A PHASE 1 PHARMACOKINETIC–PHARMACODYNAMIC STUDY OF AVELUMAB (MSB0010718C) IN PATIENTS WITH PREVIOUSLY TREATED ADVANCED STAGE CLASSICAL HODGKIN'S LYMPHOMA

JAVELIN HODGKIN'S

Compound:	MSB0010718C
Compound Name:	Avelumab
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2015-002636-41
Protocol Number:	B9991007
Phase:	1

[redacted]

Document History

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Protocol Amendment 4	13 November 2017	• Added Section 3.1.3, Safety Stopping Rules, in Section 3, Study Design. • Added Section 9.4.1, Safety Stopping Rules, in Section 9.4, Safety Analysis.
Protocol Amendment 3	09 May 2017	Major changes to the expansion phase: • Target population: only patients relapsing following a prior allogeneic hematopoietic stem cell transplant (HSCT) will be enrolled in the study, given the high response rate observed in the lead-in phase and the lack of licensed therapy for this subset of patients. • Biopsy: introduction of baseline and on-treatment mandatory biopsies to ensure availability of tumor material, to assess pharmacodynamic effects, mechanism of action and patient stratification related to response. • Criteria of disease response: change from Response Criteria for Malignant Lymphoma (Cheson et al., 2007) to Lugano Classification (Cheson et al., 2014) to reflect change in current clinical practice. • Study Design: introduction of an intra-patient dose escalation design as described below. The Protocol Summary was extensively modified to reflect changes introduced throughout the protocol. In the Schedules of Activities for the 2-week and 3-week cycles in the lead-in phase the following changes were implemented: • Footnote 2: Follow-up after last dose

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		was modified to indicate that conduct of safety assessments would be discontinued in the event of start of new anti-cancer therapy for consistency with other avelumab protocols. • Footnote 8: Contraception Check was added at the Day 30 Follow-up Visit to align to standard language from avelumab IBv7. • Footnote 10: Blood chemistry, text was added to clarify Day 7 requirements, for consistency to the table. • Footnote 12: Pregnancy Test was added at the Day 30 Follow-up Visit to align to standard language from avelumab IBv7. • Footnote 13: Urinalysis: the request for 24-hour urine collection was removed for consistency with other avelumab protocols. • Footnote 14: 12-Lead ECG: text was modified for clarity. • Footnote 15: Tumor assessment was modified to more accurately reflect the assessment schedule as outlined in the Response Criteria for Malignant Lymphoma clinical guidelines (Cheson et al., 2007). • Footnote 18: Randomization, text was deleted to align to the new study design. A new Schedules of Activities table and companion footnotes were added to outline the updated plans for the expansion phase. In the Pharmacokinetic and Pharmacodynamic Sampling Schedules for 2-week cycles and 3-week cycles in the

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		lead-in phase, the following changes were implemented: • Footnote 1 was modified to clarify that PK samples need to be collected up to cycle 20. • Footnote 3 was modified to clarify the conditions for and timing of biopsies, as well as management of biopsy samples. • Footnote 4 was modified to clarify that Anti-Avelumab Antibodies/Neutralizing Antibodies need to be collected up to cycle 20 and at the End of Treatment. A new Pharmacokinetic and Pharmacodynamic Sampling Schedule table and companion footnotes were added to outline the updated plans for the expansion phase. In Section 1, Introduction, the description of the target population of the study was changed to reflect change in the expansion phase design. Furthermore a paragraph to describe the role of allogeneic stem cell transplant in Hodgkin's Lymphoma was added. In Section 1.3.1, Avelumab (MSB0010718C), avelumab safety summary information were updated to align to standard language from avelumab IBv7. Table 1 and 2 were deleted. In Section 1.4, Rationale for Studying Avelumab in Hodgkin's Lymphoma information approval status and response data for pembrolizumab and nivolumab were updated in line with the current prescribing information. In addition updated information

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		from the nivolumab Checkmate 205 and 039 studies in Hodgkin's Lymphoma, a new paragraph describing results from a phase 1/1b study with ipilimumab in patients relapsing after allogeneic hematopoietic stem cell transplant (HSCT) and updated information on one study on nivolumab in patients with Hodgkin's Lymphoma relapsing after allogeneic HSCT were introduced. In Section 1.5.1, Avelumab Dosing Regimens the title was changed to Lead-in Phase. In addition Table 3 was renumbered as Table 1. Section 1.5.2, Preliminary Results of the Lead-in Phase, 1.5.3 Rationale for the Exploration of Fixed Dosing vs Body Weight-Based Dosing and 1.5.4 Rationale for the Dose regimens in the Expansion Phase were added. Table 2 was also added. In Section 2, Study Objectives and Endpoints, the objectives and endpoints were updated and detailed in separate lead-in and expansion phase sections. In Section 2.2 Endpoints (Lead-in Phase), Disease Control was added as a secondary endpoint; CCI [redacted] In Section 3.1, Study Overview, in Section 3.1.1, Study Phases and in Section 3.1.2, Criteria for Intra-Patient Dose Escalation text was modified to reflect the fact the lead-in phase completed enrollment, the study design for the expansion phase was modified from the evaluation of three dose regimens identified in the lead-in phase in both post-autologous HSCT patients and post-allogeneic HSCT patients to evaluation of an intra-patient dose-escalation regimen in

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		post-allogenic HSCT patients (up to 40 in total) only. In Section 3.1, Study Overview, text referring to maximum number of cycles was deleted as there is no specified duration of patient treatment. In Section 3.1.1. Table 4 was renumbered as Table 3. In Section 4.1, Inclusion criteria, the following changes were implemented: • Inclusion criterion 1 was modified to indicate that enrollment into the expansion phase is restricted to patients with a prior allogeneic HSCT with a donor chimerism >20%. • Inclusion criterion 3 was modified to indicate response assessment criteria to be used in the lead-in and expansion phases. • Inclusion criterion 8 was modified to clarify biopsy requirements for the expansion phase. • Inclusion criterion 13, the requirement for two contraception methods was updated from 60 days after the last dose to 30 days after the last dose to align to standard language from avelumab IBv7. • Multiple additional minor changes were introduced for clarity and to align language with the avelumab program standards. In Section 4.2, Exclusion criteria, the following changes were implemented: • Exclusion criterion 1, text was modified to provide improved guidance for the selection of patients

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		with prior allogeneic HSCT, especially with respect to current immunosuppressive therapy, prior and current Graft Versus Host Disease (GVHD) and timing from prior Donor Lymphocyte Infusion (DLI). • Exclusion criterion 2, text was added to clarify patient eligibility guidance with respect to prior anti-PD-1 or anti-PD-L1 therapy in the expansion phase. • Exclusion criterion 16, the requirement for two contraception methods was updated from 60 days after the last dose to 30 days after the last dose to align to standard language from avelumab IBv7. • Multiple additional minor changes were introduced to align language with the avelumab program standards. In Section 4.3.1, Contraception, the requirement of contraception methods to be used was updated from 60 days after the last dose to 30 days after the last dose to align to standard language from avelumab IBv7. In Section 5.1, Allocation to Treatment, text was added to describe the use of Interactive Response Technology system in the expansion phase. In Section 5.4.1, Avelumab, text was added to describe the use of prophylactic steroids and to refer to appropriate section of dose modification due to irAEs and GVHD. In addition text was modified to allow avelumab dose reductions. In Section 5.4.1, Avelumab, text relative to

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		the time windows permitted for infusions and text relative to the design of the lead in phase was deleted because redundant. In Section 5.4.1.1, Treatment After Initial Evidence of Disease Progression, text was modified to align to Pfizer standard text. In Section 5.4.1.2, Treatment After Complete Response, text was modified to clarify treatment for patients achieving CR. In Section 5.4.3, Recommended Dose Modifications, text was modified to allow avelumab dose reductions. In Section 5.4.3.2, Avelumab Infusion Omissions for Drug Related Toxicity, Table 5 was renumbered as Table 4. In Table 4, Hypersensitivity Reactions section was removed for consistency to other part of the protocol and in Other non-hematologic toxicities and laboratory abnormalities, text in Grade 2 and Grade 3 sections was updated for consistency with other protocol sections. In Section 5.4.4, Special Precautions for Avelumab Administration, text referring to the prophylactic use of steroids was added. In addition text describing allergic reactions was deleted to align to avelumab standard. In Section 5.4.4.1, Management of Avelumab Infusion Related Reactions Table 6 was renumbered as Table 5. In Table 5, Modification for Symptoms of Infusion-related Reactions Caused By Avelumab, text was modified to align to standard language from avelumab IBv7 and additional text was added to detail management of infusion-related reactions (IRRs), including the use of corticosteroids for both IRR treatment and prophylaxis. In Section 5.4.4.1, Management of Avelumab Infusion-Related Reactions, text

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		limiting total infusion time to ≤120 minutes was removed for consistency with avelumab program guidelines. In Section 5.4.4.2, Management of Avelumab Related Tumor Lysis Syndrome, Figure 1 was renumbered as Figure 3. Section 5.3.4.2 Management of Avelumab related Severe Hypersensitivity Reactions and Flu like Symptoms was deleted to align to avelumab standard language. In Section 5.4.4.3, Management of Avelumab Immune-Related Adverse Events, Table 7 was renumbered as Table 6. In Table 6, Management of Avelumab Immune-Related Adverse Events text was modified to align to standard language from avelumab IBv7. In Section 5.4.4.4, Management of Acute or Chronic Graft-versus-Host-Disease, text describing the management of patients developing GVHD during the expansion phase was added. In Section 5.4.5, Dose Reduction, text was modified to allow avelumab dose reduction. Section 5.7.2, Concomitant Surgery was updated to clarify timing of major surgery and interventional procedures respect to avelumab therapy. In Section 5.7.4, Other Prohibited Concomitant Medications and Therapies, Clarification about Steroid Use, "short term treatment of irAEs" was removed to align with Table 6; text describing prophylactic use of steroids was also added. In Section 7.1.1 Pregnancy Testing, language was updated to align with the Schedule of Activities. In Section 7.1.3, Laboratory Safety

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		Assessment, Table 8 was renumbered as Table 7. Table 7, Required Laboratory Tests, was updated to remove 24 hour urine collection and Erythrocyte Sedimentation Rate to align to avelumab standards; clarifications for hepatitis tests were also added. Section 7.4, Biomarker and Pharmacodynamic Assessments was extensively modified to clarify guidance on biopsy collection and management, to specify new biomarker assays included in the expansion phase, and to present in summary form the biomarker analyses planned for the lead-in and expansion phases of the study. In addition Table 9 was renumbered as Table 8 and Table 8, Biomarker Collection and Analysis, was updated to reflect changes in Biomarker Assessment. Section 7.5, Disease Response Assessment was extensively modified to clarify assessment schedules and response determination criteria for the lead-in and expansion phases of the study. Furthermore, the requirement for confirmation of response was deleted in accordance with the Response Criteria for Malignant Lymphoma (Cheson et al., 2007) and with the Lugano Classification (Cheson et al., 2014). Section 7.5.1, Blinded Independent Central Review for Disease Assessment (Expansion phase), was added to indicate requirement for central review for disease assessment in the expansion phase. In Section 7.6.1, Markers of Drug Response, the last paragraph was deleted as it conflicted with prior text in this section and text was added to reflect the new requirements for the updated study design of the expansion phase. Section 9.1, Analysis Sets, was updated for correctness.

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		Section 9.2.1, Sample Size Determination was updated to reflect that the lead-in phase completed enrollment and to address changes in the study design of the expansion phase. Table 9, Sample Size and Exact 95% CIs for ORR - Post-allogeneic HSCT cohort was added. Section 9.2.2, Efficacy Analysis was updated to reflect the new study design of the expansion phase. In Section 16, References, bibliographical information on Investigator's Brochure for avelumab was updated, full bibliographical information was added for KEYTRUDA USPI, Sarina et al. 2010, Cheson et al. 2007, Cheson et al. 2014, Barrington et al. 2014, Davids MS et al. 2016, Sala E et al. 2014, Timmerman J et al 2016, BAVENCIO USPI, Wang et al. 2009, Gangadhar et al. 2015, Zhao et al. 2016 and Yared et al. 2016. Appendix 1 was modified to update abbreviations. Appendix 2, the title was modified to indicate that Appendix 2 is to be used for the tumor assessment in the lead-in phase. Appendix 3 was added given that Lugano Classification (Cheson et al., 2014) response criteria are to be used for tumor assessment in the expansion phase. Appendix 6 was added to detail all the possible treatments for IRR. Other minor typographical errors have been fixed throughout the protocol for further clarification.
Protocol Amendment 2	15 JULY 2016	The following are changes to the protocol: In the Schedule of Assessments, Section 8.2,

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		the time period for reporting of AEs (serious and non-serious) has been extended from 30 to 90 calendar days. In the Schedule of Activities table, Section 7.1.3, and Table 8, urine albumin test, ANA, ANCA and RF assessments have been removed. In the footnotes of the Schedule of Activities table, the 48-hour (Day 3) post-dose PK sample has been removed. In the footnotes of the Schedule of Activities table for the 3-week dosing, 3 time points (ie, Cycle 3 Day 1, Cycle 3 Day 7, and Cycle 3 Day 14) were removed to reflect the blood chemistry assessments being performed weekly in the first 6 weeks of treatment. In the footnotes of the Schedule of Activities, Inclusion Criterion 12, and Section 7.1.1, "urine or serum" was added for the Pregnancy Test. Section 1.4 has been modified to include: 1) new data regarding the use of PD-1/PD-L1 inhibitors in the cHL population and 2) risk language for GVHD in the post-allo-HSCT setting. In Section 4.1, Inclusion Criterion 1 has been modified to provide additional clarity on the patient population being studied. In Section 4.1, Inclusion Criterion 7 has been modified to include CSF and/or transfusion support for adequate bone marrow functioning. In Section 4.1, Inclusion Criterion 9 has been modified to include a lower estimated creatinine clearance of ≥30 mL/min in keeping with avelumab program standard. In Section 4.1, Inclusion Criterion 14 has been modified to include clarification regarding the exclusion of adult individuals

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		who lack the capacity to provide informed consent. In Section 4.2, Exclusion Criterion 1 has been modified to allow patients with prior allo-HSCT in both the lead in and expansion phases of the study. In Section 4.2, Exclusion Criterion 1 has been modified to add additional criteria for patients who had prior allo-HSCT that are at higher risk for GVHD. In Section 4.2, Exclusion Criterion 3 has been modified to remove the statement "Systemic anti-cancer therapy ≤2 weeks of study entry". In Section 4.2, Exclusion Criterion 9 has been modified to remove the statement "any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma)". In Section 4.2, Exclusion Criterion 11 has been modified for further clarification adding the statement "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". In Section 4.2, Exclusion Criterion 12 has been modified to remove "deep vein thrombosis". In Section 4.2., Exclusion Criterion 18 has been removed. In Section 4.2., Exclusion Criterion 19 has been modified to remove "(for example, inactivated influenza vaccines)". In Section 4.3.1, The duration of contraception for sexually active male patients was changed from 28 to 60 days

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		after the last dose. In Section 5.4.1, the statement regarding weight loss or gain of >10% was removed since the dose (10 mg/kg) will be calculated for each visit for patients randomized to Cohort E. In Section 5.4.3.2, Table 5 has been modified to allow patients with Grade 2 hematologic abnormalities continue with dosing and Grade 3 hematologic abnormalities hold treatment until resolution to Grade ≤1 or baseline. In Section 5.4.3.2, Table 5 has been modified to remove the statement "Upon the second occurrence of the same Grade 2 toxicity (except for hormone deficiencies that can be managed by replacement therapy), the treatment must be permanently discontinued" under Grade 2 "Other Non-hematologic toxicities". Section 5.4.4.1, Table 6 has been modified to remove "The total infusion time for avelumab should not exceed 120 minutes" Section 5.4.4.5 "Management of Acute or Chronic Graft versus Host Disease" has been added to the protocol. Section 5.7.1 has been modified to allow the use of Hematopoietic Growth Factors throughout the study.In Section 7.1.2, reference to "including baseline signs and symptoms" was removed. In Section 7.6.1, additional sample times for banked blood biospecimens were included to make consistent with the Schedule of Assessments. In Section 8.13, "legally acceptable

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		representative" was removed. Section 12.2, an updated reference is included for the Declaration of Helsinki. Section 16 "References" includes new literature supporting the investigation in cHL and the risk of GVHD. Appendix 3 "1994 Consensus Conference on Acute GVHD Grading" was added. Appendix 4 "National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease" was added.
Protocol Amendment 1 – Reissue	24 NOVEMBER 2015	The following are changes to the protocol On the title page, an extra "0" is removed from the drug name in the title of the protocol. The Schedule of Assessments was modified to remove the window for the End of Treatment/Withdrawal visit. The Schedule of Assessments includes a Physical Examination assessment at Day 1 of Cycle 1. The Schedule of Assessments includes a modification of the Thyroid function Tests and ACTH to include sampling at Day 1 of Cycles 3 and 6 and every 6 weeks thereafter. The Schedule of Assessments includes a clarification with the Tumor Assessments to include every 6 weeks until Week 12, then every 12 weeks. The Schedule of Assessments includes a modification with the Hematology and Coagulation to include assessments weekly through Cycles 1 and 2, and then at Day 1 of every cycle throughout the duration of the study.

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		"All patients" is removed from the Pregnancy Test footnote of the Schedule of Assessments. In the Schedule of Assessments, appropriate reference to "Table 8" is included in Hematology and Coagulation and Blood Chemistry footnotes. The Schedule of Assessments for the De Novo Tumor biopsy assessment in the PK/PD Sampling Schedule was revised to make consistent with the footnotes for both the 2-week and 3-week cycles. Reference to footnote 5 in the Schedule of Assessments for the Anti-Avelumab Antibodies and Neutralizing Antibodies in the in the PK/PD Sampling Schedule was removed for the End of Treatment / Withdrawal sample. In Section 5.5, replaced reference to dosage and administration instructions with Investigational Product Manual. In Table 8, added Erythrocyte Sedimentation Rate to the Hematology assessments. CCI [redacted] In the References Section, correction of the date for Reference #15.
Protocol Amendment 1	30 OCTOBER 2015	The following are changes to the original Protocol: The primary endpoint was revised to include CD14+ monocytes and is reflected in the Protocol Summary, Protocol Sections 2.2, 7.4 and Table 9. The dosing cohorts and dosing cohort names were revised to make consistent with Table 4 throughout the Protocol including the Protocol Summary, Protocol Sections 1.5.1, 3.1 and Table 3.

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		The Schedule of Assessments for Banked Blood Biospecimen was revised to include a sample at Day 1 of Cycle 3 for 2 week cycles and Day 7 of Cycle 2 for 3 week cycles. The timing of assessments for Immune Cell Phenotyping, CCI [redacted]. The Schedule of Assessments for the De Novo Tumor biopsy assessment was revised to include clarification for the sample collection in the footnotes of the PK/PD Sampling Schedule for both the 2 week and 3 week cycles and in Protocol Section 7.4. The ECG on Day 1 of cycles greater than or equal to 3 was removed from the Schedule of Activities tables.
Original protocol	20 JULY 2015	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background and Rationale:

Hodgkin's lymphoma is a B-cell malignancy and is a lymphoma involving peripheral lymph nodes, which may also impact organs including liver, lung as well as bone marrow. Hodgkin's lymphoma affects approximately 9,000 new patients each year and represents approximately 12% of all lymphomas seen in the United States.[1] Classical Hodgkin's lymphoma (cHL) and nodular lymphocyte-predominant Hodgkin's lymphoma are the two main types of Hodgkin's lymphoma. cHL accounts for most (~95%) Hodgkin's Lymphoma diagnosed.[2] The standard initial treatment for patients with newly diagnosed cHL includes chemotherapy or combined modality therapy, followed by restaging with Positron Emission Tomography-Computerized Tomography (PET-CT) to assess treatment. While patients with cHL commonly respond well to initial therapy, a subset of patients (~25%) continue to experience relapsed disease and have very poor prognosis.[3]

cHL is defined by the subclassifications of: nodular sclerosis (60-80% of Hodgkin's lymphoma cases), mixed cellularity (25-30% of cases), lymphocyte-rich (5%) and lymphocyte-depleted (1%), depending upon histology and phenotype of the tumor cells.[2] Hodgkin's lymphoma tumor cells represent less than 2% of cells in the tissue. Mononucleated Hodgkin's and bi- or multi-nucleated Reed-Sternberg cells (HRS) are the malignant cells in cHL.[13,14]

Chromosome 9p24.1 amplification, which contains the *PD-L1* gene, is frequent in cHL.[19] It is thought that this leads to an overexpression of PD-L1 on the surface of the HRS. PD-L1 on the surface of these tumor cells is thought to be responsible in part for the down-modulation of potentially cytotoxic anti-tumor T cells, which express PD-1. PD-L1 on HRS cells may also be capable of down modulating the activity of other cell types expressing PD-1, such as natural killer (NK) cells, which might otherwise be capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) through therapeutic antibodies targeting to the HRS cells. Avelumab may block the binding of PD-1 on these key anti-tumor effector cells to PD-L1 on HRS, thereby restoring anti-tumor immunity, while at the same time stimulating NK directed ADCC toward HRS. It is not clear at this time if other mechanisms may also inhibit immune cells in this disease, such as PD-L2, another ligand for PD-1. However, this may be mitigated by the direct tumor targeting properties of avelumab through the ADCC mechanism. Therefore, cHL has been chosen as a potentially responsive tumor type for this study.

For those patients who are refractory to standard initial therapy, immunomodulation via PD-L1 inhibition may provide clinical benefit. PD-L1 blockade may reverse the inhibition of tumor-infiltrating cytotoxic $CD8^+$ T cells mediated by the HRS, restore anti-tumor immunity, and directly target the HRS through activating the innate immune system.

Blocking the PD-1/PD-L1 interaction is a novel immunotherapeutic approach for cHL. Preliminary data suggests that PD-1 blockade in specific hematologic malignancies is a safe and effective therapeutic strategy.[6,7,8] Nivolumab, a high-affinity, fully human anti-PD-1 monoclonal antibody (mAb)has been granted accelerated approval for the treatment of cHL

that has relapsed or progressed following autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin.[9,37] In a cohort of 95 patients from two studies (Checkmate 025 and 039), an objective response rate (ORR) of 65% (95% Confidence Intervals (CI): 55, 75) was reported in 62 patients, including: 7 (7%) with a complete response (CR) and 55 (58 %) with a partial response (PR).The median duration of response was 8.7 months (95% CI: 6.8, not evaluable). The other PD-1 inhibitor pembrolizumab has also been granted accelerated approval for adult and pediatric patients with refractory cHL, or those who have relapsed following three or more lines of therapy. Approval was based on data from 210 adult cHL patients enrolled in a multicenter, non-randomized, open-label clinical trial. Patients had refractory or relapsed disease after autologous HSCT (129 patients) and/or Brentuximab Vedotin (175 patients), and received a median of four prior systemic therapies (range: 1, 12). With a median follow-up of 9.4 months (range: 1-15), the ORR was 69% (95% CI: 62, 75). This included PR in 47% of patients and CR in 22%. The estimated median response duration was 11.1 months (range 0 to 11.1).[38]

While these results are encouraging, there is room for improvement with therapies able to increase the ORR.

Due to the potential risk of checkpoint inhibitors-induced Graft-Versus-Host Disease (GVHD), patients with a prior allogeneic hematopoietic stem cell transplantation (allo-HSCT) were excluded from the nivolumab studies, while pembrolizumab, although excluding only patients who had received an allo-HSCT in the past 5 years or greater than 5 years but with symptoms of GVHD, did not enroll any patient with a prior allo-HSCT. As a result, only limited data are available for the use of checkpoint inhibitors in post allo-HSCT patients, principally from case reports and small patient series. The potential to enhance the graft-versus-lymphoma response in post-allo-HSCT patients, however, provides a rational basis for the use of checkpoint inhibitors in this subgroup of cHL patients, despite the risk of checkpoint-induced GVHD.

This study comprises a lead-in phase followed by an expansion phase. The lead-in phase evaluates different avelumab dose regimens in relapsed or refractory cHL patients who had received either an autologous HSCT or an allo-HSCT or were ineligible for HSCT. Based on the preliminary target occupancy (TO), safety, and efficacy results from the lead-in phase (see Section 1.5.1), the expansion phase will further evaluate a dose-escalation regimen in patients in whom allo-HSCT has failed.

Study Objectives (Lead-in Phase)

Primary Objective

- To characterize the pharmacokinetics (PK) of different dosing regimens of avelumab and its relation to target occupancy (TO) in peripheral blood of patients with classical Hodgkin's Lymphoma (cHL).

Secondary Objectives

- To evaluate the overall safety and tolerability of different dosing regimens of avelumab.
- To assess the immunogenicity of different dosing regimens of avelumab.
- To evaluate the effect of different dosing regimens of avelumab on pharmacodynamic biomarkers of tumor immunophenotype and anti-tumor immune response.
- To evaluate the anti-tumor activity of avelumab in patients with cHL.

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Study Endpoints (Lead-in Phase)

Primary Endpoints

- Percent TO by dose/schedule in peripheral blood immune cells, including CD14+ monocytes and CD3+ T cells.
- Pharmacokinetic parameters of avelumab including, but not limited to, C_{max}, T_{max}, AUC_{last}, T_{last}, $AUC_{sd,\tau}$, $t_{1/2}$, $AUC_{sd,inf}$, CL, and Volume of distribution (V_z) as data permit. Multiple Dose (MD) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sd,\tau}$) and R_{ss} ($AUC_{ss,\tau}$ /$AUC_{sd,inf}$) as data permit.

Secondary Endpoints

- Adverse Events as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v.4.03), timing, seriousness, and relationship to study therapy.
- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v. 4.03), and timing.
- Anti-drug antibodies (ADAs; neutralizing antibodies) and serum titers against avelumab.
- Phenotype, quantity, and localization of tumor infiltrating lymphocytes (TILs) in tumor biopsy tissue by immunohistochemistry (IHC).
- Relative expression of transcripts associated with immune activation and regulation in tumor biopsy tissue by gene expression profiling.
- Phenotype, relative proportions, activation state and PD-L1 expression of peripheral blood T cell subsets by flow cytometry.
- Objective response according to Response Criteria for Malignant Lymphoma[42] per Investigator assessment.
- Disease control (DC), time to tumor response (TTR), duration of response (DR), progression-free survival (PFS) per Investigator assessment.

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Study Objectives (Expansion Phase)

Primary Objective

- To evaluate the objective response rate (ORR) of avelumab in patients with relapsed or refractory cHL who have previously been treated with an allogeneic HSCT.

Secondary Objectives

- To evaluate the overall anti-tumor activity of avelumab.
- To evaluate the overall safety profile of avelumab.
- To evaluate the incidence and severity of acute and chronic GVHD.
- To characterize the pharmacokinetics of avelumab.
- To assess the immunogenicity of avelumab.
- To evaluate the phenotype and quantity of TILs and correlate these findings with anti-tumor activity.

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Endpoints (Expansion Phase)

Primary Endpoint

- Objective response defined by the Lugano Classification[43] as evaluated by the blinded independent central review (BICR).

Secondary Endpoints

- Objective response defined by the Lugano Classification[43] as evaluated by Investigator's assessment.

- Time to tumor response (TTR), duration of response (DR), Disease Control (DC) and progression-free survival (PFS) according to the Lugano Classification[43] by BICR and by Investigator's assessment, as well as overall survival (OS).

- Adverse Events and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03; timing, seriousness, and relationship to study therapy.

- Acute GVHD, as defined by the modified Seattle Glucksberg criteria (Consensus Conference on Acute GVHD Grading Criteria-Appendix 4), and chronic GVHD, as defined by the NIH Consensus Development Project (Appendix 5).

- Pharmacokinetic parameters of avelumab including, but not limited to, C_{max}, T_{max}, $AUC_{sd,\tau}$, $t_{1/2}$, CL, and V_z as data permit. Multiple Dose (MD) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss} as data permit.

- Anti-drug antibodies (ADAs; neutralizing antibodies) and serum titers against avelumab.

- Phenotype, quantity, and localization of TILs in tumor biopsy tissue determined by IHC.

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Study Design:

This is a Phase 1b, open-label, multi-center study comprising a lead-in phase and an expansion phase. The lead-in phase is a multiple-dose, randomized, parallel-arm, pharmacokinetic and pharmacodynamic study of avelumab as a single agent in adult patients with cHL. Patients enrolled in the lead-in phase of this study are required to have relapsed following a prior autologous or allogeneic HSCT, or to be ineligible for HSCT. Based on the preliminary TO, safety, and efficacy results from the lead-in phase, the expansion phase will evaluate the anti-tumor activity and safety of single-agent avelumab utilizing an intra-patient dose escalation paradigm based on two of the dosing regimens studied in the lead-in phase in 40 cHL patients in whom an allogeneic HSCT has failed.

Lead-in Phase

In the lead-in phase of the study, which completed enrollment on November 29, 2016, a total of 31 patients were randomized across 5 treatment cohorts in a ratio of 1:1:1:1:1, The 5 treatment cohorts are: 70 mg every 2 weeks (Q2W) (Cohort A), 350 mg Q2W (Cohort B), 500 mg every 3 weeks (Q3W) (Cohort C), 500 mg Q2W (Cohort D), and 10 mg/kg Q2W (Cohort E). Each cohort enrolled 6 patients, except Cohort B in which 7 patients were randomized, but 1 was never dosed. The goal of the lead-in phase was to determine the doses and schedules of avelumab that provide greater than 90% TO over the dosing interval and to identify a dose regimen for use in the dose expansion phase.

For patients not achieving >90% TO after C1D1, the dose could be escalated to 10 mg/kg (Treatment Cohort E) starting at C2D1, after Cycle 1 assessment of TO.

Rationale for the Dosing regimens in the Expansion Phase

Based on the lead-in phase data, which includes safety, an assessment of the number of patients achieving >90% TO following 1 treatment cycle, and clinical activity that met the predefined criteria (observing at least 3 objective responses per the Response Criteria for Malignant Lymphoma[42] (Appendix 2) in each given cohort), two dose regimens (70 mg Q2W and 500 mg Q2W) were selected in the expansion phase for the intra-patient dose escalation design outlined below.

As described in Section 1.5.2, TO, safety, and efficacy data from the lead-in phase were similar across all the dose regimens tested, including a dose as low as 70 mg Q2W (~1/10 of the dose used in other studies across the avelumab program), with no evidence of a dose-response relationship either in the entire population, or in the post-allo HSCT cohort. Although the TO was >90% at all the regimens tested in the lead-in phase, peripheral TO may over-estimate TO within the tumor itself. Therefore, although responses were observed across the broad range of dose regimens tested, it is not clear whether the frequency, depth, and durability of the responses will be more optimal at higher doses. Given that the peripheral TO has the *a priori* potential to differ from the intra-tumoral TO, and the potential for life-threatening checkpoint-induced GVHD, patients will start the expansion phase with a 70 mg Q2W 'test' dosing regimen of avelumab, the lowest exposure tested in the lead-in phase.

Although there is no evidence that checkpoint-induced GVHD is dose/exposure dependent, starting patients on the lowest tested dose is expected to minimize the risk of checkpoint-induced GVHD, while also providing for the possibility that higher doses may capture responses that are not achieved at lower doses. Patients will be monitored for safety and efficacy at the test dose level.

Given that 70 mg Q2W is the lowest dose tested, and the therapeutic activity at this low dose might not be optimal, patients not achieving a CR may be dose escalated to the higher dose (500 mg Q2W) as detailed below. A target dosing regimen of 500 mg Q2W (~8x the exposure of 70 mg Q2W), provides an exposure intermediate between that of the highest (10 mg/kg Q2W) and lowest tested (70 mg Q2W) in the lead-in phase. A dose-response relationship has not been observed for either safety or efficacy in the lead-in phase. However, given the relatively small sample size and the potential life-threatening clinical sequelae of high-grade GVHD, patients will escalate to a dose which is almost a log higher than the test dose while at the same time being lower than the 10 mg/kg Q2W which is used in other studies across the avelumab program.

Expansion Phase

In this phase, an intra-patient dose-escalation design will be utilized as follows: all patients will commence dosing at 70 mg Q2W, the lowest dose that showed clinical activity, and will be monitored for safety and efficacy. Following 3 cycles of treatment at 70 mg Q2W, patients who at the 6-week tumor assessment achieve a CR will continue at the same dose regimen. Patients achieving a PR at 6 weeks will continue at 70 mg Q2W for an additional 3 cycles, and if the 12-week tumor assessment still shows a PR, patients will be dose escalated to 500 mg Q2W. Patients who at the 6-week tumor assessment achieve a stable disease (SD), will be dose escalated to 500 mg Q2W. Additionally, those patients who at the 6-week assessment are considered to have initial evidence of disease progression as confirmed by BICR but in the opinion of the Investigator are still experiencing clinical benefit (as defined in Section 5.4.1.1), may continue treatment with study drug at the Investigator's discretion and following discussion with the Sponsor. Such patients may be considered for escalation to 500 mg Q2W. Dose escalation to 500 mg Q2W after the 6 or the 12 week tumor assessment, will be only permitted so long as there is no clinical evidence of

GVHD or treatment-related Grade ≥2 AEs with a duration of more than 14 days. Patients with progressive disease (PD) at 6 weeks in the absence of clinical benefit will be permanently discontinued from study treatment.

Patients with GVHD of any grade (other than Grade 1 GVHD of the skin requiring topical therapy only) must be permanently discontinued from the study treatment.

Disease responses will be assessed by a BICR according to processes defined in the Study Manual. Intra-patient dose escalation decisions will be made following discussion between the Investigator and the Sponsor and will be informed by the BICR disease response assessment-see Section 7.5.1.

Study Treatment:

Avelumab will be administered as a 1-hour intravenous (IV) infusion once every 2 weeks or 3 weeks, with or without food, on a continuous dosing schedule. Treatment with investigational product will continue until disease progression, patient refusal, or unacceptable toxicity, patient is lost to follow-up, or until the study is terminated by the Sponsor, whichever occurs first (see Section 6.4).

Patients will be monitored closely for toxicity, and in the event of significant toxicity, dosing of avelumab may be delayed, reduced or permanently discontinued. Avelumab treatment modification for drug-related toxicities, including immune-related adverse events (irAEs) infusion-related AEs and GVHD are described in Section 5.4.3, Section 5.4.4 and Section 5.4.5.

Every effort should be made to administer avelumab on the planned dose and schedule. See STUDY DESIGN section for details of the lead-in and expansion phase study treatments.

Statistical Methods:

Percent PD-L1 target occupancy will be calculated by dose/schedule in peripheral blood CD14+ monocytes and CD3+ T cells and will be summarized descriptively (n, mean, standard deviation (SD), coefficient of variation (CV), median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by dose, cycle, day and nominal time.

Standard plasma PK parameters for avelumab will be estimated using non-compartmental analysis. For avelumab, standard PK parameters will include Cmax, Tmax, $AUC_{0-\tau}$, $t_{1/2}$, plasma clearance (CL), and volume of distribution (Vz) and others, as data permit. Avelumab plasma concentrations and PK parameters will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by treatment cohort, cycle, day and nominal time.

For the lead-in phase of the study, the evaluation of the anti-tumor activity of avelumab is a secondary objective. For the expansion phase, evaluation of the anti-tumor activity, as measured by the objective response rate, is the primary objective. Efficacy will be summarized by treatment cohort for all patients randomized in the lead-in phase, and for all patients who received at least one dose of study treatment in the expansion phase.

In the expansion phase, tumor-related endopoints will be summarized separately based on BICR assessment and based on Investigator assessment.

For statistical analysis, 'start date' refers to the date of randomization for patients enrolled in the lead-in phase, and to the date of the first dose of study treatment for patients enrolled in the expansion phase.

Objective response (OR) is defined as complete response (CR) or partial response (PR) according to the Response Criteria for Malignant Lymphoma[42] (Appendix 2 for the lead-in phase) and to the Lugano Classification[43] (Appendix 3 for the expansion phase) from 'start date'" until disease progression or death due to any cause. OR rate (ORR) is the proportion of patients with OR.

Time to Tumor Response (TTR) is defined, for patients with an objective response per the Response Criteria for Malignant Lymphoma[42] (Appendix 2 for the lead-in phase) and per the Lugano Classification[43] (Appendix 3 for the expansion phase), as the time from 'start date' to the first documentation of objective tumor response (CR or PR) .

Duration of Response (DR) is defined, for patients with an objective response per the Response Criteria for Malignant Lymphoma[42] (Appendix 2 for the lead-in phase) and per the Lugano Classification[43] (Appendix 3 for the expansion phase), as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective progression of disease (PD) or to death due to any cause, whichever occurs first. Censoring rules for DR will follow those described below for PFS.

Disease Control (DC) is defined as the best overall response of CR, PR, or SD. To qualify as a best overall response of SD, at least one SD assessment must be observed ≥6 weeks after start date and before disease progression. DC rate (DCR) is the proportion of patients with DC.

Progression Free Survival (PFS) is defined as the time from 'start date' 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 'start date' unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

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

ORR will be estimated and the corresponding exact 2-sided 95% confidence interval will be reported. TTR will be summarized using simple descriptive statistics (eg, median and range).

DCR will be summarized by frequency counts and percentages. DR, PFS, and OS will be analysed using Kaplan-Meier methods. Median DR, median PFS, and median OS and associated 95% confidence intervals will be reported.

Sample Size Determination

In the lead-in phase, a total of 31 patients were randomized across 5 different treatment cohorts. Based on results from the lead-in phase, a dose escalation design has been planned for the expansion phase, which will enroll approximately 40 patients in whom allogeneic HSCT has failed.

Approximately 70 patients will be enrolled into this study in total.

The 6 patients per treatment cohort in the lead-in phase are used to enable the initial estimation of TO; based on the historical data, with observed mean TO of 90%, the corresponding 95% confidence interval is 88.98% to 91.02%, assuming a standard deviation of 1.27%. With 40 treated patients in the expansion phase, ORR can be estimated with a standard error not exceeding 0.079.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the Assessments section of the protocol for detailed information on each 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.

SCHEDULE OF ACTIVITIES (2-Week Cycles, for Lead-In Phase)

Protocol Activities	**Screening**	**Study Treatment (1 cycle = 14 days)**							**Post-Treatment**	
		Cycle 1			**Cycle 2**			**Cycles ≥3**		
	≤28 Days Prior to Randomization	**Day 1**	**Day 2[20]**	**Day 7 (±2 days)**	**Day 1 (±3 days)**	**Day 2**	**Day 7 (±2 days)**	**Day 1 (±3 days)**	**End of Treatment /Withdrawal[1]**	**Follow-up After Last Dose (Day 30 ±3, Day 60 ±3, and Day 90 ±3)[2]**
Clinical Assessments										
Informed Consent[3]	X									
Medical/Oncological History[4]	X									
Baseline Signs/Symptoms[5]		X								
Physical Examination[6]	X	X			X			X	X	X
ECOG Performance Status	X	X			X			X	X	X
Vital Signs[7]	X	X		X	X		X	X	X	X
Contraception Check[8]	X	X			X			X	X	X
Laboratory Studies										
Hematology[9]	X	X		X	X		X	X	X	X
Blood Chemistry[10]	X	X		X	X		X	X	X	X
Coagulation[9]	X	X		X	X		X	X	X	X
Thyroid Function Tests and ACTH[11]	X							X (Cycles 3 and 6 and Q6 weeks thereafter)	X	X

Protocol Activities	Screening	Study Treatment (1 cycle = 14 days)							Post-Treatment	
		Cycle 1			Cycle 2			Cycles ≥3		
	≤28 Days Prior to Randomization	Day 1	Day 2[20]	Day 7 (±2 days)	Day 1 (±3 days)	Day 2	Day 7 (±2 days)	Day 1 (±3 days)	End of Treatment /Withdrawal[1]	Follow-up After Last Dose (Day 30 ±3, Day 60 ±3, and Day 90 ±3)[2]
HBV, HCV	X									
Pregnancy Test[12]	X	X			X			X	X	X
Urinalysis[13]	X	X			X			X	X	
12-Lead ECG[14]	X	X			X				X	
Disease Assessments										
Tumor Assessments[15]	X	X (Q6W until W12, then Q12W)							X	X
Other Clinical Assessments										
Adverse Events[16]	X	X							X	X
Concomitant Medications/Treatments[17]	X	X							X	X
Randomization and Study Treatment[18]										
Avelumab[19]		X			X			X		
Pharmacokinetics		See table below								
Biomarkers		See table below								

Footnotes for Schedule of Activities
1. **End of Treatment/Withdrawal:** Obtain these assessments if not completed in the prior week, except for tumor assessments, which need not be repeated if performed within the prior 6 weeks.
2. **Follow-up After Last Dose:** To occur at least up to 90 days (on Days 30 ±3, 60 ±3, and 90 ±3) after the last dose of study treatment. All safety assessments are to continue through this period as noted in the Schedule of Activities. Safety assessments will cease if new anti-cancer therapy is initiated during this follow-up period.
3. **Informed Consent:** Must be obtained prior to undergoing any trial-specific procedure.
4. **Medical/Oncological History:** To include information on prior systemic therapy regimens, surgery, and radiation therapy.
5. **Baseline Signs/Symptoms:** To be recorded predose for all patients on Cycle 1 Day 1. Patients will be asked about any signs and symptoms experienced within the 14 days prior to randomization.
6. **Physical Examination:** Includes an examination of major body systems, assessment of ECOG performance status, and weight (height included at Screening only).
7. **Vital Signs:** Blood pressure (BP) and pulse rate to be recorded in supine or sitting position.

Footnotes for Schedule of Activities
8. **Contraception Check:** Male patients who are able to father children and female 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, whenever one menstrual cycle is missed or if pregnancy is known or suspected in the patient or the patient's partner. Contraception checks will be routinely repeated at every treatment cycle during the active treatment period, at the End of Treatment/Withdrawal visit, and at the Day 30 Follow-up Visit.
9. **Hematology and Coagulation**: Required tests are listed in Table 7. Will be performed at screening prior to the first dose of study treatment, weekly through Cycles 1 and 2, and then at Day 1 of every cycle throughout the duration of the study. May also be performed when clinically indicated.
10. **Blood Chemistry:** Full chemistry panel (required tests are listed in Table 7) is required at Screening, on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, then every 6 weeks thereafter and at End of Treatment/Withdrawal. Core chemistry panel (required tests are listed in Table 7) is required on Cycle 3 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, then every 2 weeks (Q2 Week Schedule) thereafter. In addition a Core chemistry panel will be performed also at Day 7 through Cycles 1 and 2. If full and core chemistry panels are scheduled at the same visit, then only the full chemistry panel will be performed. For patients with documented liver involvement at study entry, ALT, AST, total bilirubin, and alkaline phosphatase tests will be performed weekly in the first 6 weeks of treatment, ie, Cycle 1 Day 1, Cycle 1 Day 7, Cycle 2 Day 1, Cycle 2 Day 7, Cycle 3 Day 1, Cycle 3 Day 7, then on Day 1 of each cycle thereafter.
11. **ACTH and Thyroid Function Tests:** ACTH, Free T4, TSH. Performed at screening, Cycle 3 Day 1, Cycle 6 Day 1, every 6 weeks thereafter, EOT, and 30, 60, 90 days after last dose of study treatment, and if clinically indicated. Test should additionally be performed in cases of suspected hypoadrenalism or hypopituitarism. See Section 7.1.3 in the full protocol for a list of the required Laboratory Tests.
12. **Pregnancy Test:** For female patients of childbearing potential, a serum or urine 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 at the baseline visit immediately before the administration of avelumab. Following a negative pregnancy result at screening, appropriate contraception must be commenced. Urine or serum pregnancy tests will also be routinely repeated at every treatment cycle during the active treatment period, at the End of Treatment/Withdrawal visit, at the Day 30 Follow-up Visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Urine pregnancy tests may also be repeated as per request of institutional review board /ethics committee (IRB/IECs) or if required by local regulations (see Section 7.1.1).
13. **Urinalysis:** Dipstick is acceptable. Will be performed at screening, Day 1 of every cycle throughout the duration of the study, and at the End of Treatment/Withdrawal.
14. **12-Lead ECG**: All patients require a single ECG measurement at screening. On-treatment ECGs will be performed on Day 1 of Cycles 1 and 2 only before avelumab infusion and at the end of avelumab infusion and at End of Treatment. 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 pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. Additional triplicate ECGs may be performed as clinically indicated. If a 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. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.
15. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging will include neck, chest, abdomen, and pelvis PET-CT at baseline and may additionally include CT with contrast or MRI if one of these two modalities (the same type of scan as baseline) will be continued for disease assessments; an additional PET-CT will be performed at 6 weeks and subsequently as clinically indicated. Imaging for tumor assessments will be conducted at screening, 6 weeks, 12 weeks and at 12-week intervals thereafter until documented disease progression regardless of initiation of subsequent anti-cancer therapy. Additional tumor assessments should also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), at End of Treatment/Withdrawal (if not done in the previous 6 weeks) and at follow-up visits. Assessment of response will be made using the Response Criteria for Malignant Lymphoma[42] s Appendix 2.

Footnotes for Schedule of Activities
16. **Adverse Events:** For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient'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 investigational product. SAEs occurring to a patient 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 investigational product are to be reported to the Sponsor. See Section 8.2. AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the patient has taken at least 1 dose of investigational product through and including 90 calendar days after the last administration of the study drug. 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 investigational product, irrespective of any intervening treatment. See Section 8.
17. **Concomitant Medications/Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).
18. **Randomization:** Patient number and treatment cohort allocation via interactive response technology (IRT) operated by the Sponsor. In the lead-in phase, doses will be randomly assigned, with patients randomized in a 1:1:1:1:1 allocation to 5 different treatment cohorts. Required information: site, patient identifiers and demographic information. Study treatment should begin on or within 3 days after randomization.
19. **Study Treatment:** Avelumab at the assigned dose level will be given as a 1-hour intravenous infusion every 2 weeks. Patients with disease progression who are continuing to derive clinical benefit from study treatment may be eligible to continue with avelumab, provided that the treating physician has determined that the benefit/risk for doing so is favorable.
20. **Day 2 Assessments**: Refer to Pharmacokinetic and Pharmacodynamic Sampling Schedule for assessments performed on Day 2.

SCHEDULE OF ACTIVITIES (3-Week Cycles, for Lead-In Phase)

Protocol Activities	Screening	Study Treatment (1 cycle = 21 days)									Post-Treatment	
		Cycle 1				Cycle 2				Cycles ≥3		
	≤28 Days Prior to Randomization	Day 1	Day 2 [20]	Day 7 (±2 days)	Day 14 (±2 days)	Day 1 (±3 days)	Day 2	Day 7 (±2 days)	Day 14 (±2 days)	Day 1 (±3 days)	End of Treatment /Withdrawal [1]	Follow-up After Last Dose (Day 30 ±3, Day 60 ±3, Day 90 ±3) [2]
Clinical Assessments												
Informed Consent [3]	X											
Medical/Oncological History [4]	X											
Baseline Signs/Symptoms [5]		X										
Physical Examination [6]	X	X				X				X	X	X
ECOG Performance Status	X	X				X				X	X	X
Vital Signs [7]	X	X		X		X		X		X	X	X
Contraception Check [8]	X	X				X				X	X	X
Laboratory Studies												
Hematology [9]	X	X		X	X	X		X	X	X	X	X
Blood Chemistry [10]	X	X		X	X	X		X	X	X	X	X
Coagulation [9]	X	X		X	X	X		X	X	X	X	X
Thyroid Function Tests and ACTH [11]	X									X (Cycles 3 and 6 and Q6 weeks thereafter)	X	X
HBV, HCV	X											
Pregnancy Test [12]	X	X				X				X	X	X
Urinalysis [13]	X	X				X				X	X	
12-Lead ECG [14]	X	X				X					X	
Disease Assessments												
Tumor Assessments [15]	X	X (Q6W until W12, then Q12W)									X	X
Other Clinical Assessments												
Adverse Events [16]	X	X									X	X

Protocol Activities	Screening	Study Treatment (1 cycle = 21 days)									Post-Treatment	
		Cycle 1				Cycle 2				Cycles ≥3		
	≤28 Days Prior to Randomization	Day 1	Day 2 [20]	Day 7 (±2 days)	Day 14 (±2 days)	Day 1 (±3 days)	Day 2	Day 7 (±2 days)	Day 14 (±2 days)	Day 1 (±3 days)	End of Treatment /Withdrawal [1]	Follow-up After Last Dose (Day 30 ±3, Day 60 ±3, Day 90 ±3) [2]
Concomitant Medications/Subsequent Treatments [17]	X	X									X	X
Randomization and Study Treatment [18]												
Avelumab [19]		X				X				X		
Pharmacokinetics		See table below										
Biomarkers		See table below										

Footnotes for Schedule of Activities
1. **End of Treatment/Withdrawal:** Obtain these assessments if not completed in the prior week, except for tumor assessments, which need not be repeated if performed within the prior 6 weeks.
2. **Follow-up After Last Dose:** To occur at least up to 90 days (on Days 30 ±3, 60 ±3, and 90 ±3) after the last dose of study treatment. All safety assessments are to continue through this period as noted in the Schedule of Activities. Safety assessments will cease if new anti-cancer therapy is initiated during this follow-up period.
3. **Informed Consent:** Must be obtained prior to undergoing any trial-specific procedure.
4. **Medical/Oncological History:** To include information on prior systemic therapy regimens, surgery, and radiation therapy.
5. **Baseline Signs/Symptoms:** To be recorded pre-dose for all patients, on Cycle 1 Day 1. Patients will be asked about any signs and symptoms experienced within the 14 days prior to randomization.
6. **Physical Examination:** Includes an examination of major body systems, assessment of ECOG performance status, and weight (height included at Screening only).
7. **Vital Signs:** Blood pressure (BP) and pulse rate to be recorded in supine or sitting position.
8. **Contraception Check:** Male patients who are able to father children and female 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, whenever one menstrual cycle is missed or if pregnancy is known or suspected in the patient or the patient's partner. Contraception checks will be routinely repeated at every treatment cycle during the active treatment period, at the End of Treatment/Withdrawal visit, and at the Day 30 Follow-up Visit.
9. **Hematology and Coagulation**: Required tests are listed in Table 7. Will be performed at screening prior to the first dose of study treatment and weekly through Cycles 1 and 2, then Day 1 of every cycle throughout the duration of the study. May also be performed when clinically indicated.

Footnotes for Schedule of Activities
10. **Blood Chemistry:** Full chemistry panel (required tests are listed in Table 7 is required at Screening, on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, then every 6 weeks thereafter and at End of Treatment/Withdrawal. Core chemistry panel (required tests are listed in Table 7) is required on, Cycle 3 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, then every 3 weeks (Q3 Week Schedule) thereafter. In addition a Core chemistry panel will be performed at Day 7 and Day 14 through Cycles 1 and 2. If full and core chemistry panels are scheduled at the same visit, then only the full chemistry panel will be performed. For patients with documented liver involvement at study entry, ALT, AST, total bilirubin, and alkaline phosphatase tests will be performed weekly in the first 6 weeks of treatment, ie, Cycle 1 Day 1, Cycle 1 Day 7, Cycle 1 Day 14, Cycle 2 Day 1, Cycle 2 Day 7, Cycle 2 Day 14, then on Day 1 of each cycle thereafter.
11. **ACTH and Thyroid Function Tests:** ACTH, Free T4, TSH. Performed at screening, Cycle 3 Day 1, Cycle 6 Day 1, every 6 weeks thereafter, EOT, and 30, 60, 90 days after last dose of study treatment and if clinically indicated. Test should additionally be performed in cases of suspected hypoadrenalism or hypopituitarism. See Section 7.1.3 in the full protocol for a list of the required Laboratory Tests.
12. **Pregnancy Test:** For female patients of childbearing potential, a serum or urine 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 (all patients) and at the baseline visit immediately before the administration of avelumab. Following a negative pregnancy result at screening, appropriate contraception must be commenced. Urine or serum pregnancy tests will also be routinely repeated at every cycle during the active treatment period, at the End of Treatment/Withdrawal visit, at the Day 30 Follow-up Visit and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations (see Section 7.1.1).
13. **Urinalysis:** Dipstick is acceptable Will be performed prior to screening, Day 1 of every cycle throughout the duration of the study and at End of Treatment/Withdrawal.
14. **12-Lead ECG**: All patients require a single ECG measurement at screening. On-treatment ECGs will be performed on Day 1 of Cycles 1 and 2 only before avelumab infusion and at the end of avelumab infusion and at End of Treatment. 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 pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. Additional triplicate ECGs may be performed as clinically indicated. If a 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. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.
15. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging will include neck, chest, abdomen, and pelvis PET-CT at baseline and may additionally include CT with contrast or MRI if one of these two modalities (the same type of scan as baseline) will be continued for disease assessments; an additional PET-CT will be performed at 6 weeks and subsequently as clinically indicated Imaging for tumor assessments will be conducted at screening, 6 weeks, 12 weeks, and at 12-week intervals thereafter until documented disease progression regardless of initiation of subsequent anti-cancer therapy. Additional tumor assessments should also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), at End of Treatment/Withdrawal (if not done in the previous 6 weeks) and at follow-up visits Assessment of response will be made using Response Criteria for Malignant Lymphoma.[42] See Appendix 2).
16. **Adverse Events:** For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient'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 investigational product. SAEs occurring to a patient 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 investigational product are to be reported to the Sponsor. See Section 8.2. AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the patient has taken at least 1 dose of investigational product through and including 90 calendar days after the last administration of the study drug.. 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 investigational product, irrespective of any intervening treatment. See Section 8.
17. **Concomitant Medications/Treatments**: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

Footnotes for Schedule of Activities
18. **Randomization:** Patient number and dose level allocation via interactive response technology (IRT) operated by the Sponsor. In the lead-in phase, doses will be randomly assigned, with patients randomized in a 1:1:1:1:1 allocation to 5 different treatment cohorts. Required information: site, patient identifiers and demographic information. Study treatment should begin on or within 3 days after randomization.
19. **Study Treatment:** Avelumab at the assigned dose level will be given as a 1-hour intravenous infusion every 3 weeks. Patients with disease progression who are continuing to derive clinical benefit from study treatment may be eligible to continue with avelumab, provided that the treating physician has determined that the benefit/risk for doing so is favorable.
20. **Day 2 Assessments**: Refer to Pharmacokinetic and Pharmacodynamic Sampling Schedule for assessments performed on Day 2.

SCHEDULE OF ACTIVITIES (Expansion Phase)

Protocol Activities	Screening	Study Treatment 70 mg Q2W and 500 mg Q2W = 1 cycle: 14 days				Post-Treatment		
	≤28 Days Prior to first dose of study treatment					End of Treatment /Withdrawal [1]	Follow-up After Last Dose (Day 30 ±3, Day 60 ±3, Day 90 ±3)[2]	Long-term Follow-up Every 12 weeks ±14 days[3]
		All Cycles	Cycles 1-3	Cycles 4-6 (patients who escalate to 500 mg Q2W at Cycle 4)	Cycles 7-9 (patients who escalate to 500 mg Q2W at Cycle 7)			
		Day 1 (±3 days for all but Cycle 1)	Day 7 (±2 days)	Day 7 (±2 days)	Day 7 (±2 days)			
Clinical Assessments								
Informed Consent[4]	X							
Medical/Oncological History [5]	X							
Baseline Signs/Symptoms[6]		X						
Physical Examination[7]	X	X	X	X	X	X	X	
ECOG Performance Status	X	X				X	X	
Vital Signs[8]	X	X	X	X	X	X	X	
Contraception Check[9]	X	X				X	X	
Laboratory Studies								
Hematology[10]	X	X	X	X	X	X	X	
Blood Chemistry[11]	X	X	X	X	X	X	X	
Coagulation[10]	X	X	X	X	X	X	X	
Thyroid Function Tests and ACTH[12]	X	Cycle 3, Cycle 6, and Q6W thereafter				X	X	
HBV, HCV	X							
Pregnancy Test[13]	X	X				X	X	

Protocol Activities	Screening	Study Treatment 70 mg Q2W and 500 mg Q2W = 1 cycle: 14 days				Post-Treatment		
	≤28 Days Prior to first dose of study treatment					End of Treatment /Withdrawal [1]	Follow-up After Last Dose (Day 30 ±3, Day 60 ±3, Day 90 ±3)[2]	Long-term Follow-up Every 12 weeks ±14 days[3]
		All Cycles	Cycles 1-3	Cycles 4-6 (patients who escalate to 500 mg Q2W at Cycle 4)	Cycles 7-9 (patients who escalate to 500 mg Q2W at Cycle 7)			
		Day 1 (±3 days for all but Cycle 1)	Day 7 (±2 days)	Day 7 (±2 days)	Day 7 (±2 days)			
Urinalysis[14]	X	X				X	X	
12-Lead ECG[15]	X	Cycle 1, Cycle 2		Cycle 4	Cycle 7	X		
Tumor Assessments[16]	X	X (Q6W until W12, then Q12W for one year after start of study treatment, and then every Q24W until documented disease progression by BICR assessment, regardless of initiation of subsequent anti-cancer therapy)						
Other Clinical Assessments								
Adverse Events[17]	X	X	X	X	X	X	X	
Concomitant Medications/Treatments[18]	X	X	X	X	X	X	X	
Avelumab[19]		X						
Subsequent anti-cancer treatments							X	X
Survival update[20]								X
Pharmacokinetics		See Table Below						
Biomarkers		See Table Below						

Footnotes for Schedule of Activities

1. **End of Treatment/Withdrawal:** Obtain these assessments if not completed in the prior week, except for tumor assessments, which need not be repeated if performed within the prior 6 weeks.
2. **Follow-up After Last Dose:** To occur at least up to 90 days (on Days 30 ± 3, 60 ± 3, and 90 ± 3) after the last dose of study treatment. All safety assessments are to continue through this period as noted in the Schedule of Activities. Safety assessments will cease if new anti-cancer therapy is initiated during this follow-up period.

Footnotes for Schedule of Activities
3. **Long Term Follow-up:** Beyond the 90 days until the end of the study, all patients will be followed every 12 weeks (+/-14 days) for survival and new anticancer treatment within the long-term follow-up
4. **Informed Consent:** Must be obtained prior to undergoing any trial-specific procedure.
5. **Medical/Oncological History:** To include information on prior systemic therapy regimens, surgery, and radiation therapy.
6. **Baseline Signs/Symptoms:** To be recorded predose for all patients on Cycle 1 Day 1. Patients will be asked about any signs and symptoms experienced within the 14 days prior to first dose of study treatment
7. **Physical Examination:** Includes on Day 1 of each cycle an examination of major body systems and assessment of ECOG performance status and weight (height included at Screening only). An abbreviated physical exam will be conducted on Day 7 of Cycles 1, 2 and 3, on Day 7 of Cycles 4, 5 and 6 for patients who are escalated to 500 mg Q2W at Cycle 4 and on Day 7 of cycles 7, 8, and 9 for patients who are escalated to 500 mg Q2W at week at Cycle 7. Particular attention must be paid to signs and symptoms of GVHD.
8. **Vital Signs:** Blood pressure (BP) and pulse rate to be recorded in supine or sitting position.
9. **Contraception Check:** Male patients who are able to father children and female 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, whenever one menstrual cycle is missed or if pregnancy is known or suspected in the patient or the patient's partner. Contraception checks will be routinely repeated at every treatment cycle during the active treatment period, at the End of Treatment/Withdrawal visit, at the Day 30 Follow-up Visit.
10. **Hematology and Coagulation**: Required tests are listed in Table 7. Will be performed at screening prior to the first dose of study treatment, at Day 1 and Day 7 through Cycles 1, 2 and 3 and on Day 7 of Cycles 4, 5 and 6 for patients who escalate to 500 mg Q2W at Cycle 4 and on day 7 of Cycle 7, 8 and 9 for patients who escalate to 500 mg Q2W at Cycle 7, and then at Day 1 of every cycle throughout the duration of the study, at End of Treatment/Withdrawal, at Day 30, Day 60 and Day 90 Follow-up after last dose, and at other times if clinically indicated.
11. **Blood Chemistry:** Full chemistry panel (required tests are listed in Table 7) is required at Screening, on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, then every 6 weeks, at End of Treatment/Withdrawal, at the 30-day Follow-up after last dose, and at other times if clinically indicated. Core chemistry panel (required tests are listed in Table 7) is required on Day 7 through Cycle 1, 2 and 3 and on Day 7 of Cycles 4, 5 and 6 for patients who escalate to 500 mg Q2W at Cycle 4 and on Day 7 of Cycles 7, 8 and 9 for patients who escalate to 500 mg Q2W at Cycle 7, at Cycle 3 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, then every 2 weeks thereafter, and at the Day 60 and Day 90 Follow-up after last dose. If full and core chemistry panels are scheduled at the same visit, then only the full chemistry panel will be performed. For patients with documented liver involvement at study entry, ALT, AST, total bilirubin, and alkaline phosphatase tests will be performed weekly in the first 6 weeks of treatment, ie, Cycle 1 Day 1, Cycle 1 Day 7, Cycle 2 Day 1, Cycle 2 Day 7, Cycle 3 Day 1, Cycle 3 Day 7, then on Day 1 of each cycle thereafter.
12. **ACTH and Thyroid Function Tests:** ACTH, Free T4, TSH. Performed at screening, Cycle 3 Day 1, Cycle 6 Day 1, every 6 weeks thereafter, EOT, and 30, 60, 90 days after last dose of study treatment, and if clinically indicated. Test should additionally be performed in cases of suspected hypoadrenalism or hypopituitarism. See Section 7.1.3 in the full protocol for a list of the required Laboratory Tests.
13. **Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL human chorionic gonadotropin , will be performed on two occasions prior to starting study therapy: once at the start of screening and at the baseline visit immediately before the administration of avelumab. Following a negative pregnancy result at screening, appropriate contraception must be commenced. Urine or serum pregnancy tests will also be routinely repeated at every treatment cycle during the active treatment period, at the End of Treatment/Withdrawal visit, at the Day 30 Follow-up Visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Urine pregnancy tests may also be repeated as per request of institutional review board /ethics committee (IRB/IECs) or if required by local regulations (see Section 7.1.1).
14. **Urinalysis:** Dipstick is acceptable. Will be performed at screening, Day 1 of every cycle throughout the duration of the study and at the End of Treatment/Withdrawal.

Footnotes for Schedule of Activities
15. **12-Lead ECG**: All patients require a single ECG measurement at screening. On-treatment ECGs will be performed on Day 1 of Cycles 1 and 2 only before avelumab infusion and at the end of avelumab infusion and at End of Treatment. 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 pharmacokinetics (PK), ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. Additional triplicate ECGs may be performed as clinically indicated. If a 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. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.
16. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging will include neck, chest, abdomen, and pelvis PET-CT. CT with contrast or MRI may be additionally performed, if clinically indicated. Imaging for tumor assessments will be conducted at screening, 6 weeks, 12 weeks, at 12-week intervals thereafter for one year from start of study treatment and every 24 weeks thereafter until documented disease progression by BICR assessment, regardless of initiation of subsequent anti-cancer therapy. Additional tumor assessments should also be conducted whenever disease progression is suspected (eg, symptomatic deterioration) and at End of Treatment/Withdrawal (if not done in the previous 12 weeks). For patient achieving a CR, a CT with contrast or MRI can be used instead of the PET-CT for tumor assessment until progression of disease which will require a PET-CT to be documented. **Disease responses will be assessed real-time by a Blinded Independent Central Review (BICR) according to processes defined in the Study Manual. The 6-week and the 12-week tumor assessment may be performed up to one week before the scheduled time so that images can undergo BICR review before Cycle 4 and Cycle 7.** Assessment of response will be made using the Lugano Classification[43] (Appendix 3).
17. **Adverse Events:** For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient'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 investigational product. SAEs occurring to a patient 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 investigational product are to be reported to the Sponsor. See Section 8.2. AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the patient has taken at least 1 dose of investigational product through and including 90 calendar days after the last administration of the study drug. 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 investigational product, irrespective of any intervening treatment. See Section 8.
18. **Concomitant Medications/Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).
19. **Study treatment:** Avelumab at the assigned dose level will be given as a 1-hour intravenous infusion every 2 weeks. The dose of 70 mg Q2W will be initially tested for safety and efficacy. Following 3 cycles of treatment, patients who at the 6-week tumor assessment achieve a CR will continue at the same dosing regimen. Patients achieving a PR at 6 weeks will continue at 70 mg Q2W for 3 additional cycles, and if the 12-week tumor assessment still shows a PR, patients will be dose escalated to 500 mg Q2W. Patients who at the 6-week tumor assessment achieve a SD will be dose escalated to 500 mg Q2W. In addition those patients who at the 6-week assessment are considered to have initial evidence of disease progression as confirmed by BICR but in the opinion of the Investigator are still experiencing clinical benefit (as defined in Section 5.4.1.1) may continue treatment with study drug at the Investigator's discretion and following discussion with the Sponsor. Such patients may be considered for escalation to 500 mg Q2W. Dose escalation to 500 mg Q2W after the 6-week or the 12-week tumor assessment, will be only permitted so long as there is no clinical evidence of GVHD or treatment-related Grade ≥2 AEs with a duration of more than 14 days. Patients with PD at 6 weeks in the absence of clinical benefit will be permanently discontinued from study treatment.
20. **Survival Assessment:** Beyond Day 90, post treatment survival status will be collected every 12 weeks ±14 days until deaths. This includes the collection of information on subsequent anti-cancer therapies. Telephone communication is acceptable.

Pharmacokinetic and Pharmacodynamic Sampling Schedule (2-Week Cycles, for Lead-In Phase)

Protocol Activities	Screening	Study Treatment (1 cycle = 14 days)							Post-Treatment	
		Cycle 1			Cycle 2			Cycles ≥3		
	≤28 Days Prior to Randomization	Day 1	Day 2	Day 7 (±2 days)	Day 1	Day 2	Day 7 (±2 days)	Day 1 (±3 days)	End of Treatment / Withdrawal	Follow-up After Last Dose (Day 30 ±3, Day 60 ±3, Day 90 ±3)
Pharmacokinetics[1]		X	X	X	X	X	X	X (Prior to dosing in Cycles 3, 4, 6, 8, then Q12W up to cycle 20)		
Banked Blood Biospecimen[2]	X							X		
De Novo Tumor Biopsy[3]	X (optional)							X (Cycle 3; optional)	X (optional)	
Anti-Avelumab Antibodies /Neutralizing Antibodies[4]		X			X			X (Cycles 3, 4, 6, 8, then Q12W up to cycle 20)	X	
Target Occupancy[5] (whole blood)		X	X	X	X	X	X	X (Cycles 3, 4)	X	
Immune Cell Phenotyping[6] (whole blood)	X	X			X			X (Cycles 3, 4, 7, 10)	X	
CCI [redacted]										

Footnotes for Schedule of Activities

1. **Pharmacokinetics:** Serial PK samples will be collected on Day 1 of Cycles 1 and 2. A 3.5 mL blood sample will be collected at pre-dose (0), 1, 6, 24 (Day 2), and 144 (Day 7) hours post-dose. Thereafter, a 3.5 mL blood sample will be collected pre-dose on Day 1 of Cycles 3, 4, 6, 8, and every 12 weeks up to cycle 20.
2. **Banked Blood Biospecimen:** A 4-mL blood sample will be collected at Screening and Day 1 (+/- 3 days) of Cycle 3 to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. CCI [redacted]
3. ***De Novo* Tumor Biopsy:** pre-treatment baseline, on-treatment, (at study Day 1 (±2 days) of Cycle 3, and/or end of treatment /disease progression *de novo* (ie, fresh) tumor biopsies (lymph node or bone marrow) are optional in the lead-in phase. If conducted, a baseline biopsy must be collected within 28 days prior to randomization. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. A portion of the *de novo* biopsy(ies) should be formalin-fixed and paraffin-embedded and a portion of the *de novo* biopsy should be added to RNAlater solution (see Study Manual). The resulting FFPE tissue block(s) and tumor sample in RNAlater should be submitted to the Central Laboratory. An archival FFPE tumor tissue block either from initial diagnosis, or from a tumor biopsy that was obtained no more than 6 months prior to enrollment and after which the patient had not received any systemic anti-cancer therapy prior to enrollment may be submitted in place of a baseline *de novo* biopsy
4. **Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (Nab):** One blood sample (3.5 mL) for anti-avelumab antibodies will be collected pre-dose on Day 1 of Cycles 1, 2, 3, 4, 6, and 8 and every 12 weeks up to cycle 20 and for the End of Treatment/Withdrawal. All samples should be drawn within 2 hours before start of avelumab infusion. Follow up samples are only collected in patients who are ADA positive at end of treatment. All the samples that are positive for ADA may also undergo characterization for Nab.
5. **Target Occupancy:** A 3-mL whole blood sample will be collected on Days 1 (pre-dose), 2, and 7 of Cycles 1 and 2, Day 1 (pre-dose) of Cycles 3 and 4 and at End of Treatment/Withdrawal. PD-L1 occupancy by avelumab on immune cells will be measured using flow cytometry.
6. **Immune Cell Phenotyping:** A 6-mL whole blood sample will be collected at screening, Day 1 (pre-dose) of Cycle 1, Day 1 of Cycles 2, 3, 4, 7, 10 and at End of Treatment/ Withdrawal. Immune cell phenotypes associated with anti-tumor immunity and immune regulation will be measured by flow cytometry.

CCI [redacted]

Pharmacokinetic and Pharmacodynamic Sampling Schedule (3-Week Cycles, for Lead-In Phase)

Protocol Activities	Screening	Study Treatment (1 cycle = 21 days)									Post-Treatment	
		Cycle 1				Cycle 2				Cycles ≥3		
	≤28 Days Prior to Randomization	Day 1	Day 2	Day 7 (±2 days)	Day 14 (±2 days)	Day 1	Day 2	Day 7 (±2 days)	Day 14 (±2 days)	Day 1 (±3 days)	End of Treatment / Withdrawal	Follow-up Day 90 Days After Last Dose (Day 30 ±3, Day 60 ±3, Day 90 ±3)
Pharmacokinetics[1]		X	X	X	X	X	X	X	X	X (Prior to dosing of Cycles 3, 4, 6, 8, then Q12W up to cycle 20)		
Banked Blood Biospecimen[2]	X							X				
De Novo Tumor Biopsy[3]	X (optional)							X (optional)			X (optional)	
Anti-Avelumab Antibodies / Neutralizing Antibodies [4]		X				X				X (Cycles 3, 4, 6, 8, then Q12W up to cycle 20)	X	
Target Occupancy[5] (whole blood)		X	X	X	X	X	X	X	X	X (Cycle 3, 4)	X	
Immune Cell Phenotyping[6] (whole blood)	X	X			X			X		X (Cycle 3, 5, 7))	X	
CCI												

Footnotes for Schedule of Activities
1. **Pharmacokinetics:** Serial PK samples will be collected on Day 1 of Cycles 1 and 2. A 3.5 mL blood sample will be collected at pre-dose (0), and 1, 6, 24 (Day 2), 144 (Day 7), and 312 (Day 14) hours post dose. Thereafter, a 3.5 mL blood sample will be collected pre-dose on Day 1 of Cycles 3, 4, 6, 8 and every 12 weeks up to cycle 20.
2. **Banked Blood Biospecimen:** A 4-mL blood sample will be collected at the Screening and Day 7 (+/-2) of Cycle 2 to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. CCI [redacted]
3. ***De Novo* Tumor Biopsy:** Pre-treatment baseline, on-treatment, (at study Day 7 (±2 days) of Cycle 2, and/or end of treatment /disease progression *de novo* (ie, fresh) tumor biopsies (lymph node or bone marrow) are optional in the lead-in phase. If conducted, a baseline biopsy must be collected within 28 days prior to randomization. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. A portion of the *de novo* biopsy(ies) should be formalin-fixed and paraffin-embedded and a portion of the *de novo* biopsy should be added to RNAlater (see Study Manual). The resulting FFPE tissue block(s) and tumor sample in RNAlater should be submitted to the Central Laboratory. An archival FFPE tumor tissue block either from initial diagnosis or from a tumor biopsy that was obtained no more than 6 months prior to enrollment and after which the patient had not received any systemic anti-cancer therapy prior to enrollment may be submitted in place of a baseline *de novo* biopsy.
4. **Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (Nab):** One blood sample (3.5 mL) for anti-avelumab antibodies will be collected pre-dose on Day 1 of Cycles 1, 2, 3, 4, 6 and 8 and at the end of treatment visit. Subsequently, testing should be performed approximately every 12 weeks up to cycle 20. All samples should be drawn within 2 hours before start of avelumab infusion. Additional samples for anti-avelumab antibodies will be collected at End of Treatment/Withdrawal. Follow up samples are only collected in patients who are ADA positive at end of treatment. All the samples that are positive for ADA may also undergo characterization for Nab.
5. **Target Occupancy:** A 3 mL whole blood sample will be collected on Days 1 (pre-dose), 2, 7, 14 of Cycles 1 and 2, Day 1(pre-dose) of Cycles 3, 4 and at End of Treatment/Withdrawal. PD-L1 occupancy by avelumab on immune cells will be measured using flow cytometry.
6. **Immune Cell Phenotyping:** A 6 mL whole blood sample will be collected at screening and Day 1 (pre-dose) and Day 14 of Cycle 1, Day 7 of Cycle 2, Day 1 (pre-dose) of Cycle 3, 5, 7; and at End of Treatment/Withdrawal. Immune cell phenotypes associated with anti-tumor immunity and immune regulation will be measured by flow cytometry.

CCI [redacted]

Pharmacokinetic and Pharmacodynamic Sampling Schedule (Expansion Phase)

Protocol Activities	Screening	Study Treatment (1 cycle = 14 days)						Post-Treatment	
		Cycle 1		Cycle 2		Cycle 3	Cycles ≥4		
	≤28 Days Prior to First dose of study treatment	**Day 1**	**Day 7**	**Day 1**	**Day 7**	**Day 1**	**Day 1**	**End of Treatment / Withdrawal**	**Follow-up After Last Dose (Day 30 ±3, Day 60 ±3, Day 90 ±3)**
Visit Window			**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±3 days)**	**(±7 days)**	
Pharmacokinetics[1]		X	X	X	X	X	X (Prior to dosing on Cycle 4, 7 & 13 for all patients)		
Banked Blood Biospecimen[2]		X							
Mandatory *De Novo* Tumor Biopsy[3]	X					X (Cycle 3 Day 7 ±7 days)			
Optional *De Novo* Tumor Biopsy[3]		As clinically indicated throughout At week 12/24 following tumor assessment scan						X	
Anti-Avelumab Antibodies and Neutralizing Antibodies[4]		X		X		X	X (Prior to dosing on Cycle 4, 7, & 13 for all patients)	X	X

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[redacted]

Footnotes for Schedule of Activities

1. **Pharmacokinetics:** Blood samples (3.5-mL whole blood at each time point) will be collected from all patients in the study at pre-dose and 1 hour post-infusion (ie, at the end of infusion) on Day 1 of Cycles 1, 2 and 3. Blood samples will also be collected on Day 7 of Cycles 1 and 2. Thereafter, a 3.5 mL blood sample will be collected pre-dose on Day 1 of Cycle 4, 7, and 13 and prior to dosing after the first dose of study treatment.
2. **Banked Blood Biospecimen:** A 4-mL blood sample (Prep D1) will be collected at Day 1 (pre-dose) of Cycle 1 to be retained for potential biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. CCI [redacted].
3. ***De Novo* Tumor Biopsy:** For the expansion phase, patients must consent to undergo a pre-treatment and an on-treatment biopsy assuming lesions to be biopsied may be safely accessed and sampled. *De novo* (ie, fresh) tumor biopsy is mandatory at baseline and at Day 7 (+/- 7 days) of Cycle 3, following the tumor assessment scan during week 6, and assuming lesions for biopsy can be accessed safely. Baseline biopsy must be collected within 28 days prior to first dose of study treatment, but where possible upon completion of screening activities. If an archival FFPE block is available from a biopsy taken within 3 months of first dose of study treatment, and there has been no intervening systemic anti-cancer therapy, this can substitute for the baseline de novo sample. Where possible, the on-treatment biopsy should be performed close to the 6 week tumor response scan, and before Cycle 4 dosing. An optional *de novo* tumor sample is particularly encouraged following the 12 or 24-week scans, in patients who dose escalate at Cycle 4 or 7, respectively, and can also be collected from all subjects as clinically indicated and/or 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. Note, if a biopsy is completed on the same day as CT scan, it must be completed after the scan so that full tumor assessment information is available. A portion of the *de novo* biopsy(ies) should be formalin-fixed and paraffin-embedded, and tissue permitting, a second portion should be prepared as fresh-frozen (details for sample collection, processing, storage and shipping will be provided in the Study Manual). The resulting FFPE and frozen tissue block(s) should be submitted to the Central Laboratory. In the event a *de novo* biopsy cannot be safely obtained, submission of an archival FFPE tumor tissue block or slides from the closest time point that is within 6 months of first dose of study treatment must be provided.
4. **Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (Nab):** One blood sample (3.5 mL) for anti-avelumab antibodies will be collected pre-dose on Day 1 of Cycles 1, 2, 3, 4, 7 and 13 after the first dose of study treatment. All samples should be drawn within 2 hours before start of avelumab infusion. Additional samples for anti-avelumab antibodies will be collected at the End of Treatment/Withdrawal. Follow up samples for ADA will also be collected on Day 30, 60 and 90 follow up visits after the last dose of avelumab. All the samples that are positive for ADA may also undergo characterization for Nab.

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1. INTRODUCTION

This is a Phase 1b dose-finding study to evaluate the pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of avelumab (MSB00100718C) in adult patients with relapsed or refractory classical Hodgkin's Lymphoma (cHL). The primary purpose of the lead-in phase of this study is to assess the pharmacokinetics, biological activity, and early signs of efficacy of various avelumab dosing regimens in patients with relapsed or refractory cHL in whom a prior autologous or allogeneic HSCT (allo-HSCT) has failed, or who are ineligible for HSCT. The primary purpose of the expansion phase of the study is to evaluate the anti-tumor activity of select dose regimen(s) of avelumab in patients with relapsed or refractory cHL in whom a prior allogeneic HSCT has failed.

1.1. Mechanism of Action/Indication

Avelumab (also referred to as MSB0010718C) is a fully human IgG1 antibody directed against programmed death ligand 1 (PD-L1), a 290 amino acid type I transmembrane protein encoded by the *Cd274* gene on human chromosome 9. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors programmed death 1 (PD-1) and B7.1 (CD80). This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response. PD-L1 (also called B7-H1 and CD274) is expressed on resting and activated T cells, B cells, macrophages, dendritic cells, and mast cells.[11]

In vivo anti-tumor effects were found to be primarily mediated by CD8+ T cells as evidenced by the observation that in vivo depletion of this cell type completely abrogated the anti-tumor efficacy of avelumab. The contribution of ADCC as a potential mechanism of anti-tumor activity was further demonstrated in vivo using a deglycosylated version of avelumab to abrogate fragment crystalline (Fc) receptor binding or via the systemic depletion of natural killer (NK) cells. In both settings, loss of in vivo ADCC potential significantly reduced the anti-tumor activity.

Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure.[15]

1.2. Background and Rationale

Hodgkin's lymphoma is a B-cell malignancy and is one of the most common lymphomas involving peripheral lymph nodes and may impact organs including liver, lung as well as bone marrow. Hodgkin's lymphoma affects approximately 9,000 new patients each year and represents approximately 12% of all lymphomas seen in the United States.[1] Classical Hodgkin's lymphoma (cHL) and nodular lymphocyte-predominant Hodgkin's lymphoma are the two main types of Hodgkin's lymphoma. cHL accounts for most (~95%) Hodgkin's Lymphoma diagnosed.[2] The standard initial treatment for patients with newly diagnosed cHL includes chemotherapy or combined modality therapy, followed by restaging with PET/CT to assess treatment. While patients with Hodgkin's Lymphoma commonly respond well to initial therapy, a subset of patients (~25%) continue to experience relapsed disease and have very poor prognosis.[3]

cHL is defined by the subclassifications of: nodular sclerosis (60-80% of Hodgkin's lymphoma cases), mixed cellularity (25-30% of cases), lymphocyte-rich (5%) and lymphocyte-depleted (1%), depending upon histology and phenotype of the tumor cells. Hodgkin's lymphoma tumor cells represent less than 2% of cells in the tissue. Mononucleated Hodgkin's and bi- or multi-nucleated Reed-Sternberg cells (HRS) are the malignant cells in cHL.[13,14] In approximately 40% of Hodgkin's lymphoma cases, the tumor cells are infected by Epstein Barr virus.[10]

The unique cellular composition of Hodgkin's lymphoma provides a number of opportunities to target either the malignant HRS cell or the inflammatory tumor microenvironment. HRS cells appear to orchestrate their microenvironment in many ways to evade host immune attack by recruiting immune bystander cells, such as non-neoplastic helper T lymphocytes, macrophages, mast cells, and eosinophils.[22,23,24,25] HRS cells are commonly surrounded by $CD4^+$ T-lymphocytes (both the Th1 and the Th2 type). These regulatory T-cells may play a pathogenic role in cHL, since they could contrast the potential cytotoxic effect of $CD8^+$ cells against HRS cells. Moreover, HRS cells secrete cytokines and chemokines creating a mobile microenvironment and utilize receptor signaling pathways to preserve their high proliferative capacity and anti-apoptotic phenotype.[26]

The programmed death 1 (PD-1) pathway functions as a barrier to limit T-cell–mediated immune responses. PD-1 ligands, such as PD-L1, induce PD-1 signaling and associated T-cell "exhaustion," a reversible inhibition of T-cell activation and proliferation.[27] In addition, several pathways are constitutively activated in cHL, including NF-kB, JAK/STAT and aberrant expression of receptor tyrosine kinases. In approximately 40% of classical Hodgkin's lymphoma cases, encoding of *SOCS1* is inactivated by mutations in the JAK/STAT pathway.[20] The chromosomal region 9p24 includes PD-L1 and several genes residing within this region have been postulated to be a factor in cHL.[4,5] Thus, PD-L1 expression may play a role in HRS cells avoiding immunosurveillance in cHL.

With regard to current treatments, early-stage cHL is generally treated with four cycles of chemotherapy using ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) followed by radiation therapy. Advanced-stage cHL is usually treated with six to eight cycles of ABVD, followed by radiation to residual masses. Current treatment algorithms for cHL patients who relapse after ABVD incorporate a platinum-based regimen followed by high dose chemotherapy with autologous HSCT. If non-responsive to the platinum-based regimen, a gemcitabine-based regimen could then be administered, and if response does not follow this regimen (transplant ineligible), then a third-line treatment could include brentuximab vedotin or an investigational agent.

Brentuximab vedotin was approved by the U.S. Food and Drug Administration (FDA) in 2011 for the treatment of patients with HL after failure of autologous Hematopoietic Stem Cell Transplant (HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidates for autologous HSCT. This agent is an antibody-drug conjugate that contains a monoclonal antibody targeting CD30 linked to an antimitotic agent. After attaching to the cell surface receptor CD30, brentuximab vedotin

internalizes into the target cell where it delivers the active component of the drug. Although brentuximab has a high response rate, it is frequently not curative and patients may then relapse. Therefore, there is need for additional therapies in relapsed cHL.

Allogeneic HSCT may also be an option for selected patients with relapsed/refractory cHL. The use of reduced intensity conditioning regimens has improved OS and reduced the non-relapse mortality of this approach, consequently the percentage of patients with cHL undergoing an allogeneic HSCT has increased. However, the prognosis of these patients remains poor with an expected 2-year PFS ranging from 18% to 39%.[46] Management of patients relapsing after allogeneic HSCT remains challenging and although different approaches have been reported (eg, reduction of immunosuppression, donor lymphocyte infusion, a second allogeneic HSCT, and clinical trials) there is no standard therapy for this patient population, which remains an area of high unmet medical need.

1.3. Pharmaceutical and Therapeutic Background

1.3.1. 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.[16] For complete details of the in vitro and nonclinical studies, refer to avelumab Investigator's Brochure (IB).[15]

Avelumab is being developed jointly by Pfizer and Merck KGaA/EMD Serono, and is being studied in Phase 1, 2 and 3 clinical protocols in a variety of cancers, including non-small cell lung cancer, gastric cancer, Merkel cell carcinoma, renal cell carcinoma, ovarian cancer, urothelial cancer, head and neck cancer, and Hodgkin's and non-Hodgkin's Lymphomas, as single agent or in combination with chemotherapy, tyrosine kinase inhibitors, radiotherapy, or other immune modulating agents.

The safety profile of avelumab administered intravenously (IV) as single agent at a dose of 10 mg/kg every 2 weeks (Q2W) has been characterized primarily in 1738 adult patients from studies EMR100070-001 in various solid tumors (N=1650) and EMR100070-003 Part A in Merkel cell carcinoma (N=88). Study EMR100070-001 consists of 2 parts, a dose escalation phase and a dose expansion phase, which is performed in selected tumor types.

As of 09 June 2016, a total of 53 patients were treated in the dose escalation phase of the EMR100070-001 study, with 4, 13, 15, and 21 patients treated with avelumab doses of 1, 3, 10, and 20 mg/kg Q2W, respectively. 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 (a Grade 3 immune related adverse event characterized by increased creatine kinase, myositis, and myocarditis) was observed in 1 patient at the dose of 20 mg/kg.

The dose expansion phase of study EMR100070-001 included patients with non-small cell lung cancer, gastric cancer, breast cancer, colorectal cancer, castration resistant prostate cancer, adrenocortical carcinoma, melanoma, mesothelioma, urothelial carcinoma, ovarian cancer, renal cell carcinoma, and squamous cell cancer of the head and neck. Study EMR100070-003 Part A was conducted in patients with Merkel cell carcinoma.

A summary of pooled safety data from patients treated at 10 mg/kg Q2W in studies EMR100070- 001 and EMR100070-003 (N=1738) is provided here.

Treatment-emergent adverse events (TEAEs) were observed in 1697 (97.6%) patients, with the most frequent (≥10%) being fatigue (32.4%), nausea (25.1%), diarrhea (18.9%), constipation (18.4%), decreased appetite (18.4%), infusion related reaction (17.1%), weight decreased (16.6%), vomiting (16.2%), anemia (14.9%), abdominal pain (14.4%), cough (13.8%), pyrexia (13.6%), dyspnea (13.2%), edema peripheral (11.9%), back pain (11.8%), and arthralgia (10.4%).

Treatment-related TEAEs were observed in 1164 (67.0%) patients, and the most frequent (≥5%) were fatigue (17.7%), infusion related reaction (17.0%), nausea (8.6%), diarrhea (7.1%), chills (6.7%), pyrexia (6.1%), decreased appetite (5.2%), and hypothyroidism (5.0%).

A total of 177 patients (10.2%) experienced Grade ≥3 treatment-related TEAEs, and the most frequent (≥0.5%) were fatigue (1.0%), lipase increased (1.0%), Gamma-Glutamyl Transferase (GGT) increased (0.6%), infusion related reaction (0.6%), and AST increased (0.5%).

A total of 777 (44.7%) patients had at least 1 serious TEAE. Treatment-related serious TEAEs were reported in 108 (6.2%) patients, with the most frequent (≥0.2%) being infusion related reaction (0.9%), pneumonitis (0.6%), pyrexia (0.3%), adrenal insufficiency (0.3%), and hypothyroidism, diarrhea, vomiting, autoimmune disorder, autoimmune hepatitis, transaminases increased, dyspnea, and colitis (0.2% each).

There were 911 deaths (52.4%) in the pooled safety data set. The majority of deaths were due to progressive disease (744, 42.8%). There were 59 (3.4%) deaths attributed to TEAEs not related to trial treatment, and 4 deaths (0.2%) attributed to a treatment-related TEAE by the investigator and which occurred up to 30 days after the last dose of avelumab: pneumonitis (1 case), acute liver failure (1 case), respiratory distress (in the context of sepsis) (1 case), and autoimmune hepatitis with hepatic failure (1 case). In addition, 1 patient died with acute respiratory failure (in the context of lung cancer progression) considered related to avelumab by the investigator 37 days after the last dose of avelumab. The cause of death was marked as “other” or “unknown” in 17 (1.0%) and 83 (4.8%) of cases, respectively.

A total of 244 patients (14.0%) permanently discontinued avelumab treatment due to TEAEs, including 107 patients (6.2%) discontinuing because of treatment-related TEAEs. The most frequent treatment related TEAEs leading to treatment discontinuation were infusion related reaction (1.8%), GGT increased (0.4%), and diarrhea, fatigue, autoimmune disorder, ALT increased, blood creatine phosphokinase (CPK) increased, lipase increased, arthralgia, and pneumonitis (0.2% each).

Immune-related adverse events (irAEs): in the pooled safety data (N=1738), a total of 247 patients (14.2%) experienced irAEs, defined as adverse events requiring use of corticosteroids (and/or hormonal therapy for endocrinopathies), and no clear alternate etiology. The median time to first onset of an irAE was 11.7 weeks. The most frequent irAEs were thyroid disorders including hypothyroidism (5.2%), hyperthyroidism (0.4%) and thyroiditis (0.2%), immune-related rash (5.2%), immune-related colitis (1.5%), immune-related pneumonitis (1.2%), immune-related hepatitis (0.9%), adrenal insufficiency (0.5%) and immune-related myositis (0.5%). In addition, irAEs reported in 0.1% of patients in the pooled safety dataset included: type 1 diabetes mellitus, immune-related nephritis/renal dysfunction, hypopituitarism, uveitis and Guillain-Barre Syndrome. The majority of irAEs were Grade 1 or Grade 2 in severity, with 39 (2.2%) being of Grade ≥3 severity. Fatal outcome was reported in 1 patient (0.1%) with immune-related pneumonitis, and 2 patients (0.1%) with immune-related hepatitis. Other relevant irAEs reported with avelumab outside the pooled safety dataset included 1 case of fatal immune-related myocarditis in Study B9991002 (avelumab in combination with axitinib for RCC), 1 case of non-fatal immune-related myocarditis in the 20 mg/kg cohort of the dose escalation phase of Study EMR100070-001, and 2 patients with non-fatal graft versus host disease (GVHD) in Study B9991007 (avelumab in patients with classical Hodgkin's lymphoma).

Infusion-related reactions (IRRs): a total of 439 patients (25.3%) experienced at least 1 IRR, defined as a TEAE coded under the PTs of infusion related reaction, drug hypersensitivity, hypersensitivity, anaphylactic reaction, type I hypersensitivity, chills, pyrexia, back pain, dyspnea, hypotension, flushing, and abdominal pain according to a predefined case definition. The most common PTs that met the definition for an IRR included: infusion related reaction (17.0%), chills (5.4%), and pyrexia (3.6%). Most of the events were of Grade 1 or Grade 2 severity. Grade ≥3 IRRs occurred in 12 patients (0.7%) including 3 patients (0.2%) who experienced Grade 4 IRRs. No Grade 5 IRRs were reported. In most cases, the first occurrence of an IRR was related to the first infusion, with only 6 patients experiencing the first IRR at the fifth or later infusion. All Grade ≥3 IRRs occurred with the first (7 patients) or second (5 patients) infusion. Overall, 21.6% of patients had 1 IRR, 2.6% of patients had 2 IRRs, 14 patients (0.8%) had 3 IRRs, and 3 patients had >3 IRRs. IRR recurrence after the fourth infusion was rare (15 patients) and all recurrent IRRs were of Grade 1 or 2 severity. In 35 patients (2.0%), treatment was permanently discontinued because of an IRR.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the avelumab IB.[15]

Avelumab pharmacokinetics: Avelumab pharmacokinetics and dose proportionality following the first 1-hour infusion have been characterized in 57 Caucasian patients treated in the dose escalation and expansion cohorts 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 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 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 μg/mL) of avelumab required for >90% TO. For patients treated with 3 mg/kg of avelumab, 10 of 13 patients reached the required serum level (3.7-8.3 μg/mL).

Complete information for avelumab may be found in the single reference safety document (SRSD), which for this study is the avelumab IB.[15]

1.4. Rationale for Studying Avelumab in Hodgkin's Lymphoma

Attempts to selectively manipulate components of the immune system involved in tumor immune surveillance and anti-tumor responses have led to the development of immune checkpoint inhibitors targeting molecules such as programmed death 1 (PD-1) and its ligand (PD-L1). Engagement of PD-1 by its ligands PD-L1 and PD-L2 leads to decreased T cell proliferation, cytotoxicity, and an increased susceptibility to apoptosis. Blockade of the PD-1/PD-L1 axis has been shown to enhance anti-tumor responses in a range of different indications and clinical trials.[38]

Immunomodulation through the inhibition of the PD-1/PD-L1 and PD-L2 or the PD-1/PD-L1 interactions has the potential to provide durable clinical benefit in some patients who are refractory to standard-of-care therapy.[38,40] Selective blockade of the PD-1/PD-L1 interaction with avelumab may, in principle, exert its anti-tumor effects though two distinct mechanisms: (i) direct tumor cell targeting through engagement of the innate immune system via the intact antibody-dependent cell-mediated cytotoxicity (ADCC) functionality that has been specifically edited out of all other PD-1 and PD-L1 checkpoint inhibitors currently in the clinic, and (ii) indirectly through impacting the immune system by reversing the inhibition of 'exhausted' tumor-infiltrating cytotoxic $CD8^+$ T cells, and restoring anti-tumor immunity.

Hodgkin's lymphoma has a distinct targetable genetic abnormality in that the majority of patients have a genetic alteration involving copy number increases and amplification of chromosome 9p24.1. This region typically encodes the PD-L1, PD-L2, and JAK2 genes.[19] The presence of abnormalities in this genetic locus leads to the overexpression of the PD-L1 and PD-L2 protein at the surface of malignant Reed-Sternberg (RS) cells. PD-L1 expressed at the surface of RS cells is thought to be responsible for the functional suppression of the activity of cytotoxic anti-tumor T cells expressing the PD-1 receptor.

PD-L1 ligand expressed on RS cells may also down-modulate the activity of other cell types expressing the PD-1 receptor, including natural killer (NK) cells, which might otherwise be capable of mediating ADCC through IgG1 isotype therapeutic antibodies that target RS cells. Avelumab may block the binding of the PD-1 receptor on key anti-tumor effector cells to PD-L1 ligand expressed on RS cells, thereby restoring the anti-tumor immune response, while also potentiating NK-directed ADCC activity directed at RS cells.

It is currently not known whether molecules other than PD-L1 contribute to the inhibition of infiltrating immune cells in cHL. In particular, the functional significance of PD-L2, the other ligand for PD-1, in contributing to the disease phenotype of cHL remains unclear. If PD-L2 does have an important role in driving the cHL disease phenotype, it might be expected that an anti-PD-L1 inhibitor would be less efficacious than a PD-1 inhibitor, which blocks the molecular interactions with both the PD-L1 and PD-L2 ligands. However, even if PD-L2 does make a significant contribution to the cHL disease phenotype, anti-PD-L1 agents like avelumab which leave the PD-L2 ligand functionally intact may, in principle, still be effective through their potential to mediate ADCC activity and direct kill of malignant HRS cells.

Emerging clinical data suggests that checkpoint blockade with anti-PD-1/PD-L1 agents may offer an effective therapeutic option in a broad selection of lymphoid malignancies, especially in those such as cHL that harbor the 9p24.1 genetic abnormality. Lymphoid malignancies such as cHL which have the 9p24.1 alteration have been found to have a higher response rate to checkpoint inhibition than those, such as non-Hodgkin's lymphoma (NHL) indications, which lack this genetic change.[6,7,8] Nivolumab, a high-affinity, fully human anti-PD-1 monoclonal antibody (mAb) has been has been granted accelerated approval for the treatment of cHL that has relapsed or progressed following autologous HSCT and post-transplantation brentuximab vedotin.[9,37] In a cohort of 95 patients from two studies (Checkmate 205 and 039), an ORR of 65% (95% CI: 55, 75) was reported in 62 patients, including: 7 (7%) with a complete response (CR) and 55 (58 %) with a partial response (PR). The median duration of response was 8.7 months (6.8, not evaluable). In addition an update of the arm B from study Checkmate 205 enrolling patients treated with Brentuximab Vedotin after failing an autologous HSCT was presented at the 2016 ASH congress: at data cut-off (April 2016) with median duration of follow-up of 15.4 months (range 1.9—18.5), 80 patients had been treated in that cohort. Independent Radiologic Review Committee (IRRC)-assessed ORR for patients in 205B was 68% (95% CI, 56%, 78%). CR and PR rates per IRRC were 8% (3%, 16%) and 60% (48%, 71%), respectively. With longer follow-up, the median duration of response was prolonged to 13.1 months (95% CI, 8.7, not reached; range, 0.0, 14.2+). The median duration of CR (DOCR) was not reached (95% CI, 4.6, not available [NA]; range, 0.7+, 10.4+) and the median duration of PR was 13.1 months (95% CI, 7.79, NA; range, 0.0, 13.4+). IRRC median PFS was 14.8 months (95% CI, 11.3 months, NA); 12-month PFS was 54.6% (95% CI, 40.9%, 66.4%), and 12-month overall survival (OS) was 94.9% (median OS not reached). Of 37 patients (46%) who discontinued nivolumab, the most common reasons were disease progression (n = 19 [24%]), allogeneic stem cell transplant (n = 7 [9%]) and adverse events (n = 5 [6%]).[47]

The other PD-1 inhibitor pembrolizumab has also been granted accelerated approval for adult and pediatric patients with refractory cHL, or those who have relapsed after three or more lines of therapy. Approval was based on data from 210 adult cHL patients enrolled in a multicenter, non-randomized, open-label clinical trial. Patients had refractory or relapsed disease after autologous HSCT (129 patients) and/or Brentuximab Vedotin (175 patients), and received a median of four prior systemic therapies (range: 1, 12). With a median follow-up of 9.4 months (range: 1-15), the ORR was 69% (95% CI: 62, 75). This included PR in 47% of patients and CR in 22%. The estimated median response duration was 11.1 months (range 0 to 11.1).[38]

While these results are encouraging, there is room for improvement with therapies that increase the ORR.

Due to the potential risk of checkpoint inhibitors-induced Graft-Versus-Host Disease (GVHD), patients with a prior allo-HSCT were excluded from the nivolumab studies, while pembrolizumab, although excluding only patients who had received an allo-HSCT in the past 5 years or greater than 5 years but with symptoms of GVHD, did not enroll any patient with a prior allo-HSCT. As a result, only limited data are available for the use of checkpoint inhibitors in post-allo-HSCT patients. The potential to enhance the graft-versus-lymphoma response in post-allo-HSCT patients, however, provides a rational basis for the use of checkpoint inhibitors in this subgroup of cHL patients despite the risk of inducing GVHD.[31]

GVHD is a common and potentially life-threatening complication of allo-HSCT. It is immunologically-mediated and contributes to the high morbidity and mortality of allo-HSCT.[32] GVHD has several clinical manifestations, and these may emerge both as a result of the disease, and its treatment. Several recent case reports and patient series indicate that checkpoint inhibitors may be efficacious in the post-allo-HSCT setting and that GVHD-related toxicities may be effectively managed. The observed efficacy and rapid kinetics of the responses following treatment of post-allo-HSCT patients with checkpoint inhibitors confirms that checkpoint inhibition has the potential to enhance the T-cell-mediated graft-versus-lymphoma response.

A Phase 1/1b multicenter, investigator-initiated study testing the safety and efficacy of ipilimumab in 28 patients with hematologic malignancies relapsing following allo-HSCT (including 7 patients with cHL) has been reported.[45] GVHD that precluded further administration of ipilimumab was observed in 14% of the patients including: 3 cases of chronic GVHD of the liver, and 1 case of Grade 2 acute GVHD of the gut, both of which resolved with glucocorticoids. Immune-related adverse events, including one death, were observed in 21% of patients. ORR was 32% and with a median follow-up of 15 months (range 8-27) the 1-year OS rate was 49%, demonstrating that CTLA-4 blockade with ipilimumab can induce clinically significant remissions in patients with recurrent malignancies following HSCT.

In a published study of 20 post-allo-HSCT cHL patients treated with nivolumab,[33] the ORR was 95% with CR and PR rates of 42% (95%CI= 21, 67; n=8) and 52% (95%CI= 29, 76; n=10), respectively. Acute GVHD (30%, 95%CI=9.9, 50.1) developed in 6 patients for two of them it was fatal. At a median follow-up of 370 days (range 24-486), median PFS and OS have not been reached. The efficacy of nivolumab in the post-allo HSCT patient population has been shown also other published case reports.[34,52] A case of fatal GVHD following treatment with the checkpoint inhibitor pembrolizumab has also been reported.[35] In both the nivolumab and the pembrolizumab product labels, a warning describing the increased risk of GVHD and GVHD-related fatality in patients that received an allogeneic HSCT after being previously treated with a checkpoint inhibitor is reported.[37,38] The nivolumab label also reports a warning describing the increased risk of hepatic veno-occlusive disease (VOD) in the same patient population.[37] Overall, however, the benefit/risk assessment in patients that have previously failed allo-HSCT favors the testing of these agents in the post-allo-HSCT setting, as there are no effective treatments available for these patients, and their life expectancy is very poor.[36]

1.5. Rationale for Avelumab Starting Dose

1.5.1. Lead-In Phase

The avelumab dosing regimens investigated in the lead-in phase of this study were 10 mg/kg every 2 weeks (Q2W), 500 mg Q2W, 500 mg every 3 weeks (Q3W), 350 mg Q2W, and 70 mg Q2W administered as 1-hour intravenous infusions. Of note, the currently used clinical dosing regimen in the clinical development of avelumab is 10 mg/kg Q2W. The specific dosing regimens were chosen to explore the influence of: 1) different nominal doses; 2) dosing frequency (Q2W vs. Q3W); and 3) fixed dosing vs body weight-based dosing on avelumab PK and the TO time course. The purpose of exploring the different dosing attributes is to gain insight on the regimens that would provide greater than 90% TO over the entire dosing interval. Moreover, this study was designed to identify pharmacodynamic (PD) markers that provide evidence of in vivo pharmacological activity, providing further support for selection of doses exhibiting sufficient target coverage (eg, tumor gene expression, T-cell infiltration).

The proposed treatment cohorts were enrolled in parallel. The plasma exposures of the different dose levels being investigated are not expected to exceed 10 mg/kg Q2W, the current clinically used dosing regimen. Since there was no expectation of a dose-related safety concern and a dose escalation design may confound results of the PD time-course (ie, carry over effect) for the different dosing regimens tested, a parallel design was implemented.

The preliminary TO data from clinical studies suggest >90% TO is required for clinical benefit. Based on *in-vitro* evidence, ≥90% receptor occupancy is reached in blood samples at avelumab concentrations greater than 1 μg/mL. In a dose escalation phase of a Phase Ib study (Trial EMR100070-001), all patients at the current recommended dose of avelumab, 10 mg/kg, reached or exceeded the serum level (median C_{trough}) of avelumab required for >90% TO. Moreover, PK simulations indicated that a 10 mg/kg Q2W dosing regimen provides >90% TO over the entire dosing interval for the majority of patients (Table 1).

Avelumab plasma exposures in the dosing regimens to be investigated in this study are expected to be less than those obtained from a 10 mg/kg Q2W dosing regimen. However, each dosing regimen is expected to provide median trough plasma concentrations (C_{trough}) greater than 1 μg/mL for the majority of the dosing interval (Table 1), and thus >90% TO is expected to be reached in all blood samples. However, given the inherent variability in avelumab PK and the corresponding variability in TO, it is uncertain whether or not a lower exposure (ie, lower dose and/or longer dosing interval) may provide a similar therapeutic benefit to that observed with 10 mg/kg. The purpose of exploring the different dosing attributes is to gain insight on the dosing regimen(s) that would provide greater than 90% TO over the entire dosing interval. For patients not achieving >90% TO in Cycle 1, the dose may be escalated to 10 mg/kg (Treatment Cohort E) starting at C2D1, after C1 assessment of TO.

The doses chosen for this study will help characterize the dose-exposure-response profile. The protocol restricts the dosing regimens to provide exposures yielding a mean TO >90% over the dosing interval based on simulations (Table 1). There is approximately a 40% difference in exposure between 350 (Cohort B) and 500 mg Q2W (Cohort D) dosing regimens. Based on simulations (Table 1), the median trough concentrations for 350 mg Q2W yields median trough exposures that are approximately half of the 10 mg/kg dosing regimen, whereas the 500 mg Q2W median exposures are between 10 mg/kg and 350 mg.

Moreover, this study is designed to identify pharmacodynamic (PD) markers that provide evidence of in vivo pharmacological activity, providing further support for selection of doses exhibiting sufficient target coverage.

Table 1. Simulated Median Ctrough (μg/mL) and 95% Prediction Interval (PI) for Proposed Avelumab Dosing Regimens

Cohort - dosing regimen	Median Ctrough	Lower 95% PI	Upper 95% PI
A - 70 mg Q2 weeks	2.6	0.98	6.2
B - 350 mg Q2 weeks	13.6	5.2	31.8
C - 500 mg Q3 weeks	7.0	1.7	20.3
D - 500 mg Q2 weeks	20.2	7.0	45.4
E - 10 mg/kg Q2 weeks	27.3	9.9	63.9

1.5.2. Preliminary Results of the Lead-in Phase

From March to November 2016, a total of 31 patients were enrolled in the lead-in phase of the study and 30 received avelumab treatment. The majority of patients were male (80.6%) or caucasian (71.0%). The median age was 38 years (range 22 to 81).

A total of 13 patients had received a prior stem cell transplant: 5 patients had previously received an autologous HSCT, and 8 patients a prior allogeneic HSCT. The remaining 19 were ineligible for HSCT. As of the cutoff date of 09 February 2017, 14 (45.2%) patients were still on treatment, 17 (54.8%) patients had discontinued, and 1 patient was randomized but never dosed. Out of the 17 patients who discontinued study treatment, 6 (19.4%) did so due to progressive disease, and 5 (16.1%) due to an adverse event (Grade 3 GVHD in 2 patients, Grade 3 infusion related reaction in 2 patients and Grade 3 elevated liver function

tests in 1 patient); 1 patient was discontinued due to physician decision, 1 because was not meeting the eligibility criteria anymore, and 4 for other reasons.

Overall, the median duration of study treatment was 14 weeks (range 2.0-46.1), for a median of 6 infusions (range 1-23).

Preliminary efficacy data from the lead-in phase are shown in Table 2.

Table 2. Preliminary Efficacy Data from the Lead-In Phase

All patients

Best Overall Response	**70 mg Q2W (N=6)**	**350 mg Q2W (N=7)**	**500 mg Q3W (N=6)**	**500 mg Q2W (N=6)**	**10 mg/kg Q2W (N=6)**	**Total (N=31) n (%)**
CR	1	0	1	0	0	2 (6.5%)
PR	3	1	4	3	4	15 (48.4%)
SD	0	4	1	0	0	5 (16.1%)
PD	0	0	0	1	2	6 (19.4%)
NE	2	2	0	2	0	6 (19.4)
ORR n (%) (95% CI)	4 (66.7)	1 (14.3)	5 (83.3)	3 (50)	4 (66.7)	17 (54.8) (36.0, 72.7)

Post-allo patients

Best Overall Response	**70 mg Q2W (N=1)**	**350 mg Q2W (N=2)**	**500 mg Q3W (N=2)**	**500 mg Q2W (N=2)**	**10 mg/kg Q2W (N=1)**	**Total (N=8) n (%)**
CR	0	0	1	0	0	1 (12.5)
PR	1	0	1	2	1	5 (62.5)
SD	0	0	0	0	0	0
PD	0	0	0	0	0	0
NE	0	1	0	0	0	1 (12.5)
ORR n (%) (95% CI)	1 (100)	0	1 (100)	2 (100)	1 (100)	6 (75) (34.9-96.8)

Source: Output for PRJB999 Submission (B9991007) Protocol (B9991007_LEADIN)
CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluable

Of the 5 patients that relapsed after an autologous HSCT, 1 patient (20%) achieved a PR in the 500 mg Q3W cohort.

Safety: Treatment-Related Adverse Events (TRAEs) were reported in a total of 24 (80.0%) patients, and were of Grade ≥3 severity in 11 (36.7%) of the patients; no Grade 5 AEs were reported. Of the 11 patients who experienced a Grade≥3 AE, 4 were in the 70 mg Q2W cohort, 1 in the 350 mg Q2W, 3 in the 500 mg Q2W, 2 in the 500 mg Q3W, and 1 in the 10 mg/kg Q2W cohort. The most common (≥10 %) TRAEs of any grade were infusion-related reaction (IRR; 26.7%), nausea (20.0%), rash (20.0%), and fatigue (13.3%).

There was no clinically significant difference between the safety profiles of the different dosing cohorts.

Two of the 8 post-allo HSCT patients developed Grade 3 acute GVHD of the liver (28%): 1 patient each in the 70 mg Q2W and 500 Q3W cohorts, respectively.

The first patient with acute GVHD was a 31-year old female who received an allogeneic HSCT from a related donor in 2011. In May 2016, after receiving a total of two doses of avelumab 70 mg Q2W, she developed Grade 3 acute GVHD of the liver which ultimately completely resolved following permanent discontinuation of avelumab, and prolonged immunosuppressive therapy (including high dose steroids, basiliximab, infliximab, tacrolimus, sirolimus, mycophenolate mofetil and ruxolitinib). The patient achieved a partial response approximately 6 weeks after receiving the first dose of avelumab, which matured into a complete response in August 2016 (approximately 4 months after the first dose of avelumab). The CR lasted until January 2017 (approximately 9 months later her first dose of avelumab), at which point progressive disease was documented.

The second patient with acute GVHD was a 30-year old male who received an allogeneic HSCT from a unrelated donor in 2014. In June 2016, after receiving a single dose of avelumab 500 mg Q3W, he developed Grade 3 acute GVHD of the liver associated with biliary sepsis and Grade 4 thrombocytopenia. The patient was treated with high dose steroids and rituximab, until complete resolution of the event. The patient achieved a CR approximately 6 weeks following the single dose of avelumab. At the time of data cutoff this response was still ongoing.

Of the 30 patients treated in the lead-in phase, 8 (26.7%) experienced at least 1 IRR; 2 (33.3%) each in the 70 mg Q2W, 500 mg Q2W, and 10 mg/kg Q2W cohorts, respectively, and 1 (16.7%) each in the 350 mg Q2W and 500 mg Q3W cohorts, respectively. Most of the IRRs were Grade 2, while 2 (6.7%) patients (1 each in the 70 mg Q2W and 500 mg Q2W cohorts, respectively) experienced a Grade 3 IRR which led to treatment discontinuation. Preliminary TO data analysis from the lead-in phase showed that >90% TO was observed throughout the dosing interval for all dosing regimens tested.

1.5.3. Rationale for the Exploration of Fixed Dosing vs Body Weight-Based Dosing

To date, avelumab has been administered at the clinically active, safe, and tolerable dose of 10 mg/kg Q2W to more than 1,700 patients across multiple (predominantly solid tumors) indications. Furthermore, the 10 mg/kg Q2W avelumab dosing regimen has been granted accelerated approval by the US Food and Drug Administration (FDA) for Merkel cell carcinoma[48]. Avelumab was originally dosed on a mg/kg basis in order to reduce the

inter-subject variability in drug exposure. However, emerging data for inhibitory monoclonal antibodies, including the marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab, and atezolizumab, reveal that body weight-based dosing regimens do not result in less variability in measures of exposure as compared with fixed (ie, body-weight independent) dosing regimens.[49-51] Additionally, fixed dosing has less potential for dispensing errors, shorter dose preparation times, and greater ease of administration.

Population PK analysis was conducted based on acquired PK data across three single-agent avelumab studies incorporating patients with 14 different types of cancer. PK simulations suggest that exposures to avelumab across the available range of body weights are less variable for fixed dosing, as compared with body weight based dosing, although exposures were similar near the population median weight. Low-weight subjects tended towards marginally lower exposures relative to the rest of the population when weight-based dosing was used, and marginally higher exposures when flat dosing was applied. However, these exposure differences are not expected to be clinically meaningful. Furthermore, the fixed doses chosen for this study are expected to result in serum concentrations (C_{trough} >1 μg/mL) required to maintain avelumab serum concentrations at >90% TO throughout the entire Q2W dosing interval across all weight categories.

Therefore, in this clinical trial, a fixed dosing regimen will be utilized for avelumab, with the avelumab dose of 70 mg administered as 1-hour IV infusions Q2W, and with the potential to increase the dose to 500 mg Q2W.

1.5.4. Rationale for the Dosing Regimens in the Expansion Phase

Given the high ORR (6/8=75%) observed in the post-allo HSCT cohort, the poor prognosis of patients with cHL relapsing after an allo-HSCT, and the lack of approved therapies in this setting, the expansion phase will enroll only patients in whom allogeneic HSCT has failed. Based on the lead-in phase data, which includes safety, an assessment of the number of patients achieving >90% TO following 1 treatment cycle, and clinical activity that met the predefined criteria (observing at least 3 objective responses per the Response Criteria for Malignant Lymphoma[42] (Appendix 2) in each given cohort), two dose regimens (70 mg Q2W and 500 mg Q2W) were selected in the expansion phase for the intra-patient dose escalation design as outlined below. As described in Section 1.5.2, TO, safety, and efficacy data from the lead-in phase were similar across all the dose regimens tested, including a dose as low as 70 mg Q2W (~1/10 of the dose used in other studies across the avelumab program), with no evidence of a dose-response relationship either in the entire population, or in the post-allo HSCT cohort. Although the TO was >90% at all the regimens tested in the lead-in phase, peripheral TO may over-estimate TO within the tumor itself. Therefore, although responses were observed across the broad range of dose regimens tested, it is not clear whether the frequency, depth, and durability of the responses will be more optimal at higher doses. Given that the peripheral TO has the *a priori* potential to differ from the intra-tumoral TO, and the potential for life-threatening checkpoint-induced GVHD, patients will start the expansion phase with a 70 mg Q2W 'test' dosing regimen of avelumab, the lowest exposure tested in the lead-in phase.

Although there is no evidence that checkpoint- induced GVHD is dose/exposure dependent, starting patients on the lowest tested dose is expected to minimize the risk of checkpoint-induced GVHD, while also providing for the possibility that higher doses may capture responses that are not achieved at lower doses. Patients will be monitored for safety and efficacy at the test dose level

Given that 70 mg Q2W is the lowest dose tested, and the therapeutic activity at this low dose might not be optimal, patients not achieving a CR may be dose escalated to the higher dose (500 mg Q2W) as detailed below. A target dosing regimen of 500 mg Q2W (~8x the exposure of 70 mg Q2W), provides an exposure intermediate between that of the highest (10 mg/kg Q2W) and lowest tested (70 mg Q2W) in the lead-in phase. A dose-response relationship has not been observed for either safety or efficacy in the lead-in phase. However, given the relatively small sample size and the potential life-threatening clinical sequelae of high-grade GVHD, patients will escalate to a dose which is almost a log higher than the test dose while at the same time being lower than the 10 mg/kg Q2W which is used in other studies across the avelumab program.

All patients will commence dosing at 70 mg Q2W, the lowest dose that showed clinical activity, and will be monitored for safety and efficacy. Following 3 cycles of treatment at 70 mg Q2W, patients who at the 6-week tumor assessment achieve a CR will continue at the same dose regimen. Patients achieving a PR at 6 weeks will continue at 70 mg Q2W for an additional 3 cycles, and if the 12-week tumor assessment still shows a PR, patients will be dose escalated to 500 mg Q2W. Patients who at the 6-week tumor assessment achieve a SD, will be dose escalated to 500 mg Q2W. Additionally, those patients who at the 6-week assessment are considered to have initial evidence of disease progression as confirmed by BICR but in the opinion of the Investigator are still experiencing clinical benefit (as defined in Section 5.4.1.1), may continue treatment with study drug at the Investigator's discretion and following discussion with the Sponsor. Such patients may be considered for escalation to 500 mg Q2W. Dose escalation to 500 mg Q2W after the 6 or the 12-week tumor assessment, will be only permitted so long as there is no clinical evidence of GVHD or treatment-related Grade ≥2 AEs with a duration of more than 14 days. Patients with PD at 6 weeks in the absence of clinical benefit will be permanently discontinued from study treatment.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives (Lead-in Phase)

Primary Objective

- To characterize the pharmacokinetics (PK) of different dosing regimens of avelumab and its relation to target occupancy (TO) in peripheral blood of patients with cHL.

Secondary Objectives

- To evaluate the overall safety and tolerability of different dosing regimens of avelumab.

- To assess the immunogenicity of different dosing regimens of avelumab.
- To evaluate the effect of different dosing regimens of avelumab on pharmacodynamic biomarkers of tumor immunophenotype and anti-tumor immune response.
- To evaluate the anti-tumor activity of avelumab in patients with cHL.

CCI

[redacted]

2.2. Endpoints (Lead-in Phase)

Primary Endpoints

- Percent TO by dose/schedule in peripheral blood immune cells, including CD14+ monocytes and CD3+ T cells;
- Pharmacokinetic parameters of avelumab including, but not limited to, C_{max}, T_{max}, AUC_{last}, T_{last}, $AUC_{sd,\tau}$, $t_{1/2}$, $AUC_{sd,inf}$, CL, and V_z as data permit. Multiple Dose (MD) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss}, R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sd,\tau}$) and R_{ss} ($AUC_{ss,\tau}$ /$AUC_{sd,inf}$) as data permit.

Secondary Endpoints

- Adverse Events as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03), timing, seriousness, and relationship to study therapy.
- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v. 4.03), and timing.

- Anti-drug antibodies (ADAs; neutralizing antibodies) and serum titers against avelumab.
- Phenotype, quantity, and localization of TILs in tumor biopsy tissue by IHC.
- Relative expression of transcripts associated with immune activation and regulation in tumor biopsy tissue by gene expression profiling.
- Phenotype, relative proportions, activation state and PD-L1 expression of peripheral blood T cell subsets by flow cytometry.
- Objective response according to Response Criteria for Malignant Lymphoma[42] per Investigator assessment.
- Disease control (DC), time to tumor response (TTR), duration of response (DR), progression-free survival (PFS) per Investigator assessment.

CCI

[redacted]

2.3. Objectives (Expansion Phase)

Primary Objective

- To evaluate the objective response rate (ORR) of avelumab in patients with relapsed or refractory cHL who have previously been treated with an allogeneic HSCT.

Secondary Objectives

- To evaluate the overall anti-tumor activity of avelumab.
- To evaluate the overall safety profile of avelumab.
- To evaluate the incidence and severity of acute and chronic GVHD.
- To characterize the pharmacokinetics of avelumab.
- To assess the immunogenicity of avelumab.

[redacted]

- To evaluate the phenotype and quantity of TILs and correlate these findings with anti-tumor activity.

CCI

[redacted]

2.4. Endpoints (Expansion Phase)

Primary Endpoint

Objective response defined by the Lugano Classification[43] as evaluated by the blinded independent central review (BICR).

Secondary Endpoints

- Objective response as defined by the Lugano Classification[43] and evaluated by Investigator's assessment.

- Time to tumor response (TTR), duration of response (DR), Disease Control (DC) and progression-free survival (PFS) according to the Lugano Classification[43] by BICR and by Investigator's assessment, as well as overall survival (OS).

- AEs and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03; timing, seriousness, and relationship to study therapy.

- Acute GVHD as defined by the modified Seattle Glucksberg criteria (Consensus Conference on Acute GVHD Grading Criteria-Appendix 4) and Chronic GVHD as defined by the NIH Consensus Development Project (Appendix 5).

- Pharmacokinetic parameters of avelumab including, but not limited to, C_{max}, T_{max}, $AUC_{sd,\tau}$, $t_{1/2}$, CL, and V_z as data permit. Multiple Dose (MD) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $t_{1/2}$, $C_{ss,min}$, $C_{ss,av}$, CL, and V_{ss} as data permit.

- Anti-drug antibodies (ADAs; neutralizing antibodies) and serum titers against avelumab.

- Phenotype, quantity, and localization of TILs in tumor biopsy tissue determined by IHC.

CCI

[redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1b, open-label, multi-center study comprising a lead-in phase and an expansion phase in patients with relapsed/refractory cHL.

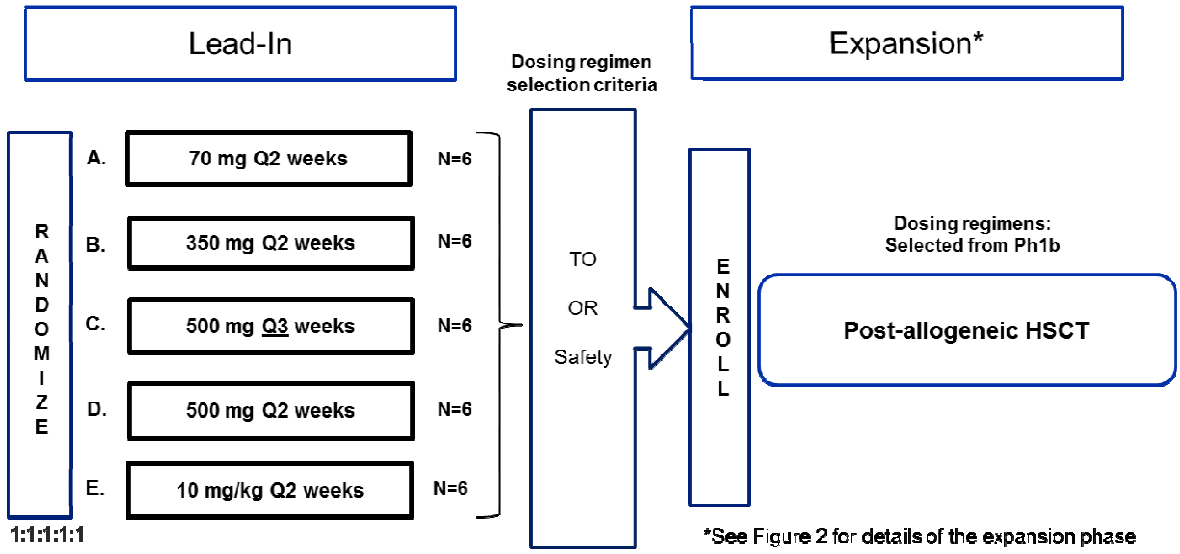
[redacted]

The lead-in is a multiple-dose, randomized, parallel-arm, pharmacokinetic and pharmacodynamic study of avelumab as a single agent in adult patients with cHL. Patients enrolled in the lead-in phase of the study were required to have relapsed following a prior autologous or allogeneic HSCT, or to be ineligible for HSCT.

In the lead-in phase of the study, which completed enrollment on November 29, 2016,a total of 31 patients were randomized across 5 treatment cohorts in a 1:1:1:1:1 ratio. The 5 treatment cohorts were: 70 mg Q2W (Cohort A), 350 mg Q2W (Cohort B), 500 mg Q3W (Cohort C), 500 mg Q2W (Cohort D), and 10 mg/kg Q2W (Cohort E). Each cohort enrolled 6 patients, except Cohort B in which 7 patients were randomized, but 1 was never dosed. The primary objective for the lead-in phase was to determine the doses and schedules of avelumab that provide >90% TO over the dosing interval and to identify a dose regimen for use in the dose expansion phase. For patients not achieving >90% TO after C1D1, the dose could be escalated to 10 mg/kg (Treatment Cohort E) starting at C2D1, after Cycle 1 assessment of TO.

The study design for the lead-in and expansion phases is detailed in Figure 1.

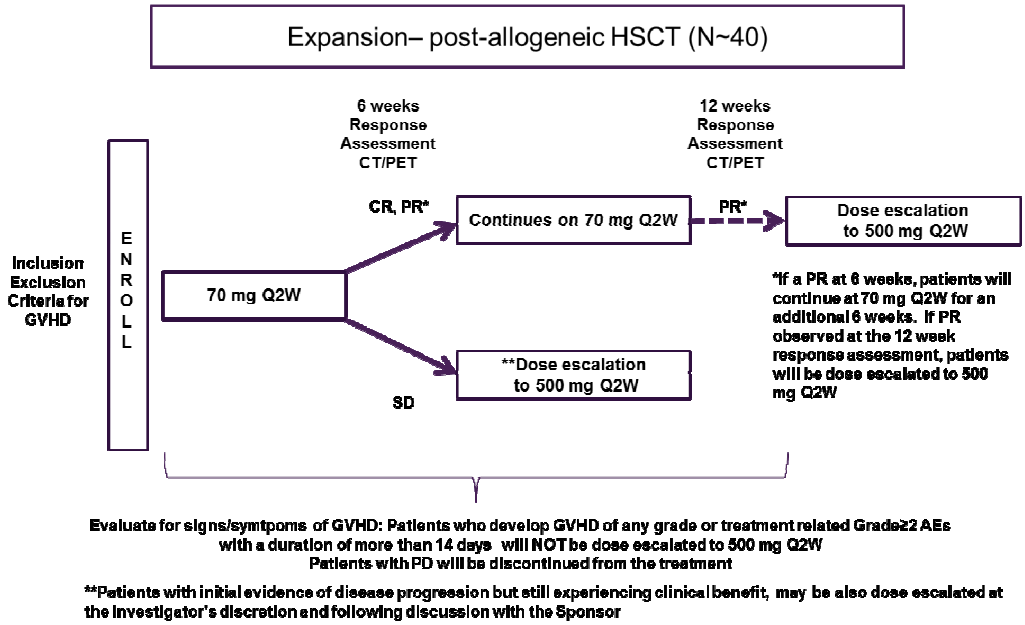
Figure 1. B9991007 Study Design for the Lead-In and Expansion Ph



Based on the preliminary TO, safety, and efficacy results from the lead-in phase, the expansion phase will evaluate the anti-tumor activity and safety of single-agent avelumab utilizing an intra-patient dose escalation paradigm based on two of the dosing regimens studied in the lead-in phase in 40 cHL patients in whom an allogeneic HSCT has failed.

The study design for the expansion phase is shown in Figure 2.

Figure 2. B9991007 Study Design for the Expansion Phase



Approximately 70 patients are expected to be enrolled into the study. Treatment with investigational product will continue until disease progression, patient refusal, or unacceptable toxicity, patient is lost to follow-up, or until the study is terminated by the Sponsor, whichever occurs first (see Section 6.4).

3.1.1. Study Phases

Lead-in Phase:

Patients were randomized to one of the 5 treatment cohorts as stipulated in Table 3 below.

Table 3. Avelumab Dosing Cohorts for the Lead In Phase

Cohort	Dose	Schedule	N
A	70 mg	Q2W	6
B	350 mg	Q2W	7
C	500 mg	Q3W	6
D	500 mg	Q2W	6
E	10 mg/kg	Q2W	6

Expansion Phase:

In this phase, an intra patient dose-escalation design will be utilized as follows: all patients will commence dosing at 70 mg Q2W, the lowest dose that showed clinical activity, and will be monitored for safety and efficacy. Following 3 cycles of treatment at 70 mg Q2W, patients who at the 6-week tumor assessment achieve a CR will continue at the same dose regimen. Patients achieving a PR at 6 weeks will continue at 70 mg Q2W for an additional 3 cycles, and if the 12-week tumor assessment still shows a PR, patients will be dose escalated to 500 mg Q2W. Patients who at the 6-week tumor assessment achieve a SD, will be dose escalated to 500 mg Q2W. Additionally, those patients who at the 6-week assessment are considered to have initial evidence of disease progression as confirmed by BICR but in the opinion of the Investigator are still experiencing clinical benefit (as defined in Section 5.4.1.1), may continue treatment with study drug at the Investigator's discretion and following discussion with the Sponsor. Such patients may be considered for escalation to 500 mg Q2W. Dose escalation to 500 mg Q2W after the 6 or the 12-week tumor assessment, will be only permitted so long as there is no clinical evidence of GVHD or treatment-related Grade ≥2 AEs with a duration of more than 14 days. Patients with PD at 6 weeks in the absence of clinical benefit will be permanently discontinued from study treatment.

Patients with GVHD of any grade (other than Grade 1 GVHD of the skin requiring topical therapy only) must be permanently discontinued from the study treatment.

Disease responses will be assessed by a Blinded Independent Central Review (BICR), according to processes defined in the Study Manual. Intra-patient dose escalation decisions will be made following discussion between the Investigator and the Sponsor and will be informed by the BICR disease response assessment-see Section 7.5.1.

3.1.2. Criteria for Intra-Patient Dose Escalation

The 5 different treatment cohorts in the lead-in phase were randomized in parallel. To ensure patients at all dose levels achieved the target level of ≥ 90% TO, the dose could be escalated to 10 mg/kg (Treatment Cohort E) starting at C2D1, after C1 assessment of TO. Criteria for Intra-Patient Dose escalation in the expansion phase have been detailed in Section 3.1.1.

3.1.3. Safety Stopping Rules

The safety stopping rules will be based on the observed incidence of acute GVHD Grade ≥3, acute GVHD-related mortality and Grade ≥4 irAEs, within 16 weeks from start of study treatment for each patient in the lead-in phase and expansion phase. Two formal evaluations of safety will be performed:

- 16 weeks after 15 patients have received the first dose of study treatment.
- 16 weeks after 30 patients have received the first dose of study treatment.

The statistical stopping criteria (see Section 9.4.1) was determined based on the following clinical thresholds:

1. Acute GVHD Grade ≥3 <33% (Grade 3 liver GVHD must be confirmed by biopsy).
2. Acute GVHD-related mortality ≤20%.
3. irAEs Grade ≥4 <15%.

Events from patients who did not meet the criteria for a minimum of 16 weeks follow-up will also be considered in the evaluation. The study will stop if the stopping boundary is crossed for any of the 3 event categories.

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 non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

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

1. Histological confirmation of classical Hodgkin's Lymphoma (cHL) with relapsed or refractory disease who, for the lead-in phase, either have had a prior autologous or allogeneic HSCT or are not eligible for HSCT, and , for the expansion phase, have had a prior allogeneic HSCT. In the expansion phase there must be a documented $CD3^+$ donor chimerism of ≥20%.
2. Patients must be off previous cHL therapy for at least 28 days prior to randomization in the lead-in phase/first dose of study treatment in the expansion phase.
3. At least 1 fluorodeoxyglucose (FDG)-PET-avid (Deauville 4/5)[21] measurable lesion >1.5 cm on PET-CT scan as defined by the Response Criteria for Malignant Lymphoma[42] (Appendix 2 for the lead-in phase) and the Lugano Classification[43] (Appendix 3 for the expansion phase) that has not previously been irradiated.
4. Age ≥18 years.
5. Estimated life expectancy of at least 3 months.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.

7. Adequate bone marrow function including:

    a. Absolute neutrophil count (ANC) ≥1,000/mm^3 or ≥1.0 x 10^9/L (may have received G-CSF support);

    b. Platelets ≥50,000/mm^3 or ≥50 x 10^9/L;

    c. Hemoglobin ≥8.0 g/dL (>4.9 mmol/L) (may have been transfused).

8. Expansion phase: *De novo* tumor biopsy and archival tumor tissue:

    a. A *de novo* baseline biopsy and consent for an on-treatment tumor biopsy that is not the only measurable lesion is required within 28 days prior to the first dose of study treatment and following the first 6-week scan respectively, unless collecting either biopsy is considered to constitute an unacceptable clinical risk to the patient. Provision of a formalin-fixed paraffin-embedded (FFPE) tumor tissue block is required for the *de novo* tumor biopsy. In the event the patient has an archival tumor tissue sample obtained within 3 months of the first dose of study treatment, and there has been no intervening systemic anti-cancer therapy, this can substitute for the baseline de novo sample. Provision of an FFPE tumor tissue block, or of at least 15 (but preferably 20) freshly cut unstained slides (if block is unavailable) is required in the event that an archival tumor tissue specimen is provided.

    b. If a *de novo* biopsy is unadvisable due to an unacceptable clinical risk to the patient, an archival tumor tissue sample from the closest time point that is within 6 months of the first dose of study treatment must be provided. Provision of an FFPE tumor tissue block, or of at least 15, (but preferably 20) unstained slides (if block is unavailable) is required in the event that an archival tumor tissue specimen is provided.

9. Adequate Renal Function: Estimated creatinine clearance ≥30 mL/min as calculated using the Cockcroft-Gault (CG) formula or by 24-hour urine collection for creatinine clearance or according to local institutional standard method.

10. Adequate Liver Function, defined by:

    a. Total serum bilirubin ≤1.5 x upper limit of normal range (ULN);

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

11. International Normalized Ratio (INR) or prothrombin time (PT) <1.5 x ULN.

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

13. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective method(s) of contraception throughout the study and for at least 30 days after the last dose of assigned treatment.

    Female patients who are not of childbearing potential (ie, 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; a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

14. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study. As inclusion of adult patients for whom consent must be provided by a legally authorized representative is not appropriate for this research, this protocol excludes adult individuals who lack capacity to consent for themselves.

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

4.2. Exclusion Criteria

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

1. Patients with prior allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) who have had:

    a. **Lead-in phase**: allo-HSCT performed <12 months prior to randomization. **Expansion phase**: allo-HSCT performed ≤4 months prior to the first dose of study treatment. NOTE: Patients who have had allo-HSCT performed >4 months prior to the first dose of study treatment must have discontinued all immunosuppressive therapy, and must have no clinical evidence of GVHD; or

    b. Immunosuppressive treatment for acute or chronic GVHD within 3 months prior to randomization for the lead-in phase or prior to the first dose of study treatment for the expansion phase (with the exception of those patients who required ≤15 mg/day oral prednisone or equivalent). Patients who required ≤15 mg/day oral prednisone or equivalent must have discontinued it within 7 days prior to first dose of study treatment; or

c. Acute Grade 3 or Grade 4 GVHD at any time in the past (as defined by the modified Seattle Glucksberg criteria (Consensus Conference on Acute GVHD Grading Criteria[29]) (Appendix 4); or

d. Prior chronic GVHD (as defined by the NIH Consensus Development Project[30]) (Appendix 5) that persisted for >6 months and required systemic immunosuppression (with the exception of those patients who required ≤15 mg/day oral prednisone or equivalent). Patients who required ≤15 mg/day oral prednisone or equivalent must have discontinued it within 7 days prior to the first dose of study treatment; or

e. A donor lymphocyte infusion (DLI) within 3 months prior to randomization for the lead-in phase or first dose of study treatment for the expansion phase.

2. Prior therapy with an anti-PD-1 or anti-PD-L1 mAb.

   a. Lead-in Phase: May be enrolled if patient stopped prior anti-PD1 or anti-PD-L1 therapy more than one year prior to randomization and had a documented prior response.

   b. Expansion Phase: Prior therapy with an anti-PD-1 or anti-PD-L1 agent *following* allo-HSCT is prohibited unless the therapy was stopped more than one year prior to the first dose of study treatment, and the patient had a documented prior response. NOTE: Prior therapy with an anti-PD-1 or anti-PD-L1 agent prior to allo-HSCT is permitted with no time limits and irrespective of a documented response.

   c. Patients with a history of ≥ Grade 3 anti-PD-1 or anti-PD-L1-related immune toxicity are not eligible.

3. Persisting toxicity related to prior therapy NCI CTCAE v4.03 Grade >1. Note that alopecia, sensory neuropathy Grade ≤2, or other Grade ≤2 AEs not constituting a safety risk to the patient based on the investigator's judgment are acceptable.

4. Major surgery within 4 weeks or radiation therapy within 14 days prior to study entry.

5. Prior palliative radiotherapy (≤10 fractions) to lesion(s) is permitted as long as there is at least one lesion evaluable for anti-tumor activity and prior radiotherapy that has been completed at least 48 hours prior to the first dose of study treatment.

6. Diagnosis of prior immunodeficiency or organ transplant requiring immunosuppressive therapy, or known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

7. Current or prior use of immunosuppressive medication within 7 days prior to randomization in the lead in phase/first dose of study treatment in the expansion phase, except the following:

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

    b. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent for the treatment of adrenal insufficiency.

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

8. 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.

9. Prior severe hypersensitivity reactions to the investigational product or any component of its formulation, including known severe hypersensitivity reactions to other monoclonal antibodies (Grade ≥3 NCI-CTCAE v 4.03).

10. Active infection requiring systemic therapy.

11. 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).

12. Clinically significant cardiovascular disease, either active or within 6 months prior to randomization for the lead-in phase or the first dose of study treatment for the expansion phase: cerebral vascular accident/stroke, myocardial infarction, unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

13. Diagnosis of any other malignancy within 5 years prior to randomization for the lead-in phase or first dose of study treatment for the expansion phase, except for: adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the breast or cervix, or low-grade (≤ Gleason 6) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration).

14. Participation in other studies involving investigational drug(s) within 4 weeks prior to study entry.

15. 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.

16. Pregnant female patients; breastfeeding female patients; male patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 30 days after the last dose of investigational product.

17. Other severe acute or chronic medical conditions including but not limited to colitis, inflammatory bowel disease, pneumonitis, or pulmonary fibrosis, or psychiatric conditions, recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product 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.

18. Vaccination with live vaccine within 4 weeks of the first dose of avelumab is prohibited except for administration of inactivated vaccines.

4.3. Lifestyle Guidelines

4.3.1. Contraception

In this study, male patients who are able to father children and female patients who are of childbearing potential will receive avelumab for which the teratogenic risk is currently unknown.

Two (2) methods of highly effective contraception must be used throughout the study and continued for at least 30 days after the last dose. The Investigator or his or her designee, in consultation with the patient, will select two appropriate methods of contraception for the individual patient and his/her partner from the list of permitted contraception methods (see below), and instruct the patient in their consistent and correct use. Patients 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 according to the Schedule of Activities 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 or to the patient's partner.

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 post-vasectomy ejaculate.

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

6. Female partner who meets the criteria for non-childbearing potential, defined as:

    - 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 within the laboratory's reference range for postmenopausal women.

All sexually active male patients must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 30 days after the last dose.

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 on 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 Harmonisation (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).

5.1. Allocation to Treatment

In the Lead-in phase, an Interactive Response Technology (IRT) System/Interactive Web Response (IWR) was used to randomize patients to treatment cohorts.

The Expansion phase is not randomized. Therefore in this phase the IRT will be used to assign patient number, record visits, and dispense drug.

In both the lead-in phase and the expansion phase, patients must receive their first dose of avelumab within 3 days of drug assignment by the IRT.

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, protocol number, the patient number and the date of birth of the patient. The site personnel will then be provided with a treatment assignment and/or dispensable unit (DU) or container number when drug is being supplied via the IRT. 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 hours-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.

5.2. Patient Compliance

The site will complete required dosage Preparation Record located in the study manual. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the Sponsor's monitor.

5.3. Investigational Product Supply

5.3.1. Formulation and Packaging

5.3.1.1. Avelumab

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

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practices (GMP) guidelines. Avelumab will be packed in boxes each containing one vial. The information on the trial drug 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.

5.3.2. Preparation and Dispensing

5.3.2.1. Avelumab

Avelumab will be dosed at the investigational site.

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 application in this trial, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection). 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 Dosage and Administration Instruction.

Avelumab must not be used for any purpose other than the trial. The administration of trial investigational product to patients who have not been enrolled into the trial is not covered by the trial insurance.

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

See the Dosage and Administration Instruction 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 biotherapeutic agents.

5.4. Administration

All trial treatment will be administered on an outpatient basis.

5.4.1. Avelumab

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

Avelumab will be administered on Day 1 of each cycle and all procedures/assessments will be completed as described in the Schedule of Activities table. Avelumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Avelumab will be administered as a 1-hour IV infusion once every 2 weeks or 3 weeks. In order to mitigate infusion-related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). This may be modified based on local treatment standards and guidelines, as appropriate. Prophylactic steroids are permitted after Cycle 1 under specific circumstances as described in Section 5.4.4.1. Sites should make every effort to target infusion timing to be as close to 1 hour as possible. 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 5.4.4.1.

A cycle is defined as the time from Day 1 dose to the next Day 1 dose. If there are no treatment delays, a cycle will be 2 weeks for Q2W dosing and 3 weeks for Q3W dosing regimens.

Avelumab dose reduction for toxicity management is permitted as detailed in Section 5.4.5. No other dose reduction for toxicity management is permitted but next cycle administration may be omitted due to persisting toxicity as described in Section 5.4.3.1, and Section 5.4.3.2. Further details on avelumab dose modifications due to infusion related reactions, tumor lysis syndrome, irAEs and GVHD can be found in Section 5.4.4.1, Section 5.4.4.2, Section 5.4.4.3 and Section 5.4.4.4, respectively.

5.4.1.1. Treatment After Initial Evidence of Disease Progression

The response kinetics observed with immunotherapeutic agents such as PD-1/PD-L1 axis inhibitors may in some instances result in an apparent initial increase in disease burden prior to any objective response being clearly discernable. Consequently, in the presence of apparent clinical benefit in the context of early evidence of radiologic disease progression, it may, in select cases, and following an individualized assessment of overall risk/benefit, be appropriate to consider treatment continuation with avelumab accompanied by radiologic and clinical monitoring.

In the event of evidence of radiological progression, patients may continue to receive avelumab if they are clinically stable as defined by the following criteria:

- Absence of clinical signs and symptoms of disease progression.
- Absence of clinically significant decline in laboratory values.
- No decline in ECOG performance status.

- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

If the patient remains clinically stable and repeat imaging at 6 weeks or earlier, no longer shows PD but rather a CR, PR, or SD compared to baseline, treatment with avelumab may be continued. In determining whether the tumor burden has increased or decreased, all lesions should be taken into consideration (refer to the Study Manual).

If repeat imaging at 6 weeks or earlier confirms PD, then treatment with avelumab should be discontinued. However, according to the Investigator's clinical judgment and following discussion between the Investigator and the Sponsor, if a patient continues to experience clinical benefit, continued treatment with avelumab may be considered. The Investigator's decision to continue treatment should be based on the overall risk-benefit assessment and the patient's clinical condition, including performance status, clinical signs, symptoms, adverse events, laboratory data and availability of alternative therapies.

Prior to treatment continuation, the patient must be re-consented via an informed consent addendum and informed that in continuing to receive the investigational product on study, they may be foregoing the opportunity of being treated with alternative approved or investigational therapies that have the potential to provide clinical benefit.

Treatment with avelumab should be permanently discontinued if the patient is found to have further disease progression according to the Response Criteria for Malignant Lymphoma[42] in the lead-in phase or to the Lugano Classification[43] in the expansion phase at the next tumor assessment or if there is evidence of further clinical disease progression.

Patients who stop avelumab treatment for reasons other than disease progression and then go on to experience disease progression will be eligible for re-treatment with avelumab at the discretion of the Investigator and after discussion with the Sponsor if 1) no cancer treatment was administered since the last dose of avelumab, 2) the patient does not meet the safety withdrawal criteria, and 3) the trial is still open. Patients will resume avelumab therapy at the same dose and schedule applied at the time of discontinuation

5.4.1.2. Treatment After Complete Response

Patients achieving CR will continue on treatment with investigational product until disease progression, patient refusal, or unacceptable toxicity, patient is lost to follow-up, or until the study is terminated by the Sponsor, whichever occurs first (see Section 6.4).

5.4.2. Food Requirements

Avelumab may be administered without regard to food.

5.4.3. 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 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.

Avelumab dose reduction for toxicity management is permitted only as detailed in Section 5.4.5. No other dose reduction for toxicity management is permitted, but dosing interruptions are allowed for toxicity, as outlined in Section 5.4.3.1, Section 5.4.3.2 and Section 5.4.4. Intrapatient dose escalations may be permitted as described in Section 3.1.2.

5.4.3.1. Avelumab Dosing Interruptions in Case of Drug-Related Toxicity

Recommended avelumab infusion interruptions in case of drug-related toxicity are shown below in Table 4. Consider consulting with Sponsor's Medical Monitor for drug-related toxicities. Always consult with the Sponsor's Medical Monitor for Grades 3 and 4 drug-related toxicities.

5.4.3.2. Avelumab Infusion Omissions for Drug-Related Toxicity

Recommendations for avelumab infusion omissions in case of drug-related toxicity are shown in Table 4.

Table 4. Avelumab Infusion Omissions for Drug-Related Toxicity

Toxicity	**NCI CTCAE Severity Grade**	**Avelumab Treatment Modification**
Hematologic Abnormalities	Grade 1	Continue as per schedule.
	Grade 2	Continue as per schedule.
	Grade 3	Hold treatment for up to 4 weeks (for every 2-week dosing) and for up to 6 weeks (for every 3-week dosing) until Grade ≤1 or baseline, then re-challenge at the same dose. Permanent discontinuation if recurrence to Grade 3. (Unless resolves to Grade ≤1 or baseline within 7 days following appropriate medical management).
	Grade 4	Permanent discontinuation. (Unless resolves to Grade ≤1 or baseline within 7 days following appropriate medical management).
Infusion-Related Reaction	Grades 1-4	See Section 5.4.4.1 and Table 5
Tumor Lysis Syndrome	Grades 1-4	See Section 5.4.4.2 and Figure 3
Immune-related AE (irAE)	Grades 1-4	See Section 5.4.4.3 and Table 6
Other Non-hematologic Toxicities and Laboratory Abnormalities	Grade 1	Continue as per schedule

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification
Other Non-hematologic Toxicities and Laboratory Abnormalities	Grade 2	If toxicity resolves to Grade ≤1 by the last day of the current cycle, treatment may continue. If toxicity does not resolve to Grade ≤1 by the last day of the current cycle despite optimal treatment, next cycle infusion should be omitted. If after 2 weeks of dose holding, the event has not resolved to Grade ≤1, the patient should permanently discontinue treatment. Exceptions are: Hormone deficiencies that can be managed by replacement therapy as described in Table 6.
Other Non-hematologic Toxicities and Laboratory Abnormalities	Grade 3	Permanent discontinuation. Exceptions are: Transient (≤6 hours) flu-like symptoms or fever, which is controlled with medical management. Transient (≤24 hours) fatigue, local reactions, headache that resolves to Grade ≤1. Nausea and vomiting controlled by medical therapy. Amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis. Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor. Laboratory abnormality that does not require medical intervention or hospitalization Single laboratory values out of normal range that are unlikely related to avelumab treatment as assessed by the Investigator, do not have any clinical correlate, and resolve to Grade ≤1 within 7 days with adequate medical management.
	Grade 4	Permanent discontinuation. Exceptions are: Laboratory abnormality that does not require medical intervention or hospitalization Single laboratory values out of normal range that are unlikely related to avelumab treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.

5.4.4. Special Precautions for Avelumab 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 regimen may be modified based on local

treatment standards and guidelines, as appropriate. However, prophylactic administration of corticosteroids is permitted only in the conditions described in Table 5.

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.

Following avelumab infusions, patients must be observed for 2 hours post-infusion for potential infusion-related reactions. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Treatment recommendations for the management of infusion-related reactions, and tumor lysis syndrome are outlined in Sections 5.4.4.1, and 5.4.4.2, respectively.

Treatment recommendations for the management of irAEs and GVHD are outlined in Section 5.4.4.1 and Section 5.4.4.3.

5.4.4.1. Management of Avelumab Infusion-Related Reactions

Since avelumab is administered IV, infusion-related reactions may occur (with symptoms such as fever, chills, rigors, diaphoresis, and headache). Treatment of the infusion-related reaction and modifications of avelumab infusion are mainly dependent upon severity, as indicated in Table 5.

Table 5. Treatment Modification for Symptoms of Infusion Related Reactions Caused by Avelumab

NCI CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the 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, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Temporarily discontinue avelumab infusion. Resume infusion at 50% of previous rate as soon as infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening. If a Grade 2 infusion-related reaction does not improve or worsens following implementation of the modifications indicated above (including reducing the infusion rate by 50%), treatment should be commenced based on the specific symptoms (see Appendix 6), and the infusion should not be resumed for that cycle. At the next cycle, consider the addition of an H2-blocker, meperidine, or ibuprofen to the mandatory premedication.

Recurrent Grade 2 – moderate	In the event of further recurrence, in spite of implementation of all measures indicated above, hydrocortisone 100 mg IV may be added to the premedication schema outlined above following discussion with the Sponsor.
Grade 3 – severe 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.	Stop the avelumab infusion immediately and disconnect infusion tubing from the subject If IV fluids to maintain blood pressure, or prolonged administration of steroids, or inotropic agents, or administration of oxygen to maintain peripheral saturations are required, or the symptoms persist for more than 48 hours: • permanently discontinue avelumab treatment If none of the conditions listed above applies, • consider resuming avelumab treatment if the risk/benefit assessment for the individual patient is positive and upon discussion with the Sponsor. • if the decision is made to resume treatment, the infusion rate must be reduced by 50% AND hydrocortisone 200 mg IV must be added to the standard premedication .
Recurrent Grade 3 - severe	Stop the avelumab infusion immediately and disconnect the infusion tubing from the patient. Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment .
Grade 4 – life-threatening Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the avelumab infusion immediately and disconnect the infusion tubing from the patient. Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment
In addition, if premedication with hydrocortisone is necessary it should be added for at least the subsequent 2 cycles of avelumab therapy. In the case of patients requiring hydrocortisone and in whom the dose of avelumab is escalated from 70 mg Q2W to 500 mg Q2W, hydrocortisone should be added to the premedication schema for at least a total of 3 cycles at 500 mg Q2W.	

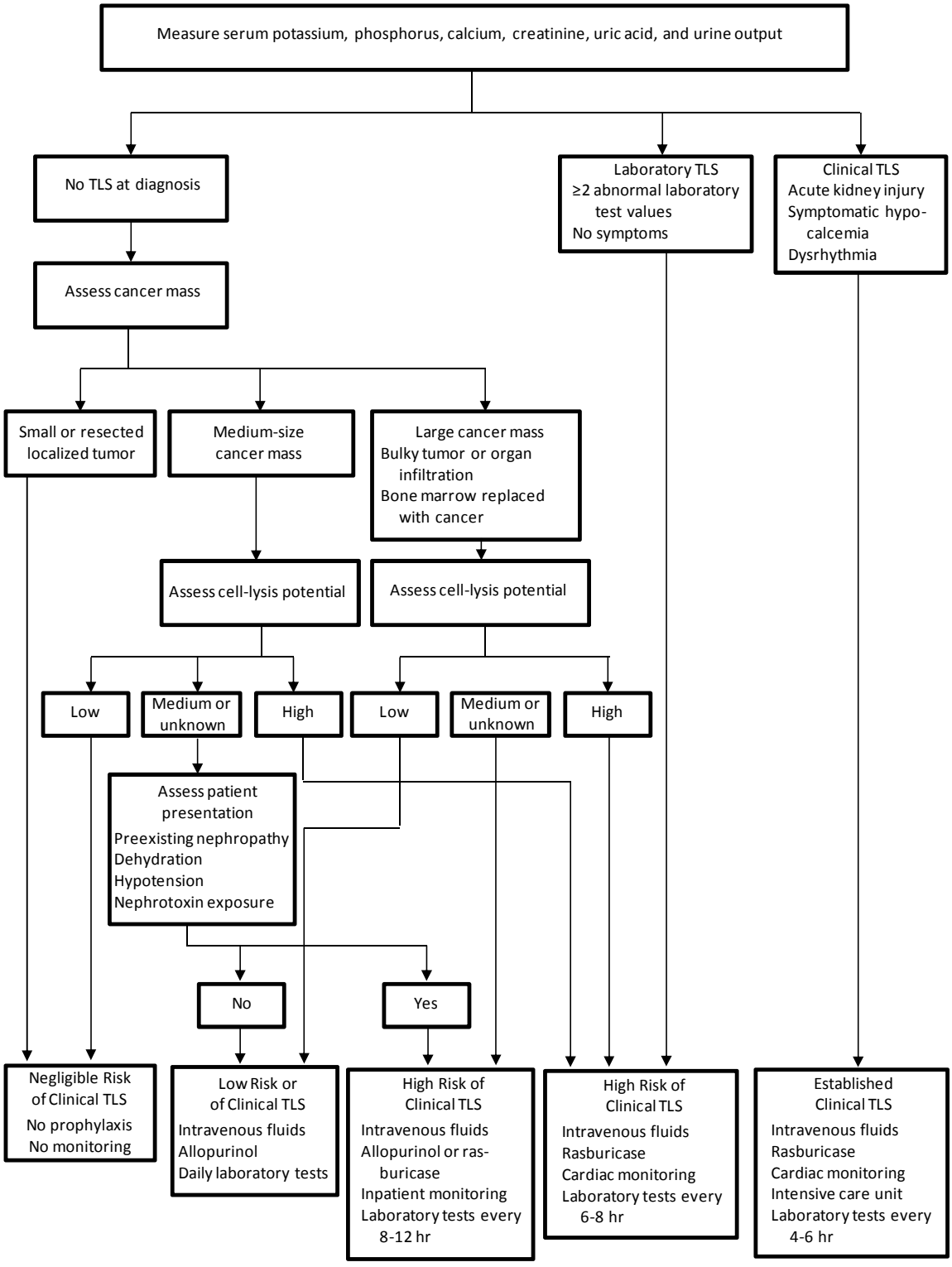
IV=intravenous, NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.

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

5.4.4.2. Management of Avelumab-Related Tumor Lysis Syndrome

Avelumab can induce antibody-dependent cell-mediated cytotoxicity (ADCC), so there is a potential risk of tumor lysis syndrome. Should this occur, patients should be treated as per local guidelines and the management algorithm (Figure 3) published by Howard et al.

Figure 3. Assessment and Initial Management of Tumor Lysis Syndrome (TLS)



5.4.4.3. Management of Avelumab Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade v. 4.03):

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

Treatment of irAEs should follow guidelines set forth in Table 6.

Table 6. Management of Avelumab Immune Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI v4)	**Initial Management**	**Follow-up Management**
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, 3 or 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	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤1: Resume avelumab therapy If persists >5-7 days or recurs: Treat as Grade 3 or 4
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hours; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent grade 3. 1.0 to 2.0 mg/kg/day prednisone 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; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, 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)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area	Continue avelumab therapy Symptomatic therapy (eg, antihistamines, topical steroids)	If persists >1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5 to 1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Covering >30% body surface area; Grade 4: life threatening consequences	Withhold avelumab for Grade 3 Permanently discontinue for Grade 4 or recurrent Grade 3 Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3)
Pulmonary irAEs		
Grade of Pneumonitis (NCI CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4

Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤1, taper steroids over at least 1 month and then resume avelumab therapy If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4:Llife-threatening	Permanently discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (eg, infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Liver Function Tests (LFTs) Increase (NCI CTCAE v4)	**Initial Management**	**Follow-up Management**
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 Grade 2 or 3 to 4
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Grade ≤1: Resume routine monitoring, resume avelumab therapy If elevations persist >5 to 7 days or worsen : Treat as Grade 3 to 4
Grade 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If returns to Grade ≤1: 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

	Consult gastroenterologist/hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	immunosuppressants per local guidelines
Renal irAEs		
Grade of Creatinine Increased (NCI CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased >1.5 and ≤6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased >6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Resume avelumab once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, BNP, troponin, CK-MB) 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 appropriate 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 per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections	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		

Other irAEs		
Grade of other irAEs (NCI CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate.	If improves to Grade ≤1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer	Permanently discontinue avelumab therapy Specialty consult.	

ACTH=adrenocorticotropic hormone; ADL=activities of daily living, ALT=alanine aminotransferase, AST=aspartate aminotransferase; BNP_B-type natriuretic peptide; CK-MB_creatine kinase MB; CT=computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1;, irAE=immune-related adverse event, IV=intravenous, LH=luteinizing hormone; LLN=lower limit of normal, MRI=magnetic resonance imaging, NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events, NSAIDs=nonsteroidal anti-inflammatory drugs, PRL=prolactin; T4=thyroxine, TSH=thyroid-stimulating hormone, ULN=upper limit of normal.

5.4.4.4. Management of Acute or Chronic Graft versus Host Disease (GVHD)

Lead-in Phase

In the event that GVHD is diagnosed, avelumab should be immediately and permanently discontinued.

Expansion Phase

Patients with GVHD of any grade must be permanently discontinued from the study treatment with the following exception: in the event of Grade 1 GVHD of the skin requiring topical therapy only, treatment with avelumab must be withheld until complete resolution of the GVHD, at which point treatment with avelumab may be resumed.

- If the event occurs during the first 6 weeks of the 70 mg Q2W dosing regimen and subsequently recovers, avelumab therapy must be resumed at the 70 mg Q2W dosing level and the dose must not be escalated to 500 mg Q2W (irrespective of the findings of the 6-week tumor assessment).

- If the event occurs during the first 12 weeks of the 70 mg Q2W, in a patient who achieves a PR at 6 week and continues on the same dosing regimen until Week 12, and subsequently recovers, avelumab therapy may be resumed only at the 70 mg Q2W dosing regimen without escalation to 500 mg Q2W (irrespective of the findings 12-week tumor assessment).

- If the event occurs in a patient while on 500 mg Q2W and then recovers, avelumab therapy may be resumed only at the 70 mg Q2W dosing regimen.

In the event of GVHD recurrence, the patient must be permanently discontinued from avelumab.

Any patient developing GVHD should be treated per local institutional guidelines, and immunosuppressive therapy and other appropriate medical interventions commenced as clinically indicated. The immunosuppression resulting from the treatment of GVHD increases the risk of life-threatening infection, and appropriate anti-microbial and anti-viral prophylactic therapy must be initiated.

It is not known whether checkpoint inhibitor-induced GVHD is more aggressive than conventional GVHD, and whether checkpoint inhibitor-induced GVHD should consequently be managed more aggressively than GVHD that occurs in the absence of checkpoint inhibition.

Early diagnosis of GVHD and close monitoring of the response to GVHD therapy is essential to prevent the progression and complications of GVHD, and to reduce the risk of mortality. The long-term goal of GVHD management is the development of immunological tolerance, which is indicated by the successful withdrawal of immunosuppressive treatment without recurrence of GVHD, or a clinically significant GVHD exacerbation.

The management of GVHD should occur within the context of an interdisciplinary team that includes the treating physician, a transplant specialist, and a microbiologist (to guide the selection of appropriate anti-microbial and anti-viral prophylaxis).

Liver function (including bilirubin, alkaline phosphatase, AST, and ALT) should be closely monitored, especially when hepatic GVHD is suspected, and the indication for a liver biopsy, and abdominal imaging should be reviewed at appropriate intervals.

In the case of hepatic GVHD, other potential underlying causes of cholestatic disease should be excluded, and the medications reviewed to identify other potential contributory or exacerbating factors.

The Sponsor's Medical Monitor must be informed within 24 hours if GVHD is suspected.

5.4.5. Dose Reductions

Avelumab dose reduction for toxicity management is only permitted as follows:

- Those patients who, following dose-escalation at the 500 mg Q2W experience any treatment related Grade ≥2 AEs lasting more than 14 days, will reduce their avelumab dose and continue treatment at the 70 mg Q2W dosing regimen.

- Additionally those patients who develop Grade 1 skin GVHD requiring topical therapy only while on 500 mg Q2W, will have their avelumab dose reduced to 70 mg Q2W as detailed in Section 5.4.4.4.

No other dose reduction for toxicity management is permitted, but next cycle administration may be omitted due to persisting toxicity as described in Section 5.4.3.1, Section 5.4.3.2 and Section 5.4.4.

5.5. Investigational Product Storage and Accountability

The Investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is stored in a secured area with controlled access, under specified storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. See the Investigational Product Manual for the storage conditions of the prepared product.

Storage conditions stated in the SRSD (ie, Investigator Brochure) will be superseded by the storage conditions stated in the labeling.

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 documented. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should 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.

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies.

5.6.1. Destruction of Investigational Product Supplies

The Sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study 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, and all destruction must be adequately documented.

5.7. Concomitant Treatment(s)

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

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from study therapy or medication/vaccination may be required. 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 wellbeing may be given at the 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 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).

Concurrent anticancer therapy with agents other than avelumab is not allowed. Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

Recommended medications to treat infusion-related reactions, tumor lysis syndrome immune-related adverse events, and GVHD are reported in Sections 5.4.4.1, 5.4.4.2, 5.4.4.3 and 5.4.4.4, respectively.

5.7.1. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is permitted during the study. They may also be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology guidelines.[18]

Use of erythropoietic growth factors is allowed during the study.

5.7.2. Concomitant Surgery

No formal studies of the effect of avelumab on wound healing have been conducted; however, caution is advised based on the mechanism of action. If a major surgery or an interventional procedure (eg, endoscopy, biopsy) is required, treatment with avelumab must be interrupted at least 24 hours before the procedure. Patients may resume avelumab as soon as the wound has completely healed and if there are no wound healing complications (eg, delayed healing, wound infection or fistula).

5.7.3. Concomitant Radiotherapy

Palliative radiotherapy to specific sites of disease is permitted 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 bone pain, the sites of bone disease should be present at baseline, otherwise, bone pain requiring radiotherapy will be considered as a sign of disease progression.

5.7.4. Other Prohibited Concomitant Medications and Therapies

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 avelumab.
- Radiation therapy (with the exception noted above in the Concomitant Radiotherapy Section 5.7.3).
- Immunosuppressive drugs, unless otherwise indicated for the treatment of irAEs (see Table 6). See below Clarification about Steroid Use.
- Other experimental pharmaceutical products.
- Any vaccine therapies for the prevention of infectious disease (eg, human papilloma virus vaccine) except for inactivated vaccines.
- 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.[12,17] 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-CTLA4 compounds indicate that short-term use of steroids may be employed without compromising clinical outcomes. Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions steroids are permitted according to the modalities indicated in Table 5.
- Physiologic use: steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.
- Prophylactic use: prior to CT or magnetic resonance imaging (MRI), steroids are permitted; prophylactic use for the prevention of acute infusion-related reactions is permitted only as described in Table 5.

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

5.8. Rescue Medications and Supportive Care

5.8.1. 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, 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.

- 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, warfarin or other coumarin derivatives or other anti-coagulants (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 Schedule of Activities (SOA).

6.2. Treatment Period

For treatment period procedures, see Schedule of Activities and Section 7.

6.3. Follow-up Visit

For follow-up procedures see Schedule of Activities and Section 7.

6.4. Patient Withdrawal

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn 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 withdrawal of study treatment may include:

- Objective disease progression;

- Global deterioration of health status requiring discontinuation;

- Unacceptable toxicity;

- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by Sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by Sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. The investigator should inquire about the reason for withdrawal, request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

If the patient refuses further visits, the patient should continue to be followed for survival (if survival is a secondary endpoint) unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study specific 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 investigator that 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 that he or 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 be performed at the time points described in the Schedule of Activities and include collection of adverse events (AEs), serious adverse events (SAEs), vital signs and physical examination, electrocardiogram (ECG [12-lead]), laboratory assessments, including pregnancy tests and verification of concomitant treatments.

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 and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatment, once at the start of screening and once at the baseline visit immediately before 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 investigational product. Pregnancy tests (urine or serum) will also be routinely repeated at every treatment cycle during the active treatment period, at the end of study treatment visit, at the Day 30 Follow-up Visit, 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 and will be withdrawn from the study. Additional pregnancy tests may also be undertaken if requested by IRB/ECs or if required by local regulations.

7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] (version 4.03) timing, seriousness, and relatedness.

Adverse events that occur during the study will be recorded on the adverse events CRF page.

7.1.3. Laboratory Safety Assessment

Hematology, blood chemistry, and urinalysis will be collected at the time points described in the Schedule of Activities (SOA) and analyzed at local laboratories. They may also be performed when clinically indicated. The required laboratory tests are listed in Table 7.

If a full and core chemistry panel are scheduled at the same visit, then only the full chemistry panel will be performed.

Table 7. Required Laboratory Tests

Hematology	Chemistry Panel (* denotes core chemistry test)	Urinalysis	Coagulation Tests	Pregnancy Tests
Hemoglobin	ALT*	Urine dipstick for protein, glucose, blood	PT or INR	For female patients of childbearing potential, serum or urine
Platelets	AST*		PTT or aPTT	
WBC	Alkaline Phosphatase*			
Absolute Neutrophils	Sodium*			
Absolute Lymphocytes	Potassium*			
Absolute Monocytes	Magnesium*			
Absolute Eosinophils	Chloride*			
Absolute Basophils	Total Calcium*			
	Total Bilirubin* °			
	BUN or Urea*			
	Creatinine*			
	Glucose (non-fasted)*			
	Phosphorus or Phosphate*			
	Albumin			
	Total Protein			
	Uric Acid			
	Amylase			
	Gamma glutamyltransferase (GGT)			
	Cholesterol			
	Creatine kinase			
	C-reactive protein (CRP)			
	Lactate dehydrogenase (LDH)			
	Lipase			
	Triglycerides			
	Thyroid Function Tests: TSH, free T4			
	Other Tests: ACTH			
	HBsAg, HBsAb, HBcAb, HCV Ab			

° 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 glutamyltransferase, prothrombin time (PT)/INR, alkaline phosphatase, and acetaminophen levels.
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, , HBsAg=Hepatitis B surface antigen, HbsAb=Hepatitis B surface antibody, HbcAb= Hepatitis B core antibody, HCV Ab= Hepatitis C virus antibody, INR=international normalized ratio, LDH=lactate dehydrogenase, TSH=thyroid-stimulating hormone, WBC=white blood cells

7.1.4. Vital Signs and Physical Examination

Patients will have a physical examination to include examination of the body systems, weight, vital signs, assessment of ECOG performance status, and height; height will be measured at screening only.

7.1.5. (12-Lead) Electrocardiogram

Single ECG measurements will be obtained at screening (all patients). On-study triplicate ECGs will be performed on Day 1 of Cycles 1 and 2, before avelumab infusion, and at the end of avelumab infusion and at End of Treatment. 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.

Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all on-treatment ECGs and at End of Treatment. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see Schedule of Activities), 3 consecutive ECGs (triplicates) will be performed at approximately 2 minutes apart to determine the mean QTc interval (average of triplicates). If the mean QTc is prolonged (>500 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTc of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 500 msec. If QTc interval reverts to less than 500 msec, and in the judgment of the investigator(s) and Sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTc intervals rise above 500 msec the investigational product will be held until the QTc interval decreases to 500 msec. Patients will then restart the investigational product at the next lowest dose level. If the QTc interval has still not decreased to 500 msec after 2 weeks, or if at any time a patient has a QTc interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

An electronic reading of prolonged QTc must be confirmed by manual reading. Prior to concluding that an episode of prolongation of the QTc interval is due to investigational product, 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 patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.

7.2. Pharmacokinetics Assessments

7.2.1. Blood Sample Collection for Pharmacokinetic analysis of Avelumab

Where noted in the Schedule of Activities blood samples will be collected at approximately the same time as other assessments wherever possible.

At each sampling time point, 3.5-mL of blood for avelumab PK will be collected as outlined in the Pharmacokinetic and Pharmacodynamic Sampling Schedule table. PK sampling schedule may be modified based on emerging PK data.

In addition to samples collected at the scheduled times, an additional blood sample may be collected from patients experiencing unexpected and/or serious AE's and the date and time of blood sample collection and of last dosing prior to PK collection documented in the CRF.

Where noted in the Schedule of Activities, blood samples for avelumab concentrations will be collected at approximately the same time as other assessments such as pharmacodynamic samples whenever possible. When PK sampling coincides with ECGs, PK samples should be taken after the ECG is performed.

All efforts will be made to obtain the pharmacokinetic 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 time may be rescheduled with agreement of the clinical investigator, patient, and Sponsor.

PK samples will be assayed for avelumab using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Study Manual.

7.3. Immunogenicity Assessment

3.5 mL of blood will be collected for evaluation of immunogenicity of avelumab. 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 Nabs. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Study Manual.

7.4. Biomarker and Pharmacodynamic Assessments

Tissue samples (including peripheral blood [redacted] and biopsies where appropriate and as indicated) will be collected pre- and post-avelumab administration from all patients participating in the study. *De novo* biopsies will be optional in the lead-in phase and mandatory in the dose expansion phase, assuming that the lesions to be biopsied can be safely accessed and sampled.

De novo biopsies will be collected at baseline during the screening period and on treatment as detailed in the Schedule of Activities. Patients who have an archival sample obtained within 3 months of the first dose of study drug and who have not received any intervening systemic anti-cancer therapy may submit this sample in lieu of a baseline de novo sample. It is strongly preferred that the 6-week on-treatment sample is collected prior to a potential dose escalation at Cycle 4. In the event a de novo biopsy cannot be safely accessed and sampled, an archival sample obtained within 6 months of enrollment must be submitted. Optional *de novo* biopsies can be collected at any time during the treatment phase as clinically indicated. In patients who have readily accessible lesions and who dose escalate to 500 mg Q2W at Cycle 4 or Cycle 7, an on-treatment biopsy at the time of the 12 or 24 -week tumor assessment scan, respectively, is desirable, but non-mandatory. An attempt should be made to collect archival tissue from patients in the lead-in phase who elect not to provide a baseline *de novo* biopsy. In this instance, an archival FFPE tumor tissue block from initial diagnosis or a previously obtained tumor biopsy of a disease lesion obtained within 6 months of enrollment and only if the patient has received no intervening systemic anti-cancer treatment during this period may be submitted. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) is not adequate and should not be submitted. Mandatory *de novo* biopsy(ies) should be processed to an FFPE block. Material-permitting, a second portion of the mandatory *de novo* biopsy(ies) should be processed to a fresh frozen block (see Study Manual for instructions on collection, processing, and shipping). The resulting FFPE, and fresh frozen blocks should be submitted to the Central Laboratory.

Biomarker evaluation will be performed on biopsies, peripheral blood, CCI [redacted]. Biopsy tissue will be submitted to analysis by immunohistochemistry to assess target expression, phenotypes of infiltrating immune cells and markers associated with immune activation and tolerance. Tumor tissue will also be submitted to RNA, CCI [redacted] Target occupancy on immune cells including, but not limited to, CD14+ monocytes and CD3+ T cells will be evaluated in the peripheral blood by flow cytometry in the lead-in phase only. Peripheral blood will also be submitted for immune cell profiling by flow cytometry, CCI [redacted]

Refer to the specific lead-in or expansion phase Schedule of Activities for details pertaining to specific days of sample collection and to the Lab Manual for details of sample preparation, storage and shipment. Note: while many biomarker collections are common to both the lead-in and expansion phases, some analyses are unique to one phase or the other, and, in addition, timepoints may differ between the two phases. The optional *de novo* tumor biopsy collections in the lead-in phase and mandatory and optional collections in the expansion phase are detailed above and in the SOA.

Table 8. Biomarker Collections and Analyses

Biomarker	Phase	Sample Type	Analysis
Target Occupancy	Lead-in only	Whole Blood	PD-L1 occupancy by avelumab on immune cells including CD14+ monocytes and CD3+ T cells by flow cytometry
Immune Cell Phenotypes	Lead-in: T cell subsets Expansion: TBNK and NK subsets	Whole Blood	Immune cell phenotypes associated with anti-tumor immunity and immune regulation by flow cytometry
CCI [redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]
Immuno-phenotypic Markers		Tumor Biopsy	Markers associated with immune cell phenotypes, regulation and activity by immunohistochemistry or immunofluorescence
Transcriptional Profile	Optional Biopsy in Lead-in; Mandatory pre- and on-treatment Biopsy in Expansion Phase	Tumor Biopsy (RNA)	RNA will be analyzed for expression profile of immune- and tumor-related transcripts
CCI [redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]

7.5. Disease Response Assessment

Lead-in Phase

In the lead-in phase, tumor assessments includes all known or suspected disease sites. Imaging will include: neck, chest, abdomen, and pelvis PET-CT at baseline and at 6 weeks. Additionally PET-CT scans may be performed as clinically indicated. Following the 6-week disease assessments, CT or MRI may be used, as long as one of these modalities was also performed at baseline and the same type of scan is used in the subsequent tumor assessments. The CT scan should be performed with contrast agents unless contraindicated. Imaging for tumor assessments will be conducted at screening, 6 weeks, 12 weeks and at 12-week intervals thereafter until documented disease progression regardless of initiation of subsequent anti-cancer therapy. Additional tumor assessments should also be conducted whenever disease progression is suspected (eg, symptomatic deterioration) and at End of Treatment/Withdrawal (if not done in the previous 6 weeks) and at follow-up visits. Responses will be assessed using the Response Criteria for Malignant Lymphoma[42] (Appendix 2).

All patient files and radiologic images must be available for source verification and for potential peer review. Imaging data from patients in the lead-in phase are being collected and retained by an independent radiology vendor. At the discretion of the Sponsor, these may be read by an independent radiologist.

Expansion Phase

In 2014, updated guidelines for initial evaluation, staging and response assessment of Hodgkin and Non-Hodgkin Lymphoma formally incorporating FDG PET-CT into standard staging for FDG-avid lymphoma were published. These guidelines will be used in the expansion phase since they represent the current standard of practice. For the expansion phase, tumor assessments will be evaluated using PET-CT at all timepoints. CT with contrast or MRI may be additionally performed if clinically indicated. Imaging for tumor assessment will be conducted at: screening, 6 weeks, 12 weeks, and at 12-week intervals thereafter for one year from the start of study treatment, and every 24 weeks thereafter until documented disease progression by BICR assessment, regardless of the initiation of subsequent anti-cancer therapy. Additional tumor assessments should be conducted whenever disease progression is suspected (eg, symptomatic deterioration) and at the End of Treatment/Withdrawal (if not done in the previous 6 weeks). For patients achieving a CR, a CT with contrast or MRI may be used instead of the PET-CT for tumor assessment until disease progression, which will require PET-CT documentation. Response assessment will be made using the Lugano Classification[43] (Appendix 3), in association with the Deauville 5 point scale.

7.5.1. Blinded Independent Central Review for Disease Assessment (Expansion Phase)

In the expansion phase disease responses will be assessed by a Blinded Independent Central Review (BICR) according to the process defined in the Study Manual.

The PET-CT imaging collected for all patients from screening to the 6 week assessment and those collected at the 12 week assessment for patients in PR at 6 week will be submitted to the BICR for real-time expedited review. Intra-patient dose escalation decisions will be made following discussion between the Investigator and the Sponsor and will be informed by the BICR disease response assessment. Due to the time-sensitive nature of this process, the 6-week and the 12-week tumor assessment may be performed up to one week prior to the scheduled time, so that images can undergo BICR review before Cycle 4 and Cycle 7.

For investigator-assessed progressive disease, real-time expedited BICR review will be also performed to inform the Investigator's decision of whether treatment should be discontinued. Upon investigator-assessed disease progression, all radiographic images collected for a patient from screening onwards will be submitted to the BICR for expedited review. Every effort should be made to keep the patient on study treatment until the BICR has completed the radiographic image review, unless treatment continuation is contraindicated (see Study Manual for details).

7.6. Banked Biospecimens

7.6.1. 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 deoxyribonucleic acid (DNA), ribonucleic (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.CCI

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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 swiping a badge. 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 be used only 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 postmarketing research. Patients can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which case 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 study.

A 4-mL blood biospecimen **Prep D1 (K_2 edetic acid [ethylenediaminetetraacetic acid][EDTA] whole blood collection optimized for DNA analysis)** will be collected at baseline and Day 1 of Cycle 3 (for Lead-in phase every 2-week dosing) baseline and Day 7 of Cycle 2 (for Lead-in phase every 3-week dosing), and baseline only (pre-dose Day 1of Cycle 1) for Expansion phase to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The banked biospecimen 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 a separate study 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.

7.6.2. 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 study, 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; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

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

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(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 AE 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 study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient'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 investigational product. SAEs occurring to a patient 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 investigational product are to be reported to the Sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product through and including 90 calendar days after the last administration of the study drug.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious 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 investigational product, 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;
- Extravasations;
- 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.

8.3.1. Avelumab Adverse Event of Special Interest

Any AE that is suspected to be a potential irAE is considered an AE of special interest (AESI). Specific guidance for the management of irAEs is provided in Section 5.4.4.3 and Table 6. AESIs are reported according to the general AE reporting rules specified in Section 8.2.

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, or at the wrong dosage strength. 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 investigational product;
- 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 AEs 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 study, an overdose of avelumab is defined as an increase ≥5% than the planned avelumab dose for that particular administration.

There is no specific treatment for avelumab overdose. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided as clinically indicated.

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

A serious adverse event 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) Grade 5 (see the section 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 the section on Serious Adverse Event 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 (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

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

- For patients with preexisting AST or ALT baseline values above the normal range, AST or ALT value ≥2 times the baseline values and ≥3 × ULN, or ≥8 × 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-glutamyltransferase, prothrombin time (PT)/international normalized ratio (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 person, 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;
- 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 workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- 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;
- Preplanned treatments or surgical procedures. These 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 noninvasive 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 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 SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product 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 investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that 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.

8.10. Exposure During Pregnancy

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

1. 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 investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   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).

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

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an 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 the 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 SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP 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). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

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 (See also the Section 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. In addition, each study patient/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 time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

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 or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames 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 autopsy findings 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

AE 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 study will be documented in a Statistical Analysis Plan, which will be maintained by the Sponsor. This document may modify the plans outlined in the protocol; however, any major modification of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Analysis Sets

- Full Analysis Set.

  For the lead-in phase the full analysis set includes all randomized patients. Patients will be classified according to the treatment assigned at randomization.

- For the expansion phase: the full analysis set includes all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment actually received. Safety Analysis Set.

  For the lead-in phase the safety analysis set includes all patients who received at least 1 dose of study treatment. Patients will be classified according to the treatment assigned at randomization unless the incorrect treatment was received throughout the dosing period in which case patients will be classified according to the first treatment received.

  For the expansion phase the safety analysis set is identical to the full analysis set.

- Target Occupancy Analysis Set.

- The TO analysis set includes patients in the safety analysis set who have at least one Receptor Occupancy blood sample collected both pre and post Cycle 1 Day 1 dose.

- Immunogenicity Analysis Set.

  The immunogenicity analysis set includes patients in the safety analysis set who have at least 1 ADA sample collected.

- PK Analysis Sets.

  The PK parameter analysis set includes patients in the safety analysis set who have sufficient information to estimate at least 1 of the PK parameters of interest.

  The PK concentration analysis set includes all randomized patients who receive at least 1 dose of study treatment and have at least 1 analyte concentration.

- Biomarker Analysis Set(s).

  The biomarker analysis set is a subset of the safety analysis set and will include patients who have at least one biomarker sample. Analysis sets will be defined separately for whole blood, plasma, and tumor biopsy biomarkers.

All other statistical analysis sets will be documented in the Statistical Analysis Plan (SAP).

9.2. Statistical Methods and Properties

9.2.1. Sample Size Determination

In the lead-in phase, 31 patients were randomized in a 1:1:1:1:1 ratio and approximately 40 patients will be enrolled in the expansion phase. In total, the study will enroll approximately 70 patients.

Lead-in Phase

In the lead-in phase, a total of 31 patients were randomized across 5 different treatment cohorts. The 6 patients per treatment cohort in the lead-in phase will be used to enable the initial estimation of TO; based on the historical data, with observed mean TO of 90%, the corresponding 95% confidence interval will be 88.98% to 91.02%, assuming a standard deviation of 1.27%.

Expansion Phase

Approximately 40 patients will be enrolled in the post-allogeneic HSCT cohort.

With 40 treated patients, ORR can be estimated with a standard error not exceeding 0.079. Table 9 provides 95% confidence intervals for ORR based on different possible observed responses in the post-allogeneic HSCT cohort.

Table 9. Sample Size and Exact 95% CIs for ORR - Post-allogeneic HSCT cohort

Number of Patients in the Post-allogeneic HSCT Cohort	Number of Observed Responses	Observed ORR	95% CI for True ORR
40	16	40%	(24.86%, 56.67%)
	20	50%	(33.80%, 66.20%)
	24	60%	(43.33%, 75.14%)
	28	70%	(53.47%, 83.44%)
	32	80%	(64.35%, 90.95%)

9.2.2. Efficacy Analysis

Efficacy will be summarized by treatment cohort based on the full analysis set, separately for each phase of the study. The evaluation of anti-tumor activity will be based on the Response Criteria for Malignant Lymphoma[42] (Appendix 2) for patients enrolled in the lead-in phase and on the Lugano Classification[43] (Appendix 2) for patients enrolled in the expansion phase.

In the expansion phase, tumor-related endpoints will be summarized separately based on BICR assessment and based on Investigator assessment.

In what follows ‘start date’ refers to date of randomization for patients enrolled in the lead-in phase and to date of first dose of study treatment for patients enrolled in the expansion phase.

Objective response (OR) is defined as complete response (CR) or partial response (PR) from 'start date' until disease progression or death due to any cause. OR rate (ORR) is the proportion of patients with OR.

Time to Tumor Response (TTR) is defined, for patients with an objective response as the time from 'start date' to the first documentation of objective tumor response (CR or PR).

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

Disease Control (DC) is defined as the best overall response of CR, PR, or SD. To qualify as a best overall response of SD, at least one SD assessment must be observed ≥6 weeks after start date and before disease progression. DC rate (DCR) is the proportion of patients with DC.

Progression Free Survival (PFS) is defined as the time from 'start date' 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 'start date' unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

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

ORR will be estimated and the corresponding exact 2-sided 95% confidence interval will be reported. TTR will be summarized using simple descriptive statistics (eg, median and range). DC will be summarized by frequency counts and percentages. DR, PFS, and OS will be analysed using Kaplan-Meier methods; median DR, median PFS, and median OS and associated 95% confidence intervals will be reported.

9.3. Analysis of Pharmacokinetics and Pharmacodynamics

9.3.1. Analysis of Pharmacokinetics

9.3.1.1. Avelumab Pharmacokinetic Analysis

Standard plasma PK parameters for avelumab will be estimated using non-compartmental analysis. For avelumab, standard PK parameters will include C_{max}, T_{max}, $AUC_{0-\tau}$, $t_{1/2}$, plasma clearance (CL), and volume of distribution (Vz) and other PK parameters, as data permit. Dose normalized parameters (eg, CDN-C_{max}, DN-AUC) will be reported as appropriate. Descriptive statistics for the PK parameters for avelumab will be provided by dose, cycle and day of assessment in tabular form.

Avelumab plasma concentrations and PK parameters will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by cohort, cycle, day and nominal time. Individual patient and median profiles of the avelumab concentration-time data will be plotted by cohort, cycle and day using nominal times. Median avelumab profiles will be presented on both linear-linear and log-linear scales.

9.3.2. Analysis of Pharmacodynamics

Percent PD-L1 TO will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by dose, cycle, day and nominal time. Mean PD-L1 TO before the second cycle (at the expected C_{trough}) will be used to decide which dose to move forward into the expansion phase of the protocol. Decision criteria are outlined in Section 3.1.

9.3.2.1. Analysis of Biomarker Endpoints

For continuous measurement biomarker results, summary statistics (eg, the mean, standard deviation, median, coefficient of variation percent, and minimum/maximum levels) will be determined at baseline and on-treatment/end of treatment time points, as appropriate. Appropriate change from baseline measurements will be provided. For discrete measurement biomarkers, frequencies and percentages of categorical biomarker measures will be determined at baseline and on-treatment/post-treatment time points, as appropriate; shift tables may also be provided.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as Wilcoxon signed-rank test, Wilcoxon rank-sum test, correlation/linear regression, box-and-whisker plots, etc. The statistical approaches will examine correlations of biomarker results (eg, PD-L1) with pharmacokinetic parameters and measures of efficacy, such as tumor response and progression free survival.

9.3.3. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between avelumab exposure and TO, biomarkers or significant safety/efficacy endpoints. The results of these analyses, if performed, may be reported separately.

9.3.4. Immunogenicity Assessment

For the immunogenicity data, the percentage of patients with positive ADA and neutralizing antibodies each will be summarized by cohort and for the entire population in the study. 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.

9.4. Safety Analysis

Safety will be summarized by treatment cohort based on the safety analysis set, separately for each phase of the study.

9.4.1. Safety Stopping Rules

Based on the clinical thresholds described in Section 3.1.3, the trial will be stopped if given the data there is at least 70% probability that the toxicity rate is above the clinical threshold for any of the event categories.

Table 10. Safety Stopping Rules

Patients	Gr ≥3 acute GVHD *	GVHD-related deaths	Gr ≥4 irAEs (excluding acute GVHD)
15	6/15 (40%)	4/15 (27%)	3/15 (20%)
20	8/20 (40%)	5/20 (25%)	4/20 (20%)
25	10/25 (40%)	6/25 (24%)	5/25 (20%)
30	12/30 (40%)	8/30 (27%)	6/30 (20%)
35	13/35 (37%)	9/35 (26%)	7/35 (20%)
40	15/40 (38%)	10/40 (25%)	8/40 (20%)

* Grade 3 liver GVHD must be confirmed by biopsy.

Only patients meeting eligibility criteria will be included in the evaluation. As such, one patient in the lead-in phase who met exclusion criterion 1 related to GVHD will be excluded.

Two formal evaluations will be conducted at the following time points:

- 16 weeks after 15 patients have received the first dose of study treatment.
- 16 weeks after 30 patients have received the first dose of study treatment.

Events from patients who at the time of the formal evaluation have not yet been followed for 16 weeks from first dose of study treatment will also be considered in the evaluation. The study will stop if the stopping boundary is crossed for any of the 3 event categories.

9.4.2. 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 (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 summarized.

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

9.4.3. Laboratory Test Abnormalities

Laboratory data will be summarized by treatment cohort and separately for each phase of the study.

The laboratory results will be graded according to the NCI CTCAE v4.03 severity grade. The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst grade for each laboratory test.

For laboratory tests without NCI CTCAE grade definitions, 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.

9.4.4. Electrocardiograms

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any 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).

CCI [redacted]

9.6. Data Monitoring Committee

An external Data Monitoring Committee will not be established for the study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases, including surveillance for serious adverse events (SAEs) according to regulatory guidelines.

Discussions between the investigators and the Sponsor of AEs and laboratory test abnormalities seen at each dose level in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and make a benefit/risk assessment to decide if further patient enrollment at one or more avelumab dose levels is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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 are true. Any corrections to entries made in the CRFs or 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 investigative 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, and telephone call reports). The records should be retained by the investigator according to 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 Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association).

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, address and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify trial 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 patients’ personal data consistent with applicable privacy laws.

The informed consent document(s) 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 and approved by the Sponsor, approved by the IRB/IEC before use, and available for inspection.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each patient 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 that might influence the evaluation of the benefits and risks of the investigational product, 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 (EU) 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 Other Participating Countries

End of Trial in all other 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, or investigational safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of 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, 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

Abbreviation	Term
Ab	Antibody
ABVD	Doxorubicin, bleomycin, vinblastine, dacarbazine
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Allogeneic-HSCT	Allo-HSCT
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
BUN	Blood urea nitrogen
BICR	Blinded independent central review
C	Cycle
C	Concentration
cHL	Classic Hodgkin's Lymphoma
CI	Confidence interval
CL	Clearance
CNS	Central nervous system
CPK	Creatine phosphokinase
CR	Complete response
CRF	Case report form
CSA	Clinical study agreement
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
CTA	Clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
D	Day
DC	Disease control
DLI	Donor lymphocyte infusion
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DR	Duration of Response
DU	Dispensable unit
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Term
EDP	Exposure during pregnancy
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
eg	For example
etc	'And other things' or 'and so forth'
EudraCT	European Clinical Trials Database
EU	European Union
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed paraffin-embedded
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GVHD	Graft-versus-host disease
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
HRS	Hodgkin and Reed-Sternberg
HSCT	Hematopoietic stem cell transplant
IB	Investigator's brochure
ICH	International Conference on Harmonisation
ID	Identification
ie	That is
IHC	Immunohistochemistry
IND	Investigational New Drug application
INR	International Normalized Ratio
irAE	Immune related adverse event
IRB	Institutional Review Board
IRR	Infusion related reaction
IRRC	Independent radiologic review committee
IRT	Interactive response technology
IUD	Intrauterine device
IV	Intravenous
JAK	Janus kinase
K_2EDTA	Dipotassium ethylene diamine tetraacetic acid
LFT	Liver function test
LPD	Local product document
LVEF	Left ventricular ejection fraction
NSAID	Non-steroidal anti-inflammatory drug
mAb	Monoclonal antibody

Abbreviation	Term
MD	Multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
N/A	Not applicable
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
NK	Natural killer
ORR	Objective response rate
OS	Overall survival
PCD	Primary completion date
PD	Pharmacodynamics
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QD	Every day
QT	Time between the start of the Q wave and the end of the T wave
RNA	Ribonucleic acid
RR	Respiratory rate
RS	Reed-Sternberg
SOA	Schedule of activities
SAE	Serious adverse event
SAP	Statistical analysis plan
HSCT	Stem cell transplantation
SD	Single dose
SIB	Suicidal ideation and behavior
SRSD	Single reference safety document
STAT	Signal Transducer and Activator of Transcription
T	Time
$T_{1/2}$	Terminal elimination half-life
TEAE	Treatment emergent adverse event
TBR	Tumor background ratio
TCR	T cell receptor
TIL	Tumor infiltrating lymphocyte
TO	Target Occupancy
TTR	Time to tumor response
ULN	Upper limit of normal

Abbreviation	Term
US	United States
Vz	Volume of distribution
VOD	Veno-occlusive disease
WBC	White blood cell
WES	Whole exome-sequencing

Appendix 2. Response Criteria for Malignant Lymphoma (Lead-in Phase)

From the International Workshop to Standardize Response Criteria for Lymphomas[42]

Complete Response (CR): Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease related symptoms if present before therapy and normalization of those biochemical abnormalities (for example LDH) definitely assignable to the lymphoma. All lymph nodes must have regressed to normal size (less than or equal to 1.5 cm in greatest diameter if >1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in greatest diameter must have decreased to less than or equal to 1 cm or by more than 75 percent in the sum of the products of the greatest diameters. The spleen, if considered to be enlarged before therapy, must have regressed in size and not be palpable on physical examination. The bone marrow must show no evidence of disease by histology. Flow cytometry, molecular or cytogenetic studies will not be used to determine response. Response must persist for 1 month. For FDG-avid or PET positive lesions prior to therapy; mass of any size is permitted if the current scan is PET negative. For variably FDG-avid or PET negative lesions; regression to normal size on CT is required.

Partial Response (PR): ≥50% decreased in the sum of products of the greatest diameters (SPD) of 6 largest dominant nodes or nodal masses. No increase in size of nodes, liver or spleen and no new sites of disease. Splenic and hepatic nodules must regress by ≥50% in the SPD. Bone marrow is irrelevant for determination of a PR. No new sites of disease should be observed. For FDG-avid or PET positive lesions prior to therapy; one or more PET positive at previously involved site is permitted. For variably FDG-avid or PET negative lesions; regression on CT is required.

Progressive Disease (PD): ≥50% increase from nadir in the SPD of any previously identified abnormal node for PRs or non-responders. Appearance of any new lesion during or at the end of therapy.

Stable Disease (SD): is defined as less than a PR but not progressive disease. ALL assessment of clinical response will be made according to the NHL guidelines.

Relapsed disease requires the following: Appearance of any new lesion or increase by ≥50% in the size of the previously involved sites. Greater than or equal to 50% increase in greatest diameter of any previously identified node >1 cm in its shortest axis or in the SPD of more than one node.

The major criteria for judging response will include physical examination and examination of blood and bone marrow. All laboratory studies that are abnormal prior to study will be repeated to document the degree of maximal response.

Appendix 3. The Lugano Classification- (Expansion Phase)

From the Recommendations of Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification[43]:

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on PSt It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5 † with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node ≥ 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by ≥ 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Appendix 4. Consensus Conference on Acute GVHD Grading[29]

Extent of organ involvement

Stage	Skin	Liver (bilirubin)	Gut (stool output/day)
0	No GVHD rash	< 2 mg/dl	< 500 ml/day or persistent nausea.
1	Maculopapular rash< 25% BSA	2–3 mg/dl	500–999 ml/day
2	Maculopapular rash 25 – 50% BSA	3.1–6 mg/dl	1000–1500 ml/day
3	Maculopapular rash > 50% BSA	6.1–15 mg/dl	Adult: >1500 ml/day
4	Generalized erythroderma plus bullous formation	>15 mg/dl	Severe abdominal pain with or without ileus
Grade			
I	Stage 1–2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	-	Stage 2–3 or	Stage 2–4
IV	Stage 4 or	Stage 4	-

Appendix 5. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report[30]

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS**				
Symptom score:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

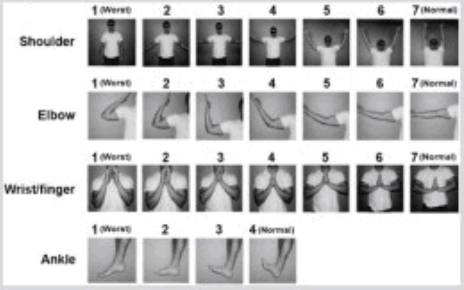
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ❑ **No GVHD** ❑ **Mild** ❑ **Moderate** ❑ **Severe**

Photographic Range of Motion (P-ROM)



NIH Global Severity of chronic GVHD

Mild chronic GVHD
1 or 2 Organs involved with no more than score 1 *plus*
Lung score 0
Moderate chronic GVHD
3 or More organs involved with no more than score 1
OR
At least 1 organ (not lung) with a score of 2
OR
Lung score 1
Severe chronic GVHD
At least 1 organ with a score of 3
OR
Lung score of 2 or 3
Key points:
In skin: higher of the 2 scores to be used for calculating global severity.
In lung: FEV1 is used instead of clinical score for calculating global severity.
If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Appendix 6. Treatment Recommendations for Symptoms of Avelumab Infusion-Related Reactions

The following treatment recommendations for symptoms of avelumab infusion-related reactions may be modified based on local treatment standards and guidelines, as appropriate.

For Grade 1 Symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

- Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
- Remain at bedside and monitor patient until recovery from symptoms.

For Grade 2 Symptoms: (Moderate reaction; Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.)

- Temporarily discontinue avelumab infusion.
- Treat based on emerging symptoms. Treatment may include:
  - Normal saline IV;
  - H1 blockers, such as diphenhydramine 25 to 50 mg IV (or equivalent);
  - H2 blockers, such as ranitidine 50 mg IV (or equivalent);
  - NSAIDs, such as ibuprofen 600 mg (or equivalent);
  - Meperidine 12.5 to 50 mg IV;
  - Corticosteroids, such as hydrocortisone 100 to 500 mg IV (or equivalent);
  - Bronchodilators.
- Remain at bedside and monitor patient until resolution of symptoms.
- Resume avelumab infusion at 50% of previous rate as soon as infusion related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening.

For Grade 3 or Grade 4 Symptoms: (Severe reaction; 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 [eg, renal impairment, pulmonary infiltrates]; Grade 4: life-threatening consequences; urgent intervention indicated).

- Stop the avelumab infusion immediately and disconnect infusion tubing from the patient.
- Begin an IV infusion of normal saline, and treat the patient with one or more of the following:
    - Airway maintenance;
    - Oxygen;
    - Bronchodilators;
    - Epinephrine 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution IM, up to a maximum dose of 0.5 mg;
    - H1 blockers, such as diphenhydramine 25 to 50 mg IV (or equivalent);
    - H2 blockers, such as ranitidine 50 mg IV (or equivalent);
    - Corticosteroids, such as hydrocortisone 100 to 500 mg IV (or equivalent).
- Remain at bedside and monitor patient until recovery from symptoms.
- Patients have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.