbearing potential must agree to use two (2) methods of highly effective contraception throughout the study and continue for 60 days after the last dose of single agent avelumab (Arm A) and for 6 months after the last dose of PLD as single agent or in combination with avelumab (Arms C and B, respectively).

The investigator or his or her designee, in consultation with the patient, will select 2 appropriate methods of contraception for the individual patient and his/her partner from the list of permitted contraception methods (see below) and instruct the patients in their consistent and correct use. Patients need to affirm that they meet the criteria for correct use of at least 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use highly effective contraception consistently and correctly according to the SOA table and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately

if a selected contraception method is discontinued or if pregnancy is known or suspected in the patient.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

6. Female patients of non-childbearing potential must meet at least one of the following criteria:

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   - Have medically confirmed ovarian failure; or

   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.

   All other female patients (including females with tubal ligations) will be considered to be of childbearing potential.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Study Manual.

To facilitate access to appropriately qualified medical personnel regarding study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a contact

center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33). For the purpose of this study, the study treatments are PLD and avelumab (MSB0010718C).

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular patient or affect the order in which patients are enrolled.

Once the patient has provided a signed Informed Consent Form (ICF) and has met inclusion and exclusion criteria, the Investigator or delegate will request the study treatment assignment using the Interactive Response Technology (IRT) system. Qualified patients will be randomized in a 1:1:1 ratio to receive avelumab, alone (Arm A) or avelumab plus PLD, (Arm B) or PLD alone (Arm C).

Allocation of patients will be stratified by platinum-refractory or platinum-resistant status, number of prior regimens (1 vs 2 or 3), and bulky disease (defined as presence of a tumor ≥5 cm) vs not.

Allocation of patients to treatment arms will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, the patient number, and the patient's date of birth. The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number when drug is being supplied via the IRT system. The IRT system will provide a confirmation report containing the patient number and DU or container number assigned. The confirmation report must be stored in the site's files.

There is a 24-hour-a-day, 365-days-a-year IRT helpdesk available for any questions or issues. The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

Note: The IRT is the source of the patient number. The IRT system will provide the patient number at the end of the first IRT patient transaction.

5.2. Investigational Product Supplies

Clinical Trial supplies will be shipped to the study sites by Pfizer Global Clinical Supply (GCS), Worldwide Research and Development (WRD), and will include a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The Investigator shall take responsibility for and take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

5.2.1. Dosage Form(s) and Packaging PLD

5.2.1.1. PLD

PLD is a sterile, translucent, red liposomal dispersion in single intraveous (IV) use vials. Each vial contains doxorubicin HCl liposome at a concentration of 2 mg/mL. Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufactoring Practice (GMP) guidelines.

Pfizer GCS, WRD will provide either branded PLD or generic product available in local region. PLD may be sourced by study sites and reimbursed by the Sponsor through the contractual agreement with the study institution unless local regulations or other limitation require direct provision of PLD by the Sponsor.

PLD will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature monitoring devices.

5.2.1.2. Avelumab

Avelumab is a sterile, clear, and colorless solution intended for IV administration. Avelumab is formulated as a 20 mg/mL solution and is supplied by the Sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

Avelumab (MSB0010718C) will be supplied for the study by Pfizer GCS, WRD.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable GMP guidelines. Avelumab will be packed in boxes each containing one vial. The information on the study treatment will be in accordance with approved submission documents.

Avelumab will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature monitoring devices.

5.2.2. Preparation and Dispensing

See the Investigational Product Manual (IP Manual) for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic and investigational agents. Both PLD and avelumab will be administered at the investigational site. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.2.2.1. PLD Preparation

The appropriate dose of PLD must be diluted in 5% dextrose solution for infusion prior to administration. For doses up to 90 mg, dilute PLD in 250 mL, and for doses greater than or equal to 90 mg, dilute PLD in 500 mL.

Refer to the IP Manual for instructions on how to prepare the investigational product for administration. Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the IP Manual. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permits. Do not use if a precipitate or foreign matter is present. Do not use with in-line filters.

The dose amount required to prepare the PLD infusion solution will be based on the patient's body surface area (m^2). All patients should be weighed within 3 days prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the PLD dose can be in accordance with institutional practice. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated.

Dose capping should not be performed.[60]

The use of gloves is required. If PLD comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in PLD.

Vials are single-use. Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

Handle and dispose of PLD in accordance with recommendations for the handling and disposal of hazardous drugs as stated in the locally approved package insert.

5.2.2.2. Avelumab Preparation

The contents of the avelumab vials are sterile and nonpyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

For administration in this trial, avelumab must be diluted with 0.9% sodium chloride (normal saline solution). Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the IP Manual. Must use tubing with in-line, low protein binding 0.2 micron filter made of polyether sulfone (PES) during administration.

The dose amount required to prepare the avelumab infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the avelumab dose can be in accordance with institutional practice. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated.

Avelumab must not be used for any purpose other than the trial. The administration of trial drug to patients who have not been enrolled into the trial is prohibited. Vials are single-use. Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

5.2.3. Administration

All study treatments will be administered at the investigational site on an outpatient basis as detailed in the IP Manual.

5.2.3.1. PLD Administration

At the visits when both PLD and avelumab are infused (every 4 weeks), PLD will be infused prior to the administration of avelumab. There is no need for a window between the infusions. Adequate visit time should be scheduled for the patients on the combination arm. PLD may be administered up to 3 days before or after the scheduled day of administration of each cycle due to administrative reasons.

PLD will be administered at the starting dose of 40 mg/m^2 every 4 weeks, on Day 1 of each cycle. The first dose of PLD should be administered at an initial infusion rate of 1 mg/min. If no infusion-related adverse reactions are observed, subsequent PLD infusions may be administered over a 60-minute period. Do not rapidly flush the infusion line. Do not mix PLD with other drugs. Do not use with in-line filters.

In order to mitigate infusion-related reactions, a premedication regimen may be administered as per local practice, which may include diphenhydramine 25 to 50 mg IV or oral equivalent, and/or acetaminophen/paracetamol 650 mg IV or oral equivalent.

The locally approved package insert should be used for prescribing details, including the special precautions for patients who reach lifetime maximums of 450 mg/m^2.

5.2.3.2. Management of PLD Extravasation

Discontinue PLD for burning or stinging sensation or other evidence indicating perivenous infiltration or extravasation. Manage confirmed or suspected extravasation as follows:

- Do not remove the needle until attempts are made to aspirate extravasated fluid;
- Do not flush the line;
- Avoid applying pressure to the site;
- Apply ice to the site intermittently for 15 min 4 times a day for 3 days;
- If the extravasation is in an extremity, elevate the extremity.

5.2.3.3. Avelumab Administration

Avelumab will be administered at 10 mg/kg on Day 1 and Day 15 of each 4-week cycle after all procedures/assessments have been completed as described in the SOA table. Avelumab may be administered up to 3 days before or after the scheduled day of administration of each cycle due to administrative reasons but there should not be less than 10 days between doses.

Avelumab will be administered as a 1-hour IV infusion once every 14 days. In order to mitigate infusion-related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol IV or oral). This may be modified based on local treatment standards and guidelines, as appropriate.

When avelumab is administered alone, premedications should be administered 30-60 minutes before the infusion. For Arm B patients, on visits when both PLD and avelumab are infused (every 4 weeks) avelumab will be infused after PLD. If premedication was administered prior to PLD, the decision whether to repeat pre-medication prior to avelumab is at the discretion of the investigator depending on the elapsed time and the half-life of corresponding premedication agent. The line should be flushed, according to local practice, between infusions, and a new administration set should be used for avelumab.

Sites should make every effort to target avelumab infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 20 minutes is permitted (ie, infusion time is 50-80 minutes). The exact duration of infusion should be recorded in both source documents and CRFs. Possible modifications of the infusion rate for the management of infusion-related reactions are described in Section 5.2.6.

5.2.4. Treatment after Initial Evidence of Radiologic Disease Progression

Immunotherapeutic agents such as avelumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with PLD, and may manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows progression as assessed by BICR, PLD should be discontinued for patients on Arm B and C. For all patients tumor assessment should be repeated ≥4 weeks later in order to confirm progression. Single agent avelumab may be continued at the Investigator's discretion while awaiting radiologic confirmation of disease progression. If repeat imaging no longer shows PD but rather CR, PR, or SD compared to the baseline scan, treatment may be continued/resumed (additionally for patients in Arm B, PLD may also be resumed). In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions (refer to the Study Manual).

Before continuation of treatment, the patient must provide new consent and be informed that in order to continue receiving the investigational products on study, the patient may be foregoing approved therapy with possible clinical benefit(s). Patients may receive avelumab while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease by radiographic imaging.
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

If repeat imaging demonstrates confirmed evidence of PD, patients should be discontinued from all study treatment. However, according to the Investigator's clinical judgment and after discussion between the Investigator and the Sponsor, if a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with single agent avelumab if above criteria are met. The Investigator's judgment should be based on the overall benefit-risk assessment and the patient's clinical condition, including performance status, clinical symptoms, adverse events, and laboratory data.

5.2.5. Food Requirements

Both study drugs may be administered without regard to food.

5.2.6. Recommended Dose Modifications

Every effort should be made to administer study treatment on the planned dose and schedule.

In the event of significant toxicity, dosing may be delayed and/or dose reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom. In addition to dose modifications, investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below.

If a PLD dose reduction is necessary, the PLD dose should be reduced initially to 30 mg/m^2, and then down to 20 mg/m^2 if a second dose reduction is required. Management of patients requiring more than 2 PLD dose reductions should be discussed with the Sponsor. Do not increase PLD dose after a prior dose reduction due to toxicity.

Table 4. Dose Modifications for PLD

Dose Level	PLD
Starting dose	40 mg/m^2
First dose reduction	30 mg/m^2
Second dose reduction	20 mg/m^2

For avelumab, no dose modifications are permitted in this study, but doses may be omitted based on persisting toxicity.

For patients on avelumab plus PLD combination treatment, PLD dose modifications as well as infusion omissions/ delays for PLD and/or avelumab may occur independently for the two drugs according to the guidance provided below for each individual drug and investigator's medical judgment and will be reported in the CRF. If PLD is delayed by 1 week, avelumab should also be delayed by 1 week so that PLD and avelumab are administered together.

Some potential immune-related adverse events described with anti-PD-L1 drugs such as avelumab may overlap with PLD toxicities such as rash or diarrhea. For patients on avelumab or combination treatment with avelumab and PLD, any adverse event suspected to be immune-related should be managed according to the guidance for management of immune-related adverse events (Table 6 Avelumab: Management of Immune-related Adverse Events). In case of a potential irAE, besides the management related to avelumab therapy, PLD doses may also be modified or interrupted based on the guidance provided for PLD toxicity management (Section 5.2.8.2 PLD Infusion-related Reaction), product labeling, and institutional guidelines according to investigator's medical judgment.

Additional guidance for the management of avelumab-PLD combination is provided for Neutropenia and Thrombocytopenia (Table 7), Palmar-Plantar Erythrodysesthesia (Hand-Foot Syndrome) (Table 9), and Stomatitis (Table 10).

For toxicity management, the following tables should be referenced as appropriate.

Section 5.2.7.1	Avelumab: Adverse Drug Reactions Requiring Avelumab Discontinuation or Delays
Section 5.2.7.2.1	Avelumab: Special Precautions for Administration
Section 5.2.7.2 Table 5	Avelumab: Infusion Related Reactions
Section 5.2.7.2.2	Avelumab Severe Hypersensitivity Reactions and Flu like Symptoms
Section 5.2.7.2.3 Table 6	Avelumab: Immune related Adverse Events
Table 7	PLD and avelumab PLD combination: Treatment Modification for Neutropenia and Thrombocytopenia
Section 5.2.8.2 Table 8	PLD: Infusion-Related Reactions (Hypersensitivity Reactions)
Table 9	PLD and avelumab PLD combination: Treatment modification for Palmar Plantar Erythrodysesthesia Hand Foot Syndrome,HFS)
Table 10	PLD and avelumab PLD combination: Treatment modification for Stomatitis
Table 11	PLD: Treatment Modification for other Non-Hematologic Toxicities and Laboratory Abnormalities
Section 5.2.9	All patients: Treatment modification for Left Ventricular Ejection Fraction Decreased
Figure 2	Tumor Lysis Syndrome

5.2.7. Guidelines for Avelumab Toxicity Management

5.2.7.1. Avelumab: Adverse Drug Reactions Requiring Discontinuation or Delays

The following adverse drug reactions (ADRs) require permanent treatment discontinuation of avelumab:

Any Grade 4 ADRs require permanent treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.

Any Grade 3 ADRs require permanent treatment discontinuation of avelumab except for any of the following:

- Transient (≤6 hours) Grade 3 flu-like symptoms or fever, which are controlled with medical management.
- Transient (≤24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolve to Grade ≤1.
- Transient Grade 3 diarrhea (≤24 hours) that resolves to Grade 1 or less without administration of steroids.
- Single laboratory values out of normal range (excluding Grade ≥3 liver function test increase) that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤1 within 7 days with adequate medical management.
- Tumor flare phenomena defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Change in ECOG PS to ≥3 that resolves to ≤2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥3 on the day of trial drug administration).

For any Grade 2 ADR, avelumab dosing should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤1 prior to the next scheduled dose, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤1 prior to the next scheduled dose, infusions should be withheld. If by the following scheduled infusion the event has not resolved to Grade 1, the patient should permanently discontinue treatment (except for hematological toxicities and hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).
- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy or hematologic toxicities) in the same patient, treatment with avelumab has to be permanently discontinued.

Avelumab infusion-related reactions, hypersensitivity reactions (Grades 1 to 4), tumor lysis syndrome, and irAEs should be handled according to guidelines in Sections 5.2.7.2.1, 5.2.7.2.2, 5.2.10, respectively.

5.2.7.2. Avelumab: Infusion-related Reactions and Hypersensitivity Reactions

5.2.7.2.1. Avelumab: Special Precautions for Administration

In order to mitigate avelumab infusion-related reactions, a premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and 650 mg IV or oral equivalent acetaminophen/paracetamol (as per local practice) is mandatory approximately 30 to

60 minutes prior to each dose of avelumab. This may be modified based on local treatment standards and guidelines, as appropriate. See Section 5.2.3.3 for instructions for patients on combination treatment.

As with all monoclonal antibody therapies, there is a risk of allergic reactions including anaphylactic shock. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Infusion of avelumab will be stopped in case of Grade ≥2 infusion-related, allergic, or anaphylactic reactions. Following the first 4 avelumab infusions, patients must be observed for 2 hours post-infusion for potential infusion-related reactions. If no infusion reaction occurs in relation to the first 4 infusions, the post-infusion observation period may be discontinued. During this 2-hour observation period the patient should remain in a location where they can be observed by site staff. Vital sign measurements or other procedures are not required unless clinically indicated. If an allergic reaction occurs, the patient must be treated according to the best available medical practice. The emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Table 5. Avelumab: Treatment Modifications for Sypmtoms of Infusion-related Reactions

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease Avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 hours.	Stop Avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the Avelumab infusion immediately and disconnect infusion tubing from the patient. Patients have to be withdrawn immediately from Avelumab treatment and must not receive any further Avelumab treatment.

i.v.=intravenous, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.

Once the Avelumab infusion rate has been decreased by 50% due to an infusion-related reaction, it must remain decreased for all subsequent infusions.

Additional Modifications for Patients with Grade 2 Infusion-related Reactions

If, in the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 5 (including reducing the **infusion rate** by 50%), the investigator may consider treatment with corticosteroids and the infusion should be stopped for that day. At the next cycle, the investigator may consider the addition of H2-blocker antihistamines (eg, famotidine or ranitidine), in addition to the mandatory premedication. However, prophylactic steroids are NOT permitted. If the patient has a second infusion-related reaction ≥ Grade 2 on the slower infusion rate, with or without the addition of further medication to the mandatory premedication, the infusion should be stopped and the patient removed from avelumab treatment.

5.2.7.2.2. Avelumab: Severe Hypersensitivity Reactions and Flu-like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Symptoms include impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale or clammy skin, and cyanosis. These symptoms can be managed with epinephrine injection and dexamethasone. Patients should be placed on monitor immediately, and the ICU should be alerted for possible transfer if required.

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (for example, paracetamol) may be given to patients at the discretion of the investigator.

5.2.7.2.3. Avelumab: Immune-related Adverse Events

Because inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grades 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring.
- Grades 1 to 2 (persistent): manage similar to high grade AE (Grades 3 to 4).
- Grades 3 to 4: treat with high dose corticosteroids.

For patients receiving avelumab or avelumab-PLD combination, any event suspected to be immune-related should be managed according to the guidance for management of

immune-related adverse events in this Section 5.2.7.2.3 and Table 6. In case of a potential irAE, besides the management related to avelumab therapy, PLD doses may also be modified or interrupted based on the guidance provided for PLD toxicity management in Section 5.2.8.2, product labeling, and institutional guidelines according to investigator's best medical judgement.

Table 6. Avelumab: Management of Immune-related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: <4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (eg, loperamide)	Close monitoring for worsening symptoms Educate patient to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay avelumab therapy Symptomatic treatment	If improves to Grade 1: Resume avelumab therapy If persists >5 to 7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy per protocol. If worsens or persists >3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue avelumab therapy per protocol 1.0 to 2.0 mg/kg/day methlyprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month If persists >3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grades 1 to 2 Covering ≤30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue avelumab therapy	If persists >1 to 2 weeks or recurs: Consider skin biopsy Delay avelumab therapy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy

		If worsens: Treat as Grades 3 to 4
Grades 3 to 4 Covering >30% body surface area; life threatening consequences	Delay or discontinue avelumab therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume avelumab therapy
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grades 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grades 2 or 3 to 4
Grade 2 AST or ALT >3.0 to ≤5 x ULN and /	Delay avelumab therapy Increase frequency of	If returns to Baseline: Resume routine monitoring, resume avelumab

or total bilirubin >1.5 to ≤3 x ULN	monitoring to every 3 days	therapy If elevations persist >5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy
Grades 3 to 4 AST or ALT >5 x ULN and / or total bilirubin >3 x ULN	Discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Cardiac irAEs		
Myocarditis	**Management**	**Follow-up**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy Hospitalize in the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management Cardiology consult to establish etiology and rule out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* Methylprednisolone 1 to 2 mg/kg/day	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A)
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue avelumab therapy If TSH <0.5 x LLN, or TSH >2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal lab / pituitary scan: Delay avelumab therapy 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal lab/pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks/MRI in 1 month	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume avelumab therapy Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component.
Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue avelumab therapy Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

ADL=activities of daily living, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography; irAE=immune-related adverse event, IV=intravenous, LFT=liver function test, LLN=lower limit of normal, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event, anti-inflammatory drugs, T4=free thyroxine, TSH=thyroid-stimulating hormone, ULN=upper limit of normal.

5.2.8. Guidelines for PLD Single Agent and Avelumab-PLD Combination Toxicity Management

Dose modification (dose delays and dose change) for PLD due to ADRs should be made in accordance with the guidance provided below, product labeling and institutional guidelines. Starting dose for PLD and dose reduction levels are described in Table 4 Dose Modification for PLD.

5.2.8.1. PLD Single Agent and Avelumab-PLD Combination: Neutropenia and Thrombocytopenia

ANC must be ≥1.5 x 10^9/L and the platelet count ≥75 x 10^9/L prior to the beginning of the following course of treatment. For patients who do not achieve haematological recovery on scheduled day of PLD treatment, complete blood counts should be performed twice weekly until the above defined limits are achieved. If haematological recovery is achieved within 14 days after the scheduled day of PLD treatment, resume PLD at the previous dose. If haematological recovery is not achieved 14 days or more after the scheduled day of the course, the patient will discontinue treatment. Administration of G-CSF or EPO is permitted according to approved indications and scientific recommendations.

Table 7. PLD Single Agent and Avelumab-PLD Combination: Treatment Modification for Neutropenia and Thrombocytopenia

Neutropenia and Thrombocytopenia	PLD single agent	Avelumab-PLD combination*
Grade 1	No PLD dose reduction/delay	No PLD dose reduction/delay Continue avelumab as per schedule
Grade 2	Delay PLD until toxicity resolves to ANC ≥ 1.5 x 109/L, platelets ≥75 x 109/L; then resume PLD at previous dose.**	Delay PLD until toxicity resolves to ANC ≥1.5 x 109/L, platelets ≥75 x 109/L; then resume PLD at previous dose.** Continue avelumab as per schedule.
Grade 3	Delay PLD until toxicity resolves to ANC ≥1.5 x 109/L, platelets ≥75 x 109/L; then resume PLD at previous dose.** If Grade 3 toxicity recurs, follow institutional guidelines.	Delay PLD until toxicity resolves to ANC ≥1.5 x 109/L, platelets ≥75 x 109/L; resume PLD at previous dose.** Continue avelumab as per schedule. If Grade 3 toxicity recurs, delay PLD and avelumab until toxicity resolves to ANC ≥1.5 x 109/L, platelets ≥75 x 109/L; then resume PLD at reduced dose** and avelumab at standard dose. If Grade 3 toxicty recurs with PLD at reduced dose, delay PLD until toxicity resolves to ANC ≥1.5 x 109/L, platelets ≥75 x 109/L: then resume PLD at the next reduced dose. ** For avelumab, • If toxicity resolves to ANC ≥1.5 x 109/L, platelets ≥75 x 109/L within ≤14 days, resume avelumab at the standard dose. • If toxicity resolves to ANC ≥1.5 x 109/L, platelets ≥75 x 109/L in >14 days, permanently discontinue avelumab.
Grade 4	Delay PLD until toxicity resolves to ANC ≥1.5 x 109/L, platelets ≥75 x 109/L; then resume PLD at reduced dose level or continue at previous dose with prophylactic granulocyte growth factor support.**	Delay PLD and avelumab until toxicity resolves to Grade ≤1; then resume PLD at reduced dose level** and avelumab at standard dose. If Grade 4 toxicty recurs with PLD at reduced dose, delay PLD until toxicity resolves to ANC ≥ 1.5 x 109/L, platelets ≥75 x 109/L: then resume PLD at the next reduced dose.** For avelumab, • If toxicity resolves to ANC ≥1.5 x 109/L, platelets ≥75 x 109/L within ≤14 days, resume avelumab at the standard dose. • If toxicity resolves to ANC ≥1.5 x 109/L, platelets ≥75 x 109/L in >14 days, permanently discontinue avelumab.

* For patients on avelumab alone, refer to Section 5.2.7.1.

**If haematological recovery is achieved within 14 days after the scheduled day of PLD treatment, resume PLD at the previous dose. If PLD is delayed by 1 week, avelumab should be delayed by 1 week so that PLD and avelumab are administered together. If haematological recovery is not achieved 14 days or more after the scheduled day of the course, the patient will permanently discontinue treatment.

5.2.8.2. PLD: Infusion-Related Reactions (Hypersensitivity Reactions)

Serious and sometimes life-threatening infusion-related reactions characterized by one of more of the following symptoms can occur with PLD: flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension. The majority of the infusion-related events occur during the first infusion.

Ensure that medications to treat infusion-related reactions, and cardiopulmonary resuscitative equipment are available for immediate use prior to initiation of PLD. Initiate PLD infusion at a rate of 1 mg/min and increase rate as tolerated. In the event of an infusion-related reaction, temporarily stop the drug until resolution, then resume at a reduced infusion rate. Discontinue PLD infusion for serious or life-threatening infusion-related reactions.

In order to mitigate PLD infusion-related reactions, a premedication regimen as described in Section 5.2.3.1 may be administered.

PLD treatment modifications for infusion-related reactions are presented in Table 8.

Table 8. PLD Single Agent and PLD-avelumab Combination: Treatment Modification for PLD Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for PLD (both PLD single agent and PLD-avelumab combination*)
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Temporarily stop PLD until resolution then resume at a reduced infusion rate per local practice.**
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 hours.	Temporarily stop PLD until resolution then resume at a reduced infusion rate per local practice.**
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Permanently discontinue PLD infusion.**
* If PLD is delayed by 1 week, avelumab should be delayed by 1 week so that PLD and avelumab are administered together. ** Following Grade 1 or Grade 2 infusion reaction to PLD, PLD should be administered as follows: 5% of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion rate may then be completed over the next hour for a total infusion time of 90 minutes.	

5.2.8.3. PLD: Palmar-Plantar Erythrodysesthesia (Hand Foot Syndrome)

Table 9. PLD Single Agent and Avelumab-PLD Combination: Treatment modification for Palmar-Plantar Erythrodysesthesia (Hand-Foot Syndrome) (HFS)

NCI CTCAE Grade	PLD single agent	PLD-avelumab combination*
Grade 1: Mild erythema, swelling, or desquamation not interfering with daily activities	If no previous Grade 3 or 4 HFS: Continue PLD as planned. If previous Grade 3 or 4 HFS: delay PLD dose up to 2 weeks, then resume PLD at decrease dose level.	If no previous Grade 3 or 4 HFS: Continue PLD as planned. If previous Grade 3 or 4 HFS: delay PLD dose up to 2 weeks, then resume PLD at decrease dose level. Continue avelumab as per schedule.**
Grade 2: Erythema,desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter	Delay PLD dosing up to 2 weeks or until resolved to Grade ≤1. • If no resolution to Grade ≤1 within 2 weeks, discontinue PLD. • If resolved to Grade ≤1 within 2 weeks, and no previous Grade 3 or 4 HFS: continue PLD treatment at previous dose. • If resolved to Grade ≤1 within 2 weeks but previous Grade 3 or 4 HFS : resume PLD treatment at decreased dose level	Delay PLD dosing up to 2 weeks or until resolved to Grade ≤1. • If no resolution to Grade ≤1 within 2 weeks, discontinue PLD. • If resolved to Grade ≤1 within 2 weeks, and no previous Grade 3 or 4 HFS: continue PLD treatment at previous dose. • If resolved to Grade ≤1 within 2 weeks but previous Grade 3 or 4 HFS : resume PLD treatment at decreased dose level Delay avelumab until resolved to Grade ≤1 then resume avelumab. If Grade 2 event HFS recurs, delay avelumab until resolved to Grade ≤1; then and resume avelumab.
Grade 3: Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing	Delay PLD dosing up to 2 weeks or until resolved to Grade ≤1, then resume PLD treatment at decreased dose level. Discontinue PLD if there is no resolution after 2 weeks.	Delay PLD dosing up to 2 weeks or until resolved to Grade ≤1, then resume PLD treatment at decreased dose level. Discontinue PLD if there is no resolution after 2 weeks. Delay avelumab until resolved to Grade ≤1; then resume avelumab. If PLD treatment was permanently discontinued and Grade ≥3 HFS subsequently recurs, avelumab should also be permanently discontinued.
Grade 4: Diffuse or local process causing infectious complications, or a bed ridden state or hospitalization	Delay PLD dosing up to 2 weeks or until resolved to Grade ≤1, then resume PLD treatment at decreased dose level. Discontinue PLD if there is no resolution after 2 weeks.	Delay avelumab until resolved to Grade ≤1; then resume avelumab. If PLD treatment was permanently discontinued and Grade 4 HFS recur, avelumab should also be permanently discontinued.

* For PLD-avelumab combination, PLD dosing should be managed as per PLD guidance.

**If PLD is delayed by 1 week, avelumab should be delayed by 1 week so that PLD and avelumab are administered together.

5.2.8.4. PLD: Stomatitis

Table 10. PLD Single and Avelumab-PLD Combination: Treatment Modification for Stomatitis

NCI CTCAE Grade	PLD single agent	Avelumab-PLD combination*
Grade 1: Painless ulcers, erythema, or mild soreness	If no previous Grade 3 or 4 stomatitis: continue PLD as planned. If previous Grade 3 or 4 stomatitis: delay PLD up to 2 weeks then resume PLD at decreased dose level.	Continue avelumab as per schedule**
Grade 2: Painful erythema, edema, or ulcers, but can eat	Delay PLD dosing up to 2 weeks or until resolved to Grade ≤1. • If no resolution within 2 weeks discontinue PLD. • If resolved to Grade ≤1 within 2 weeks, and no previous Grade 3 or 4 stomatitis: resume PLD treatment at previous dose level. • If resolved to Grade ≤1 within 2 weeks, but previous Grade 3 or 4 stomatitis, resume PLD treatment at decreased dose level.	Delay avelumab until resolved to Grade ≤1, then resume avelumab. If Grade 2 stomatitis recurs delay avelumab until resolved to Grade ≤1; then resume avelumab.
Grade 3: Painful erythema, edema, or ulcers, and cannot eat	Delay PLD dosing up to 2 weeks or until resolved to Grade ≤1; thenresume PLD at decreased dose level If after 2 weeks there is no resolution, discontinue PLD.	Delay avelumab until resolved to Grade ≤1 then resume avelumab. If PLD treatment was permanently discontinued and Grade 3 stomatits recurs, avelumab should also be permanently discontinued.
Grade 4: Requires parenteral or enteral support	Delay PLD dosing up to 2 weeks or until resolved to Grade ≤1 then resume treatment at decreased dose level. If after 2 weeks there is no resolution, discontinue PLD.	Delay avelumab until resolved to Grade ≤1; then resume avelumab. If PLD treatment was permanently discontinued and Grade 4 stomatits recurs, avelumab should also be permanently discontinued.

* For PLD-avelumab combination, PLD dosing should be managed as per PLD guidance.

**If in the combination arm, PLD is delayed by 1 week, avelumab should be delayed by 1 week so that PLD and avelumab are administered together.

5.2.8.5. PLD: Other Non-Hematologic Toxicities and Laboratory Abnormalities

Table 11. PLD: Treatment Modification for Other Non-Hematologic Toxicities and Laboratory Abnormalities

Other non-hematologic toxicities and laboratory abnormalities	PLD
Grade 1	No PLD dose reduction
Grade 2	No PLD dose reduction
Grade 3	Delay PLD until toxicity resolves to Grade ≤1; then resume PLD at decreased dose level
Grade 4	Delay PLD until toxicity resolves to Grade ≤1; then resume PLD at decreased dose level

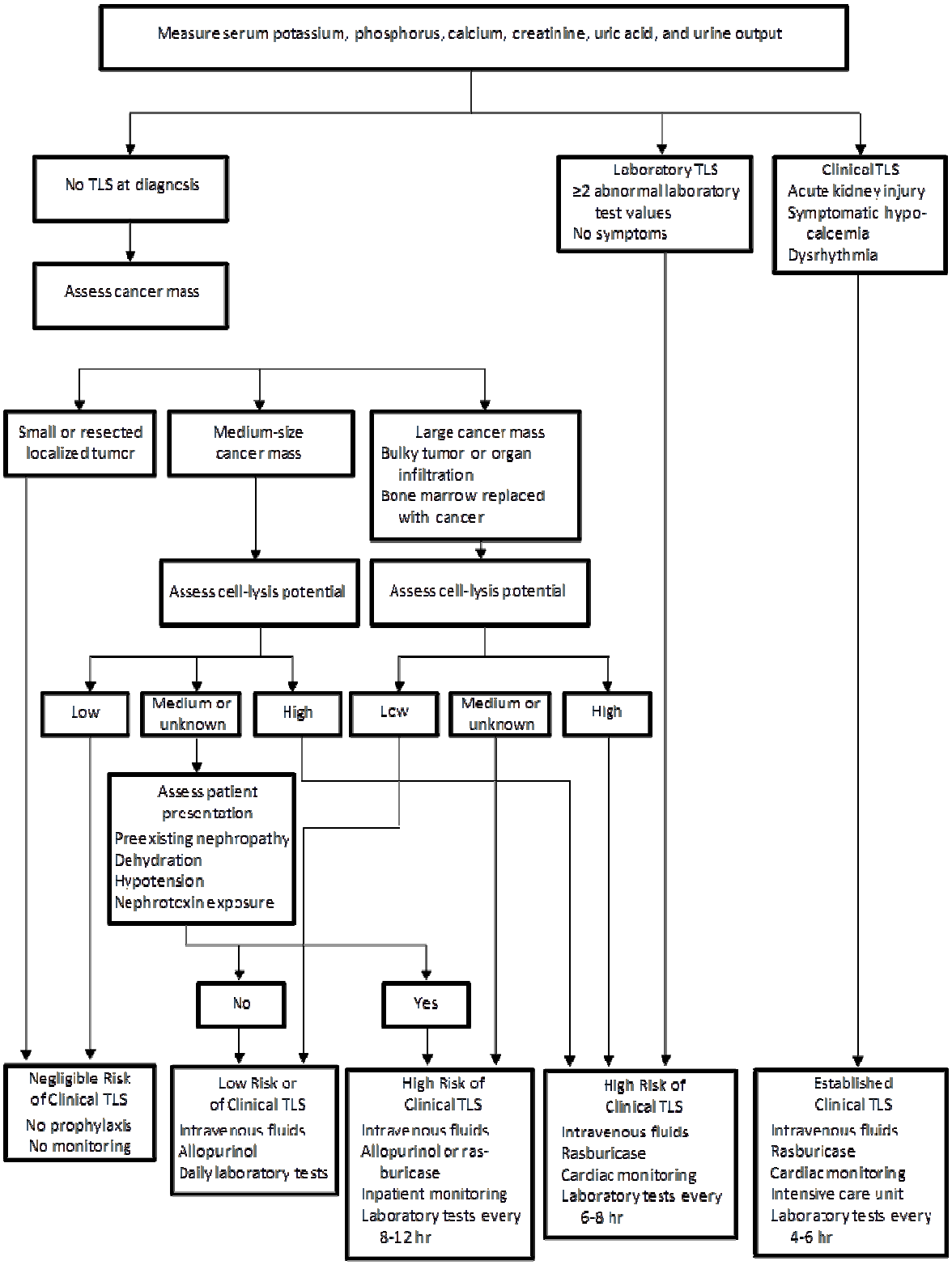
5.2.9. Left Ventricular Ejection Fraction Decreased

If a patient's LVEF drops below institutional limit of normal or by at least 15% (absolute percentage points) from baseline value, study treatment (avelumab, PLD or combination) should be discontinued. LVEF should be re-assessed within 45 days and every three months until full recovery. Upon full recovery, defined as LVEF increase to within 5% (absolute percentage points) of baseline within ≤45 days from LVEF nadir, study treatment (avelumab, PLD or combination) can be resumed at investigator's discretion. Continuation of treatment should be followed by additional LVEF evaluation within 2 weeks.

5.2.10. Tumor Lysis Syndrome

Tumor lysis syndrome should be treated per the local guidelines and the management algorithm published by Howard et al.[19]

Figure 2. Assessment and Initial Management of Tumor Lysis Syndrome



TLS=tumor lysis syndrome.

5.3. Drug Storage and Drug Accountability

5.3.1. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure avelumab and PLD are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

The Investigational Product should be stored in its original container and in accordance with the locally approved label.

- Refrigerate unopened vials of PLD at 2° - 8°C (36° – 46°F). Do not freeze. Handle and dispose of PLD consistent with recommendations for the handling and disposal of hazardous drugs.

- Avelumab must be stored in the refrigerator at 2° - 8°C (36° – 46°F). Do not freeze. Protect from light. Do not shake vigorously.

Storage conditions stated in the single reference safety document (SRSD) (Investigator Brochure) will be superseded by storage conditions stated in the labeling. Reference the locally approved label for PLD storage recommendations.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, must be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions must be reported upon discovery. The site must actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of the temperature range described in the labeling are not considered excursions.

All study drug supplies must be kept in a locked, limited access room. The study drug must not be used outside the context of this protocol. Under no circumstances should the Investigator or other site personnel supply study drug to other Investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from the Sponsor. The Investigator and or site staff must report any unacceptable condition of the investigational product to the site monitor.

5.3.2. Investigational Product Accountability

The Investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product. Pfizer may supply drug accountability forms that must be used or may approve use of standard institution forms. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a patient-by-patient basis, including specific dates and quantities.

The prescribed dose must be recorded in the patient's medical records. Drug dispensing needs to be verified and documented by a second individual and the forms must be signed by both the individual who dispensed the drug and the second individual who verified the dispensing. Copies must be provided to Pfizer.

At the end of the trial, or at appropriate points during the trial, Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction at the trial site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented. If drug destruction is not permitted locally, Pfizer should be contacted for further directions.

5.4. Concomitant Treatments

Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period, except for administration of inactivated vaccine(s).

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from study therapy may be required. The Investigator should consult with the Sponsor about individual cases. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the patient.

Concomitant treatment considered necessary for the patient's well-being may be given at discretion of the treating physician.

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications and Non-Drug Supportive Interventions should be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

The restrictions described within this paragraph apply to patients receiving PLD (Arm B and C) and should not be applied to patients receiving avelumab only (Arm A). Doxorubicin is a major substrate of cytochrome P450 CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4 (eg, ketoconazole, erythromycin, ciprofloxin), CYP2D6 (eg, paroxetine, fluoxetine, and/or P-gp (eg, verapamil), resulting in increased concentration and clinical effect of doxorubicin. Inducers of CYP3A4 (eg, phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin. Avoid concurrent use of doxorubicin with strong inhibitors and strong inducers of CYP3A4, CYP2D6, or P-gp.

5.4.1. Concomitant Radiotherapy

Local radiotherapy (limited field) of isolated lesions with palliative intent is acceptable and allowed throughout the study (ie, starting from the screening through end of treatment) if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. If palliative radiotherapy is needed to control pain, the site(s) of disease causing pain should be present at baseline; otherwise, painful lesion(s) requiring radiotherapy will be considered as a sign of disease progression. The sponsor's Medical Monitor should be consulted prior to starting radiotherapy and prior to restarting study treatment after the end of radiotherapy.

5.4.2. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

5.4.3. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first 4 weeks (1 cycle) of treatment but they may be used at any time to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.[42]

In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines. Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician.

5.4.4. Therapy for Nausea, Vomiting, and Diarrhea

Primary prophylaxis of nausea and vomiting is permitted for PLD according to institutional guidelines. The choice of the prophylactic drug is up to the investigator assuming the drug is not included in the Concomitant Treatment(s) section, as well as the duration of treatment assuming there is no known or expected drug-drug interaction. If so it must be approved by the sponsor.

Primary prophylaxis of diarrhea is not permitted.

5.4.5. Surgery

No formal studies of the effect of PLD or avelumab on wound healing have been conducted; however, caution is advised based on the mechanism of action. Of note, no surgical risk has been identified with immune checkpoint inhibitors. No surgical precautions are mentioned in pembrolizumab, nivolumab or atezolizumab product labels. If a major surgery or an interventional procedure (eg, endoscopy) is required, treatment with PLD or avelumab must be interrupted. Patients may resume PLD or avelumab 2-3 weeks after major surgery, assuming the wound has completely healed and there are no wound healing complications (eg, delayed healing, wound infection or fistula).

Avelumab treatment does not need to be delayed for minor surgical procedures that do not involve general anesthesia.

5.4.6. Other Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Investigational agents other than PLD and avelumab.
- Radiation therapy (with the exception noted above in the Concomitant Radiotherapy Section 5.4.1).
- Immunosuppressive drugs, unless otherwise indicated for the treatment of IrAEs (see Table 5. See below Clarification about Steroid Use.
- Any vaccine therapy for the prevention of infectious disease except for inactivated vaccines.
- Herbal remedies or vitamins used as anticancer treatments.Herbal remedies with immunostimulating properties (eg, mistle toe extract) or known to potentially interfere with major organ function (eg, hypericin).

Clarifications About Steroid Use: Data indicate that corticosteroids have an adverse effect on T cell function and that they inhibit and damage lymphocytes.[26,27] Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA-4 compounds indicate that short-term use of steroids may be employed without compromising clinical outcomes.[28] Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in Table 6 Avelumab Management of Immune-related Adverse Events; they are also permitted for any other medical condition requiring short-term use of steroids.

- Physiologic use: steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.

- Prophylactic use, eg, for the prevention of acute infusion-related reactions: is prohibited in the combination arm and in the avelumab-alone arm (steroid premedication for CT scan is permitted if needed).

- Prophylactic use of steroids for nausea/vomiting or for prevention of infusion-related reactions is permitted in the PLD alone arm.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5. Rescue/Escape/Salvage Medication

5.5.1. Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator including but not limited to the items outlined below:

- Diarrhea: All patients who experience diarrhea 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.

- Nausea/Vomiting: Nausea and vomiting should be treated aggressively in accordance with clarifications about steroid use in Section 5.4.6, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in Table 6 Avelumab Management of Immune-related Adverse Events.

- Anti-inflammatory or narcotic analgesics may be offered as needed. Acetaminophen/paracetamol to a maximum total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.

- Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, coumadin or other coumarin derivatives or other anticoagulants (including direct Xa inhibitors) may be allowed; however, appropriate monitoring of prothrombin time/international normalized ratio (PT/INR) should be performed.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures, see SOA table.

6.1.1. Tumor Biospecimens

A mandatory archived FFPE tumor tissue block must be provided that is of sufficient size to allow, if possible, for sectioning of ten (10) 5-micron tissue sections. If an FFPE tumor tissue block cannot be provided, sites should provide preferably, fifteen (15), but a minimum of ten (10) unstained slides each containing a 5-micron tissue section cut serially (and numbered accordingly) from the same FFPE block. If tissue from multiple surgeries is available, the most recent specimen should be submitted. If archived FFPE tissue is not available, a de novo (ie, fresh) tumor sample must be obtained in accordance with the details specified in the Study Manual. These biospecimens should be provided at the time of screening. Archived or *de novo* tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) is not adequate and should not be submitted.

In this study, archival tissue is expected to come from primary diagnosis, and may be months or years old. Therefore, in addition to archival FFPE tumor tissue block, a *de novo* (ie, fresh biopsy) tumor sample must be collected prior to enrollment unless clinically contraindicated. If a patient underwent tumor tissue collection within 3 months prior to enrollment with no intervening treatment, and the sample is provided, then a new *de novo* tumor biopsy is not required. An optional *de novo* tumor biospecimen is encouraged to be collected at End of Treatment if a patient discontinues due to disease progression. Assessments on the de novo biospecimens will mirror the assessments on the archival biospecimens to provide more data on tumoral and immunological changes which may occur over the course of therapy. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted.

The biopsy sample(s) should be formalin-fixed and paraffin-embedded as specified in the Study Manual, and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory. Additional information on tumor biospecimen collection procedures is included in the Study Manual.

Following informed consent, patients who complete baseline studies and are eligible for randomization should start study treatment within 3 days of randomization.

6.2. Study Period

For On-Treatment procedures, see SOA Table.

6.3. End of Treatment and Follow-up Visits

6.3.1. Safety

Safety follow-up visits will be scheduled up to 90 days after the last dose of study treatment.

6.3.2. Follow-upVisits

Patients who discontinue study treatment for reasons other than disease progression will be followed until documented disease progression regardless of the start of a new anti-cancer therapy. Tumor assessments should continue as specified in the SOA table every 8 weeks until disease progression is documented regardless of the start of new anti cancer therapies.

Patients will be followed every 12 weeks by telephone call for survival and subsequent therapies until death or the end of the study. The information collected for subsequent therapies should include details of the anti-cancer therapies, surgery, and date of initiation and discontinuation of each anti-cancer drug, and will be recorded in the CRF.

For End of Treatment and Follow-Up visit procedures, see SOA.

6.4. End of Study

The study will end when at least 196 OS events and 325 PFS events by BICR assessment have occured within each comparison.

For patients who remain on treatment at the end of study, a rollover study or another source of avelumab will be proposed.

6.5. Patient Withdrawal

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Reasons for discontinuation of study treatment may include:

- Objective disease progression confirmed by BICR. However, patients in Arms A and B with disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue with study treatment, provided that the treating physician has determined that the benefit/risk for doing so is favorable (see Section 5.2.4);
- Global deterioration of health status;

- Unacceptable toxicity. For patients receiving the avelumab-PLD combination, if the unacceptable toxicity is attributed to one of the two study drugs, the Investigator (in discussion with the Sponsor) may continue treatment with the other study drug;
- Pregnancy;
- Significant protocol deviation;
- Loss to follow-up;
- Refusal of further treatment (follow-up permitted by patient);
- Study termination by Sponsor;
- Death.

Patients must be withdrawn from the study in case of:

- Completed study follow-up;
- Study terminated by Sponsor;
- Lost to follow-up;
- Refusal of further follow-up;
- Death;
- If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the reason for withdrawal, request the patient to return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs;
- If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigatorthat may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the

safety and well being of the patient. When a protocol required test cannot be performed the Investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Safety Assessment

Safety assessments will include collection of AEs, Serious Adverse Events (SAEs), vital signs, and physical examination, ECG (12-lead), ECHO or MUGA, laboratory assessments, including pregnancy tests and verification of concurrent medications. Abnormal findings identified prior to first dose of study treatment should be documented in medical history.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study therapy - once at the start of screening and once at baseline visit immediately before the investigational product administration. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy test result will then be required at the baseline visit before the patient may receive the study treatment. Urine pregnancy tests will also be routinely repeated at every treatment cycle during the active treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive hCG test, the patient will be withdrawn from treatment but may remain in the study.

Additional pregnancy tests may also be undertaken if requested by Institutional Review Board/IRB/IECs or if required by local regulations.

7.1.2. Adverse Events

7.1.2.1. Adverse Events of Special Interest for Avelumab

- Any AE that is suspected to be a potential irAE is considered an AE of special interest (AESI). Specific guidance for the management of immune-related AEs is provided in Section 5.2.7.2.3 Table 6 Avelumab Management of Immune-related Adverse Events. AESIs are reported according to the general AE reporting rules specified in Section 8.2.

7.1.3. Laboratory Safety Assessments

Hematology, blood chemistry, and urinalysis will be collected at the time points described in the SOA and analyzed at local laboratories. They may also be performed when clinically indicated. The required laboratory tests are listed in Table 12. Chemistry and hematology results should be available for review prior to infusion of treatment.

Table 12. Required Laboratory Tests

Hematology	Hemoglobin Platelets WBC Absolute Neutrophils Absolute Lymphocytes Absolute Monocytes Absolute Eosinophils Absolute Basophils Percentages allowed only if Absolute not available
Chemistry (*denotes core chemistry panel)	ALT∗° AST∗° Alkaline Phosphatase∗° Sodium* Potassium∗ Magnesium∗ Chloride∗ Calcium∗ Total Bilirubin∗° BUN or Urea∗ Creatinine∗ Glucose (non-fasted) ∗ Phosphorus or Phosphate∗ Albumin∗° Total Protein∗ Uric Acid Amylase Gamma glutamyl transferase (GGT)° Cholesterol Creatine kinase° C-reactive protein (CRP) Lactate dehydrogenase (LDH) Lipase Triglycerides
Urinalysis	Protein, glucose, blood
Pregnancy Tests	For female patients of childbearing potential, serum or urine
Thyroid Function Tests:	TSH, free T4
Coagulation Tests	PT or INR° aPTT
Other Tests:	ACTH, HBV, HCV serology

° For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase.

ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, , aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, GGT=gamma-glutamyltransferase, HBV= hepatitis B virus, HCV= hepatitis C virus, INR=international normalized ratio, LDH=lactate dehydrogenase, TSH=thyroid-stimulating hormone, WBC=white blood cell

7.1.4. Vital Signs and Physical Examinations

Patients will have physical examinations to include major body systems,weight, blood pressure, pulse rate, assessment of ECOG performance status, and height (height will be measured at screening only) at the time points described in the SOA table. Blood pressure and pulse rate should be taken with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.Vital signs should be taken before any other assessments (eg, PK, laboratory blood draws,)

7.1.5. Electrocardiogram Measurements

A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs.

All patients require a triplicate ECG measurement at screening. On-treatment ECGs will be performed on Day 1 of Cycles 1, 2, and 3 pre-infusion and Day 15 of Cycle 1. At each time point, three (3) consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If a patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicateECGs should be obtained at time of the event. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.

To ensure safety, if there is a finding of QTc >500 msec (ie, CTCAE Grade >2), then ECG must be reviewed by qualified personnel at the site as soon as the finding is made, including verifying that the machine reading is accurate and that the Fridericia correction formula is applied. If manual reading verifies a rate corrected QTc of >500 msec, repeat ECG should be immediately performed at least two times approximately 2 to 4 minutes apart.

An electronic reading of prolonged QTc must be confirmed by manual reading. Prior to conclusion that an episode of prolongation of the QTc interval is due to study treatment, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist. If QTc interval reverts to less than 500 msec, and in the judgment of investigator and sponsor is determined to be due to a cause other than study treatment, treatment may be continued with regular ECG monitoring.

7.2. Patient-Reported Outcome Assessments

In the treatment of ovarian cancer it is important to increase survival and palliate symptoms as disease symptoms have a negative impact on health related quality of life.[29,30,31] To assess quality of life in clinical trials, patient-reported outcomes (PROs) are frequently measured to quantify changes in disease-specific symptoms, health-related concerns, and patient well-being. It is critical to assess the PROs using validated instruments.[32] In this trial, PROs will be assessed using published and validated instruments: EORTC QLQ-C30, EORTC QLQ-OV28, and EQ-5D-5L (Appendix 6).

7.2.1. EORTC QLQ-C30

The EORTC QLQ-C30 is a published, validated and self-administered patient reported outcome questionnaire.[33,34] The EORTC QLQ-C30 is a 30-question surbvey and includes 5 functional domain subscales, including a physical functioning sub-scale, a role functioning subscale, an emotional functioning sub-scale, a cognitive functioning sub-scale and a social functioning subscale. Higher scores on the functioning domains are indicative of higher levels of functioning. Oncology-related symptoms of the EORTC QLQ-C30 include fatigue (3 items), pain (2 items), nausea and vomiting (2 items), and dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact (1 item each). Higher scores are reflective of a greater presence of symptoms.

The EORTC QLQ-C30 questionnaire will be administered on the first day of each treatment cycle as well as upon End of Treatment/Study Withdrawal and Post-Treatment Safety Follow-up. The amount of time for a patient to complete the EORTC QLQ-C30 questionnaire is estimated to be about 10 minutes.

7.2.2. EORTC QLQ-OV28

The EORTC QLQ-OV-28 is the ovarian cancer-specific module of the EORTC quality of life questionnaire.[35,36] The EORTC QLQ-OV-28 is a 28 item instrument with seven (7) functional domain subscales. The 7 subscales include: (i) an abdominal/gastrointestinal symptom subscale (7 items); (ii) a peripheral neuropathy subscale (3 items); (iii) an other chemotherapy side effects subscale (7 items); (iv) a hormonal/menapausal symptoms subscale (2 items); (v) a body image subscale (2 items); (vi) an attitude to disease and treatment subscale (3 items) and (vii) a sexual function subscale (4 items). Similar to the EORTC QLQ-C30 higher scores are reflective of a greater presence of symptoms.

The EORTC QLQ-OV-28 questionnaire will be administered on the first day of each treatment cycle as well as upon End of Treatment/Study Withdrawal and Post-Treatment Safety Follow-up. The amount of time for a patient to complete the EORTC QLQ-C30 questionnaire is estimated to be about 10 minutes.

7.2.3. EQ-5D-5L

The EQ-5D-5L is a patient-completed questionnaire designed to assess health status in terms of a single index value or utility score.[37,38,39] There are 2 components to the EQ-5D-5L: a Health State Profile which has individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a Visual Analogue Scale (VAS) in which patients rate their overall health status from 0 (worst imaginable) to 100 (best imaginable). Published weights are available that allow for the creation of a single summary score.[39]

The EQ-5D-5L questionnaire will be administered on the first day of each treatment cycle as well as upon End of Treatment/Study Withdrawal and Post-Treatment Safety Follow-up. The amount of time for a patient to complete the EORTC QLQ-C30 questionnaire is estimated to be about 2 minutes.

7.3. Pharmacokinetic Assessments

Plasma/serum samples will be obtained from patients for PK analysis of doxorubicin (PLD samples) and avelumab. Sparse PK samples for avelumab PK will be collected from all patients treated with avelumab in the study (Arms A and B). Serial samples for doxorubicin PK analysis will be collected from 18 patients each in Arms B and C. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Study Manual.

7.3.1. Blood Sample Collection for Pharmacokinetic Analysis

Where noted in the SOA, blood samples will be collected at approximately the same time as other assessments wherever possible. Blood for PK samples should be taken from the contraleral arm of the IV infusion.

The SOA table indicates PK blood sampling time points for avelumab alone, PLD alone and PLD in combination with avelumab. For all collections, the actual time of PLD and avelumab dosing, as well as actual times of PK collections will be recorded in the source documents and CRF.

Blood samples for doxorubicin PK and avelumab PK will be collected as outlined in the SOA.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing.

However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) will be considered protocol compliant, and the exact time of the sample collection noted on the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample collection may be rescheduled with agreement of the investigator and sponsor.

At each time point for PLD, a3 mL whole blood sample will be collected at the designated times for doxorubicin PK analysis. At each time point for avelumab, 3.5 mL of whole blood will be collected at the designated times for avelumab PK analysis.

PK samples will be assayed for doxorubicin (PLD samples) and avelumab using validated analytical methods. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the study manual. As part of the understanding of the PK of the study drug, samples may be used for potential qualitative and/or quantitative metabolite analyses and/or evaluation of the bioanalytical methods for PLD and avelumab. The results of such analyses may be included in the clinical report.

7.3.2. Immunogenicity Assessment

Blood samples (3.5 mL) will be collected at the designated times for the evaluation of immunogenicity of avelumab. Blood samples for ADA asseements should be taken from the contraletral arm of the IV infusion. Immunogenicity blood samples will be assayed for anti

avelumab antibodies using a validated analytical method. All of the samples that are positive for ADA may also undergo characterization for neutralizing antibodies (NAb).

Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Study Manual.

7.4. Translational and Pharmacodynamic Assessments

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers that may have predictive value in identifying those patients who may benefit from treatment with the combination of avelumab and PLD. In addition, analyses of sequentially obtained blood biomarkers will provide an opportunity to investigate pharmacodynamic effects. Samples collected at the End of Treatment visit will also help understand potential acquired mechanisms of resistance to the drug combination.

7.4.1. Archived Tumor Biospecimens and De Novo Tumor Biopsies

Archived tumor tissue samples and *de novo* biopsies of primary and/or metastatic lesions (see Section 6.1.1) will be used to analyze candidate DNA, RNA, or protein markers, or relevant signature of markers for their ability to identify those patients who are most likely to benefit from treatment with the study drugs.

Markers that may be analyzed include, but may not necessarily be limited to, the presence/absence of tumor-infiltrating CD8+ T lymphocytes and/or expression of PD-L1, FoxP3, PD-1, PD-L2 within the tumor microenvironment by immunohistochemistry.

Optional tumor biopsies obtained upon disease progression (End of Treatment) may be assessed relative to the mandatory pre-treatment biospecimens to examine tumoral and immunological changes which may occur over the course of therapy, including acquired mechanisms of resistance. Only core needle, excisional biopsies, or resection specimens are suitable. Cytologic preparations, such as fine needle aspirate biopsies, are not acceptable. Additional information on tissue collection procedures can be found in the Study Manual.

7.4.2. BRCA 1/2 Mutation Status

BRCA1/2 germline mutational status will be collected when available at baseline, or when it becomes available during study participation. If results are not available, testing will not be mandated.

7.5. Banked Biospecimens

7.5.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA, RNA, protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker

analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited as such by local regulations or ethics committee decision.

To protect patients' confidentiality, the banked biospecimens and data generated from them will be coded with the patient's study identification (ID) number. Samples will be kept in a facility accessible only by badge-swipe. Data will be stored on password-protected computer systems. The key between the code and the patient's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Patients can withdraw their consent for the use of their biospecimens at any time by making a request to the Investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Patients are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the Investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the patient's medical record. There is no intention to contact patients after completion of the clinical trial.

CCI

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[redacted]

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CCI [redacted]

The banked biospecimens will be collected from all patients **unless prohibited by local regulations or ethics committee decision**. Detailed collection, processing, storage, and shipment instructions are provided in the laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Patients will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

7.5.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, patients will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical trial, and related conditions.
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; CCI [redacted]

Patients need not provide additional biospecimens for the uses described in this section; the biospecimens specified in Section 7.5.1 will be used. Patients may still participate in the clinical trial if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.6. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging must include chest, abdomen, and pelvis CT or magnetic resonance imaging (MRI) scans and will be conducted every 8 weeks until documented disease progression as assessed by BICR regardless of subsequent anti-cancer therapy. Brain CT or MRI scan at baseline is only required when there is suspected brain metastases or new lesion during the study. The CT scans should be performed with contrast agents unless contraindicated for medical reasons.

Bone scan (bone scintigraphy) or ^{18}F-FDG-PET/CT are only required at baseline if bone metastases are suspected, then every 16 weeks if bone metastases are present at baseline. Otherwise, bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of confirmation of complete response for patients who have bone metastases. MRI is acceptable for bone imaging if consistent with local practice.

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The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Antitumor activity will be assessed through radiological tumor assessments conducted at baseline (screening) and every 8 weeks thereafter until documented disease progression as assessed by BICR.

In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration) and at the time of withdrawal from the treatment (if not done in the previous 4 weeks). Complete, partial responses and progressive disease must be confirmed on repeated imaging ≥4 weeks after initial documentation. See SOA and Section 5.2.4 for treatment after initial evidence of disease progression.

Assessment of response will be made using RECIST version 1.1 (Appendix 3)CCI [redacted]

All patients' files and radiologic images will be collected for BICR.

7.7. Expedited Blinded Independent Central Review for Disease Progression

To mitigate the potential for bias in determining disease progression, expedited BICR will be performed for investigator-assessed disease progression. Upon investigator-assessed disease progression, all radiographic images collected for a patient from baseline onwards will be submitted to the BICR for expedited review. See the Study Manual for process details. Every effort should be made to keep the patient on study treatment until the BICR has completed their imaging review.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of study treatment or suspected causal relationship to the study treatment(s) will be reported as described in the following sections.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality. Follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical trial.

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8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the study treatment.

SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study treatment are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of study treatment through 90 calendar days after the last administration of the study treatment.

If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;

- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, at the wrong dosage strength, or inadvertent exposure. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the study treatment;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

The guidance on reporting of medication errors also applies to the reporting of overdose.

For purposes of this trial, overdose of avelumab or PLD is defined as any dose ≥5% over the calculated dose for that particular administration as described in this clinical trial protocol. Acute over dosage with PLD causes increased risk of severe mucositis, leukopenia and thrombocytopenia.

No specific information is available on the treatment of overdose of avelumab. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. The Study Manual contains

specific instructions for PLD dose calculation, reconstitution, preparation of the infusion fluid, and administration.

If a dose of avelumab meeting the protocol definition of overdose is administered without inducing any associated clinical symptoms or abnormal laboratory results, then the overdose is reported in CRF as a non-serious adverse event, using the terminology "accidental or intentional overdose without adverse effect". If the overdose is accompanied by an AE, as determined by the Investigator, the associated adverse event(s) has to be captured on an adverse event (AE) CRF page.

The IP Manual contains specific instructions for avelumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing outside of protocol-stipulated dose adjustments or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE (version 4.03) Grade 5 (see Section 8.8 on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

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

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the Investigator as described in previous sections, and will be handled as SAEs in the safety database (see Section 8.14.1 the section on SAE Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin values ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available.

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

- For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

- Concurrent with

  - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;

- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study treatment caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the Investigator does not know whether or not the study treatment caused the event, then the event will be handled as "related to study treatment" for reporting purposes, as defined by the Sponsor (see Section 8.14 Reporting Requirements). If the Investigator's causality assessment is "unknown but not related to study treatment", this should be clearly documented on study records.

In addition, if the Investigator determines an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

For combination treatment, causality assessment will be performed for each of the individual drugs included in the combination.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the study treatment; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the study treatment.

- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, due to environmental exposure) to the study treatment prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient becomes or is found to be pregnant during the study patient's treatment with the study treatment, the Investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event report form and an Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE has occurred. In addition, the Investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy, and its outcome for all EDP reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion.

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the Investigator assesses the infant death as related or possibly related to exposure to the study treatment.

Additional information regarding the exposure during pregnancy may be requested by the Investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (Also see Section 6.5 on Patient Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient/legal guardian/legally acceptable representative. In addition, each study patient/legal guardian/legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of Investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding cases and occupational exposure.

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the Investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines and/or illnesses must be provided. In the case of a patient death, a summary of available autopsyfindings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by Pfizer. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The primary objective of this study is to demonstrate that avelumab given alone or in combination with PLD is superior to PLD alone in prolonging OS or PFS in patients with platinum-resistant/refractory ovarian cancer.

The study is designed to test in parallel 4 hypotheses.

- The first null hypothesis is that the true OS hazard rate for PLD and avelumabalone arms are the same (HR=1) versus the alternative hypothesis that the true hazard rate is smaller in the avelumab alone arm than in the PLD alone arm (HR<1).

- The second null hypothesis is that the true OS hazard rate for PLD and avelumab in combination with PLD arms are the same (HR=1) versus the alternative hypothesis that the true hazard rate is smaller, in the avelumab in combination with PLD arm than in the PLD-alone arm (HR<1).

- The third null hypothesis is that the true PFS hazard rate for PLD and avelumab alone arms are the same (HR=1) versus the alternative hypothesis that the true hazard rate is smaller in the avelumab alone arm than in the PLD-alone arm (HR<1).

- The fourth null hypothesis is that the true PFS hazard rate for PLD and avelumab in combination with PLD arms are the same (HR=1) versus the alternative hypothesis that the true hazard rate is smaller in the avelumab in combination with PLD arm than in the PLD-alone arm (HR<1).

Approximately 550 patients will be randomized using a 1:1:1 randomization, stratified by platinum-refractory or platinum-resistant status, number of prior regimens (1 vs 2 or 3), and bulky disease (defined as presence of a tumor ≥5 cm) vs not.

The study or an experimental arm is planned to stop early for futility or efficacy only if the associated criteria are met for both PFS and OS. The sample size is hence determined based on the following assumptions.

- OS

It is assumed that the median OS for patients receiving PLD is 12 months,[24] and that treatment with avelumab alone or avelumab in combination with PLD is expected to increase the median OS to 20 months, corresponding to a hazard ratio (HR) of 0.6 under the exponential model assumption. The sample size further assumes a 5% drop-out rate within each arm, a non-uniform patient accrual over a 19-month period and minimum follow-up of 12 months after the last patient is randomized.

If the true HR is 0.6 under the alternative hypothesis, 196 OS events within each comparison will be required to have 90% power to detect a HR of 0.6 using a one-sided log rank test at a significance level of 0.0115 (overall significance level in the study one-sided 0.025), and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-10) β-spending function to determine the non-binding futility boundary

- PFS

It is assumed that the median PFS for patients receiving PLD is 3.5 months,[24] and that treatment with avelumab alone or avelumab in combination with PLD is expected to increase the median PFS to 5.8 months, corresponding to a hazard ratio (HR) of 0.6 under the exponential model assumption. The sample size further assumes a 15% drop-out rate within each arm, and non-uniform patient accrual over a 19-month period and minimum follow-up of 12 months after the last patient is randomized.

If the true HR is 0.6 under the alternative hypothesis, 325 PFS events by BICR assessment within each comparison will provide 93% power to detect a HR of 0.6 using a one-sided log rank test at a significance level of 0.001 (overall significance level in the study one-sided 0.025), and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming)

α-spending function to determine the efficacy boundary and a Gamma Family (-10) β-spending function to determine the non-binding futility boundary.

9.2. Analysis Population

9.2.1. Full Analysis Set

The full analysis set will include all patients who are randomized. Patients will be classified according to the treatment and stratum assigned at randomization. The full analysis set will be the primary population for evaluating all efficacy endpoints and patient characteristics.

9.2.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least 1 dose of study treatment (ie, avelumab or PLD). Patients will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) are received throughout the dosing period in which case patients will be classified according to the first treatment received. The safety analysis set will be the primary population for evaluating treatment administration/compliance and safety.

9.2.3. PK Analysis Set

The PK concentration analysis set is a subset of the safety analysis set including patients who have at least 1 concentration above the below limit of quantitation (BLQ) of either of the study drugs.

The PK parameter analysis set is a subset of the safety analysis set including patients who have at least 1 of the PK parameters of interest of either of the study drugs.

9.2.4. Immunogenicity Analysis Set

The immunogenicity analysis is a subset of the safety analysis set including patients who have at least 1 ADA sample collected.

9.2.5. Biomarker Analysis Set

The biomarker analysis set is a subset of the safety analysis set including patients who have at least one screening biomarker assessment. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

9.3. Efficacy Analysis

All efficacy analyses will be performed on the Full Analysis Set unless otherwise specified. Some efficacy analyses will also be performed on the Safety Analysis Set.

All analyses will be performed by using SAS® Version 9.1.3 or higher.

All secondary endpoints based on radiological assessments of tumor burden (ie, PFS, OR, DR, DC) will be derived using the local radiologist's/investigator's assessment. Radiographic images and clinical information collected on study will also be reviewed by a

BICR to verify investigator reported tumor assessments. This information will be used for supportive analyses, except for PFS whose assessment by BICR is a primary endpoint.

Sensitivity analyses will be described in the SAP.

9.3.1. Analysis of Primary Endpoints

9.3.1.1. Overall Survival

OS is defined as the time from the date of randomization to the date of death due to any cause. Patients last known to be alive will be censored at date of last contact.

The primary analyses of OS will be performed based on the Full Analysis Set. A stratified log-rank test (one-sided) stratified by stratification factors described in Section 3 will be used within each comparison at the interim and/or final analyses with the overall significance level preserved at 0.0115 (one-sided). OS time associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratios and the corresponding 95% CI.

OS will also be evaluated based on the safety analysis set as a supportive analysis, using a stratified log-rank test (one-sided, α=0.0115).

9.3.1.2. Progression Free Survival by BICR Assessment

PFS is defined as the time from randomization to the date of the first documentation of objective progression of disease (PD) or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), for patients who start new anti-cancer treatment prior to an event, or for patients with an event after two or more missing tumor assessments. Patients who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the day of randomization, with a duration of 1 day, unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

The primary analyses of PFS will be performed based on BICR assessment using the Full Analysis Set (FAS). A stratified log-rank test (one-sided) stratified by stratification factors described in Section 3 will be used within each comparison at the interim and/or final analyses with the overall significance level preserved at 0.001 (one-sided). PFS time will be summarized by treatment arm using the Kaplan-Meier method and displayed graphically where appropriate. CIs for the 25th, 50th, and 75th percentiles of the event-free time will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratios and the corresponding 95% CI.

PFS will also be evaluated based on a per-protocol analysis set (a subset of the safety analysis set including patients who have measurable disease at baseline per BICR assessment and have no key deviations from the protocol expected to impact PFS) as supportive analysis, using a stratified log-rank test (one-sided, α=0.001). The full criteria for the per-protocol analysis set will be pre-specified in the Statistical Analysis Plan.

9.3.2. Analysis of Secondary Endpoints

The secondary efficacy endpoints and associated analyses described below will be analyzed in the FAS. All analyses except PFS analysis will be performed using investigator's assessment, as well as the review of the BICR. PFS will only be analyzed according to the investigator's assessment as secondary endpoint.

Progression-Free Survival by Investigator Assessment

PFS time will be summarized by treatment arm using the Kaplan-Meier method and displayed graphically where appropriate. CIs for the 25th, 50th, and 75th percentiles of the event-free time will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratios and the corresponding 95% CI.

Objective Response (OR)

Objective response is defined as a complete response (CR) or partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1; Appendix 3) recorded from randomization until disease progression or death due to any cause. Only tumor assessments performed prior to start of new anti-cancer therapy will be included. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. A patient will be considered to have achieved an OR if the patient has a sustained complete response (CR) or partial response (PR) according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as a non-responder in the OR rate analysis. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the OR rate analysis.

The OR rate (ORR) on each randomized treatment arm will be estimated by dividing the number of patients with objective response (CR or PR) by the number of patients randomized to the respective treatment arm. The corresponding exact 2-sided 95% CIs will be provided by treatment arm.

In addition, the best overall response for each patient will be summarized by treatment arm.

Duration of Response (DR)

Duration of response (DR) is defined, for patients with an objective response per RECIST v1.1, as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first. Censoring rules for DR will follow those described above for PFS.

DR will be summarized by treatment arm using Kaplan-Meier method and displayed graphically, where appropriate. The median DR and 95% CI for the median will be provided for each treatment arm.

Disease Control (DC)

Disease control (DC) is defined as complete response (CR), partial response (PR), or stable disease (SD) according to the RECIST version 1.1 (Appendix 3) recorded from randomization until disease progression or death due to any cause. The DC rate (DCR) on each randomized treatment arm will be estimated by dividing the number of patients with CR, PR, or SD by the number of patients randomized to the treatment arm. The corresponding exact 2-sided 95% CI for the DC rates will be provided by treatment arm.

Patient-Reported Outcomes

The EORTC QLQ-C30, EORTC QLQ-OV28, and EQ-5D-5L, will be scored according to their respective validation papers and user's guides.[33,34,35,36, 37,38,39] All PRO analyses will include data from baseline up to EOT assessment (not including EOT). A sensitivity analysis will be conducted including all assessments from baseline to end of treatment and also any assessments captured on Days 30, 60, and 90 during the safety follow-up period.

Abdominal/gastrointestinal symptoms (GI) have been regarded as the most frequent and clinically relevant disease-related symptoms experienced by patients with ovarian cancer. As such, our primary analysis will focus on measuring Time to Deterioration (TTD) of abdominal/GI-related symptoms as measured by items 31 to 37 of the EORTC QLQ-OV28. TTD is defined as the time from randomization (baseline) to the first time the patient's score shows a 15 point or higher increase in patient abdominal/GI-related symptoms. Patients will be censored at the last time when they completed a sub-scale assessment if they have not deteriorated.

Osoba et al, established that a 10-point or a greater minimally important difference (MID) from baseline on the scales of the EORTC QLQ-C30 would correlate with significant (moderate) change in disease symptoms and functioning.[40] However, Stockler et al established a primary PRO hypothesis threshold of at least a 15% (≥15-point) absolute difference on the QLQ-OV28 abdominal/GI symptom subscale.[41] Hence, in the analysis of time to deterioration, a minimally important difference (MID) of 15 points or greater is proposed for the abdominal/GI symptom subscale of the OV-28. Sensitivity TTD analyses of 20 point, 2-grade increase in the raw score, and 10 point increases will also be conducted to assess the robustness of the endpoints. To explore the effect of the open-label nature of the study design on the PRO endpoints, additional analyses of the relationship between OS (and/or PFS) and the OV-28 GI subscale will be performedTTD of primary abdominal/GI symptom sub-scales will be summarized using Kaplan-Meier methods. The estimated Kaplan-Meier plots will be provided and the unstratified log-rank test will be the primary method to compare (pairwise) the time to first deterioration among the three (3) treatment arms. The median TTD and 2-sided 95% CI for the median will also be provided based on the Brookmeyer Crowley method.[42]

The proportion of patients who improved from baseline, defined as a ≥10 point decrease on the abdominal/GI subscale (items 31-37) of the EORTC QLQ-OV28, will be summarized and compared between each of the treatment arms at Cycle 3 (beginning of Week 9). Patients with missing questionnaires at Cycle 3 will be counted as not having improved.

Patient reported HRQOL, disease/treatment-related symptoms of ovarian cancer and general health status will also be assessed. Summary statistics (mean (and SE), median, range and 95% CI) of absolute scores will be reported for the items and subscales of the EORTC QLQ-C30 questionnaire, the items and remaining subscales of the EORTC QLQ-OV28, and the EQ-VAS scale. The mean change of absolute scores from baseline (and 95% CI) will also be assessed. Line charts depicting the means and mean changes of items and subscales over time will be provided for each treatment arm.

The number and proportion of patients who improved, worsened, or remained stable for all of the symptom and functional domains, global QOL and single items of the EORTC QLQ-C30, and the QLQ-OV28 will be summarized over time. For the EQ-5D-5L health state profiles, the proportions of patients reported having none, slight, moderate, severe, extreme/unable problems at each time point will be reported.

Additional exploratory analyses may be performed such as repeated measures mixed-effects modeling.

Pharmacokinetic Analysis of Avelumab and doxorubicin (PLD samples)

The central laboratory, analytical laboratories (eg, PK, ADA, Nab), and Pfizer clinical assay group (CAG) colleagues will be unblinded. If the need arises for early analysis of the PK data (before database lock and release of the randomization codes for the study), a PK unblinding plan will be developed. A PK analyst, who is not associated with the study team, will conduct the analysis to avoid unblinding of the study team.

Standard plasma PK parameters for doxorubixin (PLD samples) will be estimated using non-compartmental. Analysis and will include C_{max}, T_{max}, AUC_{336}, AUC_{inf} $t_{1/2}$, plasma clearance (CL), and volume of distribution (V_d). Dose normalized parameters (eg, CDN-C_{max}, DN-AUC) will be reported as appropriate. Descriptive statistics for the PK parameters for doxorubixin will be provided by dose in tabular form.

Doxorubicin plasma concentrations will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by nominal time. Individual patient and median profiles of the PLD profiles will be presented on both linear-linear and log-linear scales.

C_{trough} and C_{max} for avelumab will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by cycle and day. The trough concentrations for avelumab will be plotted, using a box-whisker plot by cycle and day in order to assess the attainment of steady-state.

Effect of Avelumab on Doxorubicin (PLD Samples) Pharmacokinetics

The effect of avelumab dosing on doxorubicin PK will be evaluated based on overall assessment of the geometric mean ratios and associated 90% CI for C_{max}, AUC_{inf}, and AUC_{336} of PLD on Day 1 of Cycle 2 in Arm B (PLD + avelumab) compared to those on Day 1 of Cycle 2 of Arm C.

Effect of PLD on Avelumab Pharmacokinetics

The effect of PLD dosing on avelumab PK will be evaluated based on the overall assessment of the geometric mean ratios of C_{max} and C_{trough} of Arm B on Day 1 of Cycle 2 compared to those on Day 1 of Cycle 2 of Arm A.

Immunogenicity Assessment

For the immunogenicity data, the percentage of patients with positive ADA and neutralizing antibodies each will be summarized by Arm (A or B). For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit.

Because the observed incidence of ADA is highly dependent on multiple factors including the assays used for ADA detection, timing of sample collection and immune status of the patients, the incidence of ADA observed in the planned study may differ from the incidence reported in historical clinical trials.

Exposure/Response Analysis

In addition, the relationship between exposure and efficacy and safety endpoints may be explored, as necessary, based on emerging efficacy and safety data. Refer to SAP for details of the analyses. The results of these modeling analyses may be reported separately from the clinical study report.

Biomarker Analysis for Secondary and Exploratory Endpoints

For baseline continuous endpoint data, such as PD-L1 and CD8, descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, will be provided by treatment arm. For baseline categorical data, the number and percentage of patients in each category will be provided by treatment arm. Appropriate statistical methods may be used to investigate any possible relationship of biomarker levels with avelumab anti-tumor efficacy relative to appropriate control arms.

9.4. Analysis of Other Endpoints

Descriptive statistics will be used to summarize all patient characteristics, treatment administration/compliance, safety parameters, and biomarkers. Data will also be displayed graphically, where appropriate.

9.5. Safety Analysis

The Safety Analysis Set will be the primary population for safety evaluation. Summaries of Aes and other safety parameters will be provided by treatment arm as appropriate.

Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 whenever possible (http://ctep.info.nih.gov/reporting/ctc.html).

The frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term will be reported. Adverse events will be graded by worst NCI CTCAE v4.03 Grade. Adverse events will be summarized by cycle and by relatedness to trial treatment.

Emphasis in the analysis will be placed on Aes classified as treatment emergent. Adverse events leading to death or discontinuation of trial treatment, events classified as NCI CTCAE v4.03 Grade 3 or higher, trial drug-related events, and serious adverse events will be considered with special attention. As appropriate, the difference in risk between treatment arms for Aes of clinical interest may be further assessed as described in the SAP.

Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study treatment, action taken, and clinical outcome.

Laboratory Abnormalities

The laboratory results will be graded according to the NCI CTCAE v4.03 severity grade. The frequency of patients with laboratory test abnormalities will be summarized according to the worst grade for each laboratory test.

For laboratory tests without an NCI CTCAE grade definition results will be categorized as normal (within normal ranges), abnormal, or not done.

Shift tables will be provided to examine the distribution of laboratory abnormalities.

Electrocardiograms

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Single ECGs and data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors [ie, Fridericia's (default correction), Bazett's, and possibly a study specific factor, as appropriate]. Data will be summarized and listed for QT, HR, RR, PR, QRS, and QTc.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline corrected QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment. Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

9.6. Interim Analysis

The interim analysis will be performed based on the Full Analysis Set. Any safety evaluation performed at the time of the IA will be based on the safety analysis set.

The study is designed to have, within each of the 4 hypotheses tested, one formal interim analysis and the final analysis based on the primary OS and PFS endpoints.

The goals of the interim analyses are to allow early stopping of one or both experimental treatment arms for efficacy or futility (if efficacy or futility boundaries are crossed for both OS and PFS) and to assess the safety of avelumab alone or in combination with PLD.

If the results of the interim analyses indicate serious safety concerns, the company will communicate with the Health Authorities regarding stopping one of the experimental arms or the clinical trial.

9.6.1. Overall Survival

A formal efficacy boundary (O'Brien-Fleming) for rejecting the null hypothesis is constructed by using the spending function methodology of Lan-DeMets. To protect the integrity of the study and to preserve the type-1 error rate, a fraction of alpha (0.002) for efficacy will be spent at the interim analysis and accounted for in the overall type I error rate if the interim analysis is performed exactly at the planned number of events. The nominal significance levels for the interim and final efficacy analyses of OS will be determined by using the Lan-DeMets procedure with an O'Brien-Fleming stopping efficacy boundary[43] and a Gamma Family (-10) β-spending function to determine the non-binding futility boundary. The overall significance level for the efficacy analysis of OS, within each comparison, will be preserved at 0.0115 (1-sided test).

Within each comparison, the interim analysis will be performed after 550 patients have been randomized in the study and approximately 131 OS events have occurred (67% of the 196 events expected for each comparison at the end of the study).

9.6.2. Progression-Free Survival

A formal efficacy boundary (O'Brien-Fleming) for rejecting the null hypothesis is constructed by using the spending function methodology of Lan-DeMets. To protect the integrity of the study and to preserve the type-1 error rate, a fraction of alpha (0.0003) for efficacy will be spent at the interim analysis and accounted for in the overall type I error rate if the interim analysis is performed exactly at the planned number of events. The nominal significance levels for the interim and final efficacy analyses of PFS will be determined by using the Lan-DeMets procedure with an O'Brien-Fleming stoppingefficacy boundary[43] and a Gamma Family (-10) β-spending function to determine the non-binding futility boundary. The overall significance level for the efficacy analysis of PFS, within each comparison, will be preserved at 0.001 (1-sided test).

Within each comparison, the interim analysis will be performed after 550 patients have been randomized in the study and approximately 267 PFS events have occurred (82% of the 325 events expected for each comparison at the end of the study).

The interim analyses for PFS and OS will occur at the same time.

9.6.3. Non-Comparative Objective Response Rate Assessment

Summary of ORR by treatment arm (based on confirmed partial or complete responses per BICR assessment) will be performed on all patients randomized 6 months or more prior to the time of the interim analysis for OS and PFS. It is estimated that approximately 450 patients (150 patients within each treatment arm) will be included in this analysis.

9.6.4. Stopping Rules

At the interim analysis, the experimental treatment (or the study) may be stopped for

1. Futility, if the value of the test statistics for both OS and PFS exceed the futility boundaries. OS futility boundary is ($z > -0.2339$, $p > 0.4075$) and PFS futility boundary is ($z > -1.8938$, $p > 0.0291$).

2. Efficacy, if the value of the test statistics for both OS and PFS exceed the efficacy boundaries. OS efficacy boundary is ($z < -2.8791$, $p < 0.002$) and PFS efficacy boundary is ($z < -3.4474$, $p < 0.0003$).

3. Crossing of only one boundary (for either OS or PFS) will not trigger an evaluation of early termination for futility or efficacy.

9.7. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of patients in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions,

which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the Investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the Investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to International Conference on Harmonisation (ICH) guidelines, according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another Investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The Investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient's personal data consistent with applicable privacy laws.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The Investigator must ensure that each study patient, or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each patient or the patient's legal representative before any study-specific activity is performed. The Investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by IRBs/Ecs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study patients before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the study treatment, Pfizer should be informed immediately.

In addition, the Investigator will inform Pfizer immediately of any urgent safety measures taken by the Investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Participating Countries

End of Trial in all participating countries is defined as Last Patient Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, study treatment safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PLD or avelumab at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the Investigator. After notification, the Investigator must contact all participating patients and the hospital pharmacy (if applicable) within 1 month. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, “Publication”) before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II — "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

This is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ADA	Anti-Drug Antibody
AE	Adverse event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANC	Absolute Neutrophil Count
AUC	Area Under the Curve
CRF	Case report form
CSA	Clinical study agreement
BICR	Blinded Independent Central Review
BOR	Best Overall Response
BP	Blood Pressure
BRCA	Breast Cancer Antigen
BUN	Blood Urea Nitrogen
CRF	Case Report Form
Cmax	Maximum Plasma Concentration
CTA	Clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete Response
CT	Computerized Tomography
CI	Confidence Interval
DU	Dispensible Unit
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DLT	Dose-Limiting Toxicity
DR	Duration of Response
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
E-DMC	External data monitoring committee
EDP	Exposure during pregnancy
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
EMA	Europeon Medical Authority
EOC	Epithelial Ovarian Cancer
EudraCT	European Clinical Trials Database
EU	European Union
FAS	Full Analyses Set
FDA	Food and Drug Administration (United States)

Abbreviation	Term
FDAAA	Food and Drug Administration Amendments Act (United States)
FFPE	Formalin Fixed, Paraffin Embedded
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMP	Good Manufactoring Practice
HCV	Hepatitis C Virus
HBV	Hepatitis B Virus
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
INR	International normalized ratio
IP	Investigational Product
irAE	Immune-related Adverse Event
IRB	Institutional review board
irRC	Immune-Related Response Criteria
IRT	Interactive response technology
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MUGA	multiple gated acquisition
NSAID	Non-steroidal anti-inflamatory drug
OR(R)	Objective Response (Rate)
OS	Overall Survival
PARP	Poly ADP ribose polymerase
PR	Partial Response
PK	Pharmacokinetics
PCD	primary completion date
PD-1	Programmed Death-1
PD-L1L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PLD	Pegylated Liposomal doxorubicin
PT	prothrombin time
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SCL	Supply Chain Lead
SIB	Suicidal ideation and behavior
SD	Stable Disease
SD	Standard Deviation
SOA	Schedule of Activities
SOP	Standard operating procedure
SRSD	Single reference safety document

Abbreviation	Term
TEAE	Treatment Emergent Adverse Event
ULN	Upper limit of normal
US	United States
USPI	United States package insert
WBC	White Blood Cell

Appendix 2. ECOG Performance Status

Score	Definition
0	Fully active, able to carry on all pre-disease activities 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 or office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 3. Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented, and

  - One or more target measurable lesions have not been assessed;

    or

  - Assessment methods used were inconsistent with those used at baseline;

    or

  - One or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

    or

  - One or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Objective/Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 13. Objective Response Status at each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

Table 14. Objective Response Status at each Evaluation for Patients with Non Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum on study). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

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Appendix 5. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (version 4.03, dated 14 June 2010) has been placed in the Study Manual for this protocol. Alternatively, the NCI CTCAE may be reviewed online at the following NCI website:

http://ctep.cancer.gov/reporting/ctc.html

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