PHASE 1B/PHASE 3 MULTICENTER STUDY OF AVELUMAB (MSB0010718C) IN COMBINATION REGIMENS THAT INCLUDE AN IMMUNE AGONIST, EPIGENETIC MODULATOR, CD20 ANTAGONIST AND/OR CONVENTIONAL CHEMOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

JAVELIN DLBCL

Investigational Product Number:	MSB0010718C PF-05082566
Investigational Name:	Avelumab (MSB0010718C) Utomilumab (PF-05082566)
United States (US) Investigational New Drug (IND) Number:	CCI
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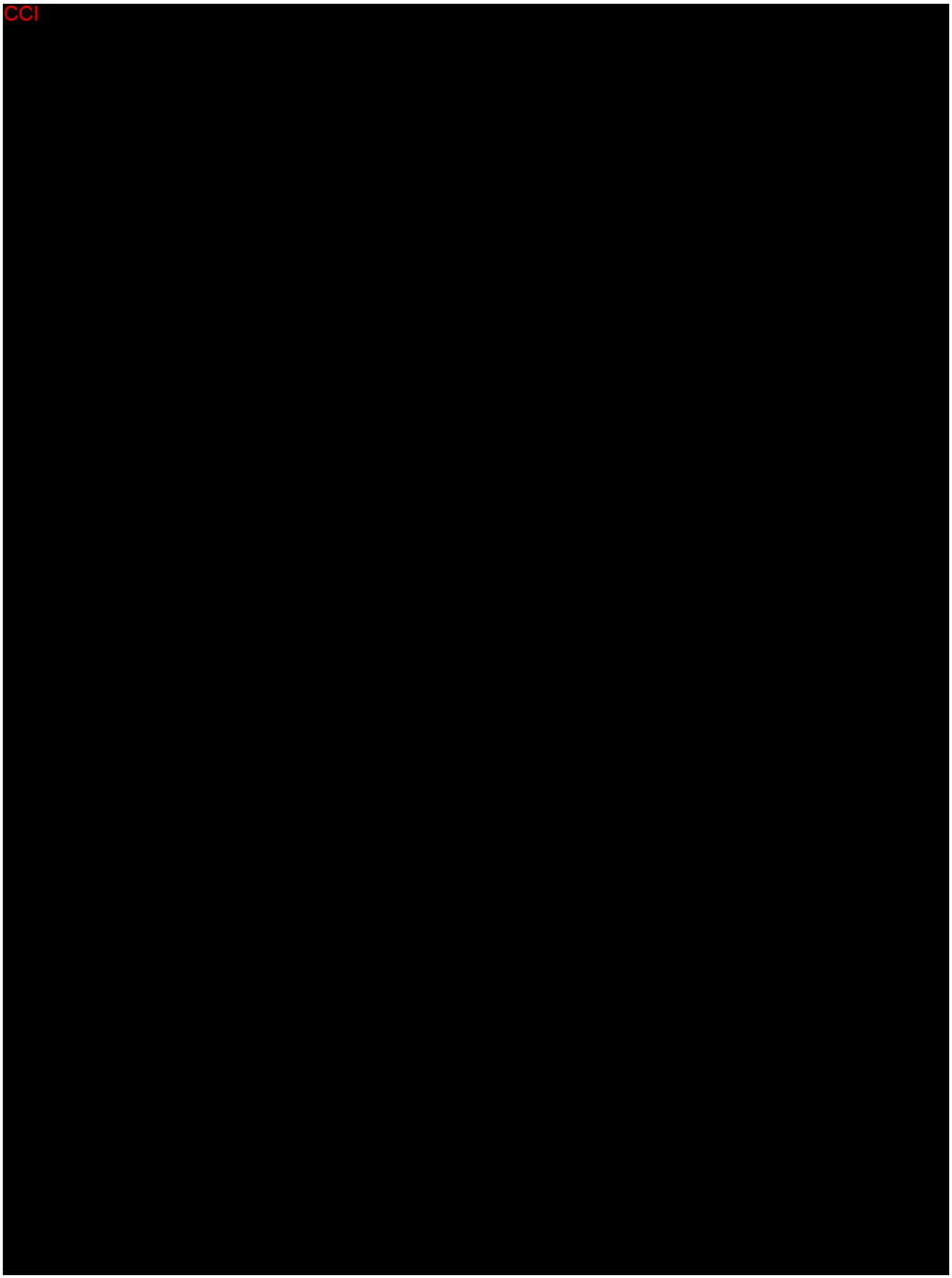
Phase:	1b/3

Document History

CCI



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PROTOCOL SUMMARY

Study B9991011 is a multi-center, international, randomized, open-label, 2-component (Phase 1b followed by Phase 3), parallel-arm study of avelumab in combination with various agents for the treatment of Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL). Agents that will be tested include:

(i) Utomilumab, a novel fully human IgG2 monoclonal antibody agonist of 4-1BB (CD137, TNFRSF9),

(ii) Azacitidine, a deoxyribonucleic acid (DNA) methyltransferase inhibitor (DNMTi) and epigenetic agent which has been shown to have potential immune priming activity through various mechanisms that include the induction of Programmed Death 1 (PD-1) on tumor infiltrating lymphocytes (TILs) and PD-L1 on tumor cells as well as the induction of tumor neo-antigen expression,

(iii) Rituximab, a CD20 antagonist antibody, and

(iv) Bendamustine, an alkylating chemotherapy agent, which is one of the National Comprehensive Cancer Network (NCCN) recommended agents for the salvage therapy of patients with DLBCL who are ineligible for high dose chemotherapy and autologous stem cell transplant (ASCT).[1]

The treatment regimens in the study include avelumab combined with:

(i) Rituximab plus utomilumab,

(ii) Azacitidine plus utomilumab, or

(iii) Rituximab plus bendamustine.

Avelumab will be administered as a 1 hour intravenous (IV) infusion once every 2 weeks of each 28-day cycle. 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.

Premedication prior to rituximab is mandatory; if avelumab is administered more than 1 hour after rituximab then the premedication must be repeated. The line should be flushed, according to local practice, between infusions, and a new administration set should be used for avelumab.

Site staff should make every effort to target the timing of avelumab infusion to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 20 minutes is permitted (ie, infusion time is 50-80 minutes). The exact duration of infusion should be recorded in both source documents and Case Report Forms (CRFs).

Utomilumab is administered in this study as a 1 hour IV infusion at 100 mg fixed dose of each 28-day cycle. Avelumab must be administered at least 1 hour after the end of utomilumab administration until the patient is no longer achieving clinical benefit. If Cycle 1 and 2 dosing administration is well tolerated; Cycle 3 and subsequent cycles may decrease administration of utomilumab and avelumab from at least 1 hour apart to 30-60 minutes apart.

Utomilumab is administered for as long as the patient is benefitting. Treatment through progression of disease is permitted if the Investigator and Sponsor agree and the patient has provided written consent.

Azacitidine 40 mg/m^2 (SC) will be administered in the morning on Days 1 - 5 of each 28-day cycle, until the patient is no longer achieving clinical benefit.

Rituximab is administered in this study at the dose of 375 mg/m^2 up to 8 cycles maximum as an IV infusion in the morning of each 28 day cycle on Day 1. Rituximab infusion must be completed at least 1 hour prior to utomilumab and bendamustine.

Rituximab should not be administered as an IV push or bolus. Premedication with acetaminophen and an antihistamine should be administered 30 minutes before each IV infusion.

Premedication prior to rituximab is mandatory; if avelumab is administered more than 1 hour after rituximab, then the premedication must be repeated. The first infusion should be initiated at a rate of 50 mg/hr. In the absence of infusion toxicity, the rate of infusion may be increased by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Subsequent infusions of rituximab should be initiated at a rate of 100 mg/hr. In the absence of infusion toxicity, the rate of infusion may be increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr.

Bendamustine is administered in the Phase 1b (Treatment Arm C) and in the Phase 3 investigational arm (in the event that Treatment Arm C advances to the Phase 3 component of the study) at 90 mg/m^2 IV infusion up to 6 cycles maximum. Intra-patient dose escalation is not permitted. Note that in the Phase 3 Investigator's Choice option (Arm E), bendamustine is administered at a higher dose of 120 mg/m^2 on Days 1 and 2 of each 28-day cycle, for up to 6 cycles.

Gemcitabine is administered at 1000 mg/m^2 IV infusion up to 6 cycles maximum on Day 2 and Day 17 of each 28 day cycle as part of the Investigator's Choice option (Arm E) in Phase 3. Gemcitabine must be administered at a fixed dose rate of 16.7 mg/m^2/minute over 60 minutes. This prolonged administration schedule has been shown to achieve superior intracellular drug concentration as compared with the 30 minute IV schedule.

Oxaliplatin is administered at 100 mg/m^2 IV infusion up to 6 cycles maximum on Day 2 and Day 17 of each 28-day cycle as part of the Investigator's Choice option (Arm E) in Phase 3.

Gastrointestinal toxicity related to oxaliplatin may manifest as nausea and vomiting, and may be managed with prophylactic and/or therapeutic anti-emetic therapy. Oxaliplatin is administered over 2 hours on Day 2 following gemcitabine.

If a patient with documented progression of disease (PD) per Lugano criteria continues to experience clinical benefit, per Investigator's clinical judgment and following discussion between the Investigator and the Sponsor, the patient may be eligible for continued treatment with avelumab and/or utomilumab. The Investigator's judgment should be based on the overall benefit-risk assessment and on the patient's clinical condition, including: performance status, clinical symptoms, adverse events, and laboratory data. Other agents in the regimen combination with avelumab and/or utomilumab may also be considered for continuation if in the Investigator's clinical judgment the patient may achieve clinical benefit. See Section 5.4 for treatment duration limits for agents other than avelumab and utomilumab.

The criteria that must be met are as follows: (i) No decline in Eastern Cooperative Group Performance Status (ECOG PS), (ii) Absence of rapid progression of disease by radiographic imaging, (iii) Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention, and (iv) Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression.

Before continuation of treatment, the patient must be re-consented and informed that by continuing receiving the investigational products on study, they may be foregoing treatment with approved therapies with possible clinical benefits.

Based on the safety and efficacy observed in the Phase 1b part of this study, one (1) regimen will potentially be selected for further investigation in the Phase 3 component of this study. In the Phase 3 component, patients will be randomized in a 1:1 ratio to either the avelumab-based treatment regimen selected in the Phase 1b component or the Investigator's Choice treatment option to determine whether the selected avelumab-based treatment regimen is superior to the Investigator's Choice treatment option in prolonging progression-free survival (PFS).

The target study population of this Phase 1b/Phase 3 registration study will comprise patients with R/R DLBCL who have completed at least 2 (but not more than 4) lines of prior rituximab/multi-agent chemotherapy, and/or in whom ASCT has failed, or who are not eligible for intensive chemotherapy or who are not candidates for ASCT. The study will assess the safety, efficacy, pharmacokinetics (PK), immunogenicity, and patient-reported outcomes (PROs) of each avelumab-based combination regimen.

The primary objective of the Phase 1b component of the study will be to make a preliminary assessment of safety and efficacy for each combination regimen. Each treatment arm after safety is confirmed in the first 6 and/or 12 patients will be expanded to a total of 28 patients per arm in order to potentially select a treatment regimen to be advanced to the Phase 3 component of the study. This decision will be based upon the objective response rate (ORR),

6-month durable response rate (DRR), progression-free survival (PFS) rate at 6 months, and the safety profile of each avelumab-based combination regimen.

In the Phase 3 component, the primary objective will be to demonstrate superiority in PFS (as assessed by Blinded Independent Central Review [BICR]) of the avelumab-based combination regimen identified in Phase 1b, over the control treatment, Investigator's Choice treatment option chemotherapy (ie, rituximab/bendamustine or rituximab/gemcitabine/oxaliplatin) in 220 patients (110 patients per arm).

SCHEDULE OF ACTIVITIES

The Schedule of Activities tables provide an overview of the protocol visits and procedures. Refer to Table 1 and Table 2 of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Table 1. Phase 1b Schedule of Activities

Cycle Length: 28 Days Each		Cycle 1						Cycles 2, 3, 4, 5, and 6			Cycles >6	End of Treatment/Follow-Up		
Visit Identifier	**Screen (≤28 days prior to randomization)**	**Day 1**	**Day 2/3**	**Day 7**	**Day 8**	**Day 15/16**	**Day 22**	**Day 1/2**	**Day 2/3**	**Day 15/16**		**End of Treatment/ Withdrawal**	**Follow-Up Visits Days: 30, 60, and 90 after last dose**	**Survival Follow-Up[27]**
Visit window ± days		**±0**	**±0**	**±1**	**±1**	**±1**	**±1**	**±0**	**±0**	**±2**	**±3**	**±7**	**±3**	**±7**
Written informed consent	X													
Medical oncology history (including prior treatment regimens)	X													
CCI [redacted]	[redacted]	[redacted]				[redacted]		[redacted]		[redacted]		[redacted]		
General medical history	X													
Full physical examination (PE)[1]	**Full PE** during Screening and first day of Cycles 3, 6, 9, 12, every 3 cycles thereafter, and at EOT[1]													
Contraception check[2]		X						X			X	X	X	
Baseline signs and symptoms[3]		X												
ECOG PS and IPI Score[4]	X							X			X	X		
Weight		X				X		X		X	X	X		
Vital signs[5]		X						X			X	X		
Disease staging and response assessment (Lugano Classification)[6]	**18F-FDG PET-CT**: Performed ≤6 weeks prior to randomization, then once every 12 weeks (±1 week) from randomization and at EOT (unless performed ≤6 weeks before EOT) After 12-months from randomization, 18F-FDG PET-CT is performed every 24 weeks (±1 week) until PD.												X[6]	X[6]
Blood collection for Minimal residual disease (MRD) assessment[7]	MRD assessment to align with time-points for tumor staging and response assessment (PET-CT): Prior to randomization, then once every 12 weeks and at EOT (unless performed ≤6 weeks before EOT). After 12-months from randomization, performed every 24 weeks (±1 week) until PD.													
12-Lead ECG[8]	ECGs will be performed in singlicate during screening or prior to the first day of study treatment, and in triplicate during the study, pre- and post-infusion/SC dose on the first dosing days (Day 1 and Day 2) of Cycles 1 and 2, on the second avelumab dose of Cycle 1 (Day 16), at EOT/early withdrawal and as clinically indicated.													
LVEF (by MUGA or ECHO) (time window ±5 days)[9]	X											X		
Laboratory tests[10]	X	X				X		X		X	X	X		
Hematology[11]	X	X				X		X		X	X	X		
Blood Chemistry[12]	X	X				X		X		X	X	X		
Coagulation		X				X		X		X	X	X		

Cycle Length: 28 Days Each		Cycle 1						Cycles 2, 3, 4, 5, and 6			Cycles >6	End of Treatment/Follow-Up		
Visit Identifier	**Screen (≤28 days prior to randomization)**	**Day 1**	**Day 2/3**	**Day 7**	**Day 8**	**Day 15/16**	**Day 22**	**Day 1/2**	**Day 2/3**	**Day 15/16**		**End of Treatment/ Withdrawal**	**Follow-Up Visits Days: 30, 60, and 90 after last dose**	**Survival Follow-Up[27]**
Visit window ± days		**±0**	**±0**	**±1**	**±1**	**±1**	**±1**	**±0**	**±0**	**±2**	**±3**	**±7**	**±3**	**±7**
ACTH, FT4, and TSH[13]	Measured at screening, every 8 weeks from first dose of treatment for 2 additional measurements, and then every 12 weeks thereafter while on treatment											X	X	
HBV, HCV[14]	Measured at screening and then every 6 months from first dose of treatment and as clinically indicated											X		
Urinalysis[15]	X	X				X		X		X	X	X		
Pregnancy test[16]	X	X				X		X		X	X	X	X	
Registration/ Randomization[17]		X												
Premedication[18]		X	X			X		X		X	X			
Avelumab administration: All study Treatment Arms; A, -B and -C[19]			X			X		X		X	X			
Utomilumab administration – Treatment Arms A and B[20]			X					X			X			
Rituximab administration Treatment Arms A and C[21]		X						X			X			
Azacitidine administration Treatment Arm B[22]		X Days 1-5						X Days 1-5			X			
Bendamustine administration Treatment Arm C[23]			X					X	X					
Adverse Events[24]		X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications[25]		X	X	X	X	X	X	X	X	X	X	X	X	
Subsequent anti-cancer treatments[26]													X	X
Survival update[27]														X

Cycle Length: 28 Days Each		Cycle 1						Cycles 2, 3, 4, 5, and 6			Cycles >6	End of Treatment/Follow-Up		
Visit Identifier	**Screen (≤28 days prior to randomization)**	**Day 1**	**Day 2/3**	**Day 7**	**Day 8**	**Day 15/16**	**Day 22**	**Day 1/2**	**Day 2/3**	**Day 15/16**		**End of Treatment/ Withdrawal**	**Follow-Up Visits Days: 30, 60, and 90 after last dose**	**Survival Follow-Up[27]**
Visit window ± days		**±0**	**±0**	**±1**	**±1**	**±1**	**±1**	**±0**	**±0**	**±2**	**±3**	**±7**	**±3**	**±7**
Mandatory provision of FFPE tumor tissue[28]	X													
Optional provision of *de novo* tumor biopsy[29]	X											X		
CCI [redacted]														
CCI [redacted]														
Blood for Avelumab PK[36]			X		X	X		After Cycle 1, blood for avelumab, rituximab, utomilumab, azacitidine, and bendamustine PK will be collected prior to dosing and post dose at 0.5 hour for						
Blood for Rituximab PK[37]		X		X		X	X							
Blood for Utomilumab PK[38]			X			X								
Blood for Azacitidine PK[39]		X Day 1 and Day 5												
Blood for Bendamustine PK[40]			X											
Blood for Avelumab ADA (Immunogenicity) Testing[41]			X									X	30 (±3) days after the end of therapy	

Cycle Length: 28 Days Each		Cycle 1						Cycles 2, 3, 4, 5, and 6			Cycles >6	End of Treatment/Follow-Up		
Visit Identifier	**Screen (≤28 days prior to randomization)**	**Day 1**	**Day 2/3**	**Day 7**	**Day 8**	**Day 15/16**	**Day 22**	**Day 1/2**	**Day 2/3**	**Day 15/16**		**End of Treatment/ Withdrawal**	**Follow-Up Visits Days: 30, 60, and 90 after last dose**	**Survival Follow-Up[27]**
Visit window ± days		**±0**	**±0**	**±1**	**±1**	**±1**	**±1**	**±0**	**±0**	**±2**	**±3**	**±7**	**±3**	**±7**
Blood for Rituximab ADA (Immunogenicity) Testing[42]		X						azacitidine and 1 hour for bendamustine on the first day of Cycles 4 and 6 **and** **ADA (Immunogenicity Testing)** after Cycle 1 will be collected prior to dosing on the first day of Cycles 4 and 6. See footnotes for details.				X	30 (±3) days after the end of therapy	
Blood for Utomilumab ADA (Immunogenicity) Testing[43]			X									X	30 (±3) days after the end of therapy	

Abbreviations: →= ongoing/continuous event; ECG = electrocardiogram; HRQL = health-related quality of life; EC = ethics committee; IRB = institutional review board, [redacted]

1. **Physical Examination (PE):** Includes an examination of major body systems: general appearance, as well as head, eyes, ears, nose, and throat (HEENT), neck, cardiovascular, lungs, abdomen, lymph nodes, genitourinary, extremities, neurological, skin, musculoskeletal, and weight (height at screening only).
2. **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 the 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 the conversation in the patient's medical 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 in the patient's partner.
3. **Baseline Signs and Symptoms**: Patients will be asked about any signs and symptoms experienced within the 14 days prior to randomization.
4. **Eastern Cooperative Oncology Group Performance Status (ECOG PS) performed as part of screening** (ECOG PS 0 or 1) and at time points noted in schedule above and **International Prognostic Index (IPI) Score** (≤2 or ≥3) [assessed at Screening].
5. **Vital Signs:** Temperature, Blood pressure (BP) and heart rate (HR) to be recorded in the seated position after the patient has been sitting quietly for at least 5 minutes on the first day of each treatment cycle.
6. **Staging and Response Assessment: Lugano Classification**: 18F-FDG PET-CT performed ≤6 weeks prior to randomization. Then it should be performed once every 12 weeks (±1 week) from randomization and at EOT (unless performed within the prior 6-weeks). After 12-months from randomization, 18F-FDG PET-CT is performed every 24 weeks (±1 week). If a patient discontinues treatment for reasons other than disease progression, Staging and Response Assessment will be performed until disease progression regardless of initiation of subsequent anti cancer therapy. See Study Manual for more details. All radiographic images must be collected.

7. **Blood Collection for Minimal Residual Disease (MRD) Assessment:** 6 mL whole blood draw for processing into plasma will be collected to align with time-points for tumor staging and response assessment by PET-CT, prior to randomization then once every 12 weeks and at EOT (unless performed ≤6 weeks before EOT). After 12-months from randomization, performed every 24 weeks (±1 week) until PD. See 7.4 and Laboratory Manual for additional details.
8. **12-Lead ECG:** All patients require a single ECG measurement at screening or prior to the first day of the first treatment cycle in the study to confirm eligibility. On-treatment ECGs will be performed pre- and post-infusion/SC dose on the first dosing days (Day 1 and Day 2) of Cycles 1 and 2, for the second dose of avelumab in Cycle 1 (Day 16) and EOT/early withdrawal. At each time point, three (3) consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTcF (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. If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event. If the mean QTcF is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated. Clinically significant findings observed on any 12-lead ECGs should be recorded as adverse events.
9. **ECHO/MUGA for LVEF (**multiple gated acquisition (MUGA) or echocardiogram (ECHO)**:** An ECHO/MUGA must be performed for patients within 60-days of randomization (and as clinically warranted thereafter) and EOT. Same method throughout study for each individual patient, if possible.
10. **Laboratory Tests**: Please refer to Laboratory Manual for detailed instructions and Table 19.
11. **Hematology:** No need to repeat for Cycle 1 Day 1 if Screening assessment performed within 3 days prior to the first day of the first cycle.
12. **Blood Chemistry:** Includes all tests indicated on the Chemistry Panel. No need to repeat for Cycle 1 Day 1 if screening assessment performed within 3 days prior to the first day of the first cycle.
13. **ACTH, FT4, and TSH:** ACTH, Free T4 and TSH will be measured at screening, every 8 weeks from first dose of treatment for 2 additional measurements, and then every 12 weeks thereafter while on treatment, End of Treatment, at the 30-day post-treatment visit, and as clinically indicated.
14. **HBV Serology and HCV Serology**: measured at screening and then every 6 months from first dose of treatment, End of Treatment, and as clinically indicated.
15. **Urinalysis:** Dipstick is acceptable. Microscopic analyses should be performed if dipstick abnormal. No need to repeat on for Cycle 1 Day 1 if Screening assessment performed within 3 days prior to the first day of the first cycle.
16. **Pregnancy Test (serum/urine):** For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on two occasions prior to starting study therapy, once at the start of screening and once at the baseline visit immediately before investigational product administration. Urine pregnancy tests with sensitivity of at least 25 mIU/mL will also be routinely repeated at every treatment cycle during the active treatment period, at the end of study therapy, at 30, 60, and 90 days during safety follow up period, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Urine test kits with sensitivity of at least 25 mIU/mL may be utilized at every treatment cycle during the study in accordance with instructions provided in its package insert. Patients of childbearing potential who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative qualitative serum pregnancy test conducted at a certified laboratory). Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.

17. **Randomization:** Allocation of patients to treatment groups will proceed through the use of an Interactive Response Technology (IRT) System. Study treatment must start within 7 days after patient randomization.
18. **Premedications:** In regimen with: **avelumab 5.4.1**; **utomilumab 5.4.2**; **rituximab 5.4.3**; **azacitidine 5.4.4**; **bendamustine 5.4.5**; **gemcitabine 5.4.6**; **oxaliplatin 5.4.7**. See Sections 3.1.1 and 3.1.3 for details regarding sequencing of treatment.
19. **Avelumab Administration, please refer to Sections 3.1.1 and 5.4.1.**
20. **Utomilumab Administration please refer to Sections 3.1.1 and 5.4.2.**
21. **Rituximab Administration please refer to Sections 3.1.1 and 5.4.3.**
22. **Azacitidine Administration please refer to Sections 3.1.1 and 5.4.4.**
23. **Bendamustine Administration please refer to Sections 3.1.1 and 5.4.5.**
24. **Adverse Events:** The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the patient provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), during each patient clinic visit, through and including a minimum of 90 days after the last administration of the investigational product. For patients who are screen failures, the active collection period ends when screen failure status is determined. If a patient begins a new anti-cancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.
25. **Concomitant Medications:** Concomitant medications and treatments including herbal supplements will be recorded from 28 days prior to the start of study treatment, during each patient clinic visit, and up to 90 days after the last dose of study treatment (at Days 30, 60, and 90 post-treatment ±3 days). 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).
26. **Subsequent Anti-Cancer Treatments:** To be collected.
27. **Survival Update:** After discontinuation of study treatment, post-study survival status will be collected every 2 months until death or withdrawal of consent for survival follow-up. This includes the collection of information on subsequent anti-cancer therapies. Telephone communication is acceptable.
28. **Mandatory provision of FFPE Tumor Tissue:** A biopsy (archived or Screening) will be collected at Screening. Archival samples can be provided as an FFPE block containing tumor tissue or as a minimum of 15 (preferably 25) unstained FFPE tumor slides suitable for PD-L1 expression and other tissue/molecular profiling assessments (blocks are preferable, see Section 7.4 and Laboratory Manual for details). Note that a *de novo* tumor biopsy must be obtained at Screening if an archival sample is not available (see #32 below).
29. **Optional Provision of *de novo* Tumor Biopsy:** An optional baseline *de novo* (ie, fresh) biopsy of an accessible tumor lesion may be obtained during screening and/or at EOT (note that a *de novo* tumor biopsy must be obtained at Screening if an archival specimen is not available to satisfy the requirement for the mandatory FFPE tumor tissue). The *de novo* biopsy or biopsies should be processed as FFPE (see Central Lab Manual), and the resulting FFPE tissue block(s) [one per time point] should be submitted to the Central Laboratory.

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36. **Blood for Avelumab PK: (All Phase 1b Treatment Arms A, B and C):** 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 (at the end of infusion) following the first dose on the Day 2 of Cycle 1, and additional samples will be collected on Day 8 and 16 of Cycle 1. Pre-dose samples will also be collected on Day 1 of Cycles 4 and 6.
37. **Blood for Rituximab PK: (Treatment Arms A and C):** Blood samples (4 mL whole blood at each time point) will be collected from all patients at pre-dose and at the end of infusion on Cycle 1, and then on Days 7, 15 and 22 of Cycle 1. Pre-dose samples will also be collected on Day 1 of Cycles 4 and 6.
38. **Blood for Utomilumab PK (Treatment Arm A and Arm B):** Blood samples (4.0 mL whole blood at each time point) will be collected from all patients at pre-dose, and 1 hour (at the end of infusion) following the first dose on Day 2 of the first cycle in the study, and then on Day 16 of Cycle 1. Pre-dose samples will also be collected on Day 1 of Cycles 4 and 6.
39. **Blood for Azacitidine PK (Treatment Arm B):** Blood samples (2 mL whole blood at each time point) will be collected from all patients in the study at pre-dose, 0.5, 1, 2, and 4 hours on Day 1 and 5 of Cycle 1. Samples pre-dose and at 0.5 hour will also be collected on Day 1 of Cycles 4 and 6.
40. **Blood for Bendamustine (and M3 metabolite) PK (Treatment Arm C):** Blood samples (2 mL whole blood at each time point) will be collected from all patients at pre-dose and at 1 hour (at the end of infusion), 2, and 4 hours following the first dose in the first cycle. Samples at pre-dose and 1 hour will also be collected following the first dose of Cycles 4 and 6.
41. **Blood for Avelumab ADA (Immunogenicity) Testing (All Treatment Arms):** All samples (3.5 mL) should be drawn within 2 hours prior to the start of dosing. Blood samples (3.5 mL whole blood at each time point) for avelumab immunogenicity testing will be collected pre-dose on Day 2 of Cycle 1 and pre-dose on Day 1 of Cycles 4 and 6. Additional samples for ADAs will be collected at 30 (±3) days after the end of therapy. A sample for ADA analysis will be drawn at the time of early withdrawal.
42. **Blood for Rituximab ADA (Immunogenicity) Testing (Treatment Arms A and C):** All samples (4.0 mL) should be drawn within 2 hours prior to the start of dosing. Blood samples (3.5 mL whole blood at each time point) for rituximab immunogenicity testing will be collected pre-dose on Day 1 of Cycle 1 and pre-dose on Day 1 of Cycles 4 and 6. Additional samples for ADAs will be collected at 30 (±3) days after the end of therapy. A sample for ADA analysis will be drawn at the time of early withdrawal.
43. **Blood for Utomilumab ADA (Immunogenicity) Testing (Treatment Arm A and Arm B):** All samples (4.0 mL) should be drawn within 2 hours before the start of treatment. Blood samples (3.5 mL whole blood at each time point) for utomilumab immunogenicity testing will be collected pre-dose on Day 2 of Cycle 1 and pre-dose on Day 1 of Cycles 4 and 6. Additional samples for ADAs will be collected at 30 (±3) days after the end of therapy. A sample for ADA analysis will be drawn at the time of early withdrawal.

Table 2. Phase 3 Schedule of Activities

		Cycle 1				Cycles 2, 3, 4, 5, and 6				Cycles >6	End of Treatment/Follow-Up		
Visit Identifier	**Screen (≤28 days prior to randomization)**	**Day 1**	**Day 2**	**Day 15**	**Day 17**	**Day 1**	**Day 2**	**Day 15**	**Day 17**		**End of Treatment/ Withdrawal**	**Follow-Up Visits Days: 30, 60, and 90 after last dose**	**Survival Follow-Up[27]**
Visit window ± days		±0	±0	±2	±2	±0	±0	±2	±2	±3	±7	±3	±7
Written informed consent	X												
Medical oncology history (including prior treatment regimens)	X												
General medical history	X												
Full physical examination (PE)[1]		**Full PE** during Screening and first day of Cycles 3, 6, 9, 12, every 3 cycles thereafter, and at EOT[1]											
Contraception check[2]		X				X				X	X	X	
Baseline signs and symptoms[3]		X											
ECOG PS and IPI Score[4]	X					X				X	X		
Weight		X		X		X			X	X	X		
Vital signs[5]		X				X				X	X		
Disease staging and response assessment (Lugano Classification)[6]	**18F-FDG PET-CT**: Performed ≤6 weeks prior to randomization, then every 12 weeks (±1 week) from randomization, and at EOT (unless performed ≤6 weeks before EOT). After 12-months from randomization, 18F-FDG PET-CT is performed every 24 weeks (±1 week) until PD											X	X
Blood collection for MRD assessment[7]	MRD assessment to align with time-points for tumor staging and response assessment by PET-CT prior to randomization then once every 12 weeks and at EOT (unless performed ≤6 weeks before EOT). After 12 months from randomization, performed every 24 weeks (±1 week) until PD												
12-Lead ECG[8]	ECGs will be performed in singlicate during screening or prior to the first day of study treatment, and in triplicate during the study, pre- and post-infusion/SC dose on the first dosing days (Day 1 and Day 2) of Cycles 1 and 2 on the second avelumab dose of Cycle 1 (Day 16) at EOT/early withdrawal and as clinically indicated												
LVEF (by MUGA or ECHO) (time window ±5 days)[9]	X										X		
Laboratory tests[10]	X	X		X		X			X	X	X		
Hematology[11]	X	X		X		X			X	X	X		
Blood Chemistry[12]	X	X		X		X			X	X	X		
Coagulation		X		X		X			X	X	X		

		Cycle 1				Cycles 2, 3, 4, 5, and 6				Cycles >6	End of Treatment/Follow-Up		
Visit Identifier	**Screen (≤28 days prior to randomization)**	**Day 1**	**Day 2**	**Day 15**	**Day 17**	**Day 1**	**Day 2**	**Day 15**	**Day 17**		**End of Treatment/ Withdrawal**	**Follow-Up Visits Days: 30, 60, and 90 after last dose**	**Survival Follow-Up[27]**
Visit window ± days		**±0**	**±0**	**±2**	**±2**	**±0**	**±0**	**±2**	**±2**	**±3**	**±7**	**±3**	**±7**
ACTH, FT4, and TSH[13]	Measured prior to study enrollment, every 8 weeks from first dose of treatment for 2 additional measurements, and then every 12 weeks thereafter while on treatment										X	X	
HBV, HCV[14]	Measured prior to study enrollment and then every 6 months from first dose of treatment and as clinically indicated										X		
Urinalysis[15]	X	X		X		X			X	X	X		
Pregnancy test[16]	X	X				X				X	X	X	
Randomization[17]		X											
Premedication[18]		X	X	X		X			X	X			
Treatment Arm D: Selected Regimen from Phase 1b Advancing to Phase 3[19]		Follow Schedule for Selected Regimen from Phase 1b.											
Treatment Arm E Investigator's Choice Rituximab of the R/Benda and R/GemOx Investigator's Choice Option[20]		X				X				X			
Treatment Arm E Investigator's Choice Bendamustine of the R/Benda Investigator's Choice Option[21]		X	X			X	X						
Treatment Arm E Investigator's Choice Gemcitabine of the R/Gem/Ox Investigator's Choice Option[22]			X		X		X		X				
Treatment Arm E Investigator's Choice Oxaliplatin of the R/Gem/Ox Investigator's Choice Option[23]			X		X		X		X				

		Cycle 1				Cycles 2, 3, 4, 5, and 6				Cycles >6	End of Treatment/Follow-Up		
Visit Identifier	**Screen (≤28 days prior to randomization)**	**Day 1**	**Day 2**	**Day 15**	**Day 17**	**Day 1**	**Day 2**	**Day 15**	**Day 17**		**End of Treatment/ Withdrawal**	**Follow-Up Visits Days: 30, 60, and 90 after last dose**	**Survival Follow-Up[27]**
Visit window ± days		**±0**	**±0**	**±2**	**±2**	**±0**	**±0**	**±2**	**±2**	**±3**	**±7**	**±3**	**±7**
Adverse Events[24]		X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication[25]		X	X	X	X	X	X	X	X	X	X	X	
Subsequent anti-cancer treatments[26]												X	X
Survival update[27]													X
Mandatory provision of FFPE Tumor Tissue[27]	X												
Optional provision of *de novo* tumor biopsy[29]	X										X		
CCI [redacted]													
Blood for Avelumab PK[36]			X	X Days 8 and 16		After Cycle 1, blood for avelumab PK will be collected prior to dosing on the first day of Cycles 4 and 6.							

		Cycle 1				Cycles 2, 3, 4, 5, and 6				Cycles >6	End of Treatment/Follow-Up		
Visit Identifier	**Screen (≤28 days prior to randomization)**	**Day 1**	**Day 2**	**Day 15**	**Day 17**	**Day 1**	**Day 2**	**Day 15**	**Day 17**		**End of Treatment/ Withdrawal**	**Follow-Up Visits Days: 30, 60, and 90 after last dose**	**Survival Follow-Up[27]**
Visit window ± days		**±0**	**±0**	**±2**	**±2**	**±0**	**±0**	**±2**	**±2**	**±3**	**±7**	**±3**	**±7**
Blood for Rituximab PK[37]		X		X Days 7 15 and 22		After Cycle 1, blood for rituximab PK will be collected prior to dosing on the first day of Cycles 4 and 6.							
Blood for Utomilumab PK[38]			X	X Day 16		After Cycle 1, blood for utomilumab PK will be collected prior to dosing on the first day of Cycles 4 and 6							
Blood for Azacitidine PK[39]		X Days 1 and 5				After Cycle 1, blood for azacitidine PK will be collected prior to dosing and at 0.5 hr on the first day of Cycles 4 and 6.							
Blood for Bendamustine PK[40]		X				After Cycle 1, blood for bendamustine PK will be collected prior to dosing and at 1 hr on the first day of Cycles 4 and 6.							
Blood for Avelumab ADA (Immunogenicity) Testing[41]			X			After Cycle 1, blood for ADA (immunogenicity testing) will be collected prior to dosing on the first day of Cycles 4 and 6. See footnotes for details.					X	30 (±3) days after the end of therapy	
Blood for Rituximab ADA (Immunogenicity) Testing[42]		X									X	30 (±3) days after the end of therapy	
Blood for Utomilumab ADA (Immunogenicity) Testing[43]			X								X	30 (±3) days after the end of therapy	
Patient Reported Outcomes: BFI, and EQ-5D-5L)		X[44]	ePRO device will be used to administer the questionnaires every 7 days[44]									X[44]	

		Cycle 1				Cycles 2, 3, 4, 5, and 6				Cycles >6	End of Treatment/Follow-Up		
Visit Identifier	**Screen (≤28 days prior to randomization)**	**Day 1**	**Day 2**	**Day 15**	**Day 17**	**Day 1**	**Day 2**	**Day 15**	**Day 17**		**End of Treatment/ Withdrawal**	**Follow-Up Visits Days: 30, 60, and 90 after last dose**	**Survival Follow-Up[27]**
Visit window ± days		**±0**	**±0**	**±2**	**±2**	**±0**	**±0**	**±2**	**±2**	**±3**	**±7**	**±3**	**±7**
Patient Reported Outcomes: NCCN-FACT FLymSI-18		X[45]	ePRO device will be used to administer the questionnaires every 28 days[45]									X[45]	
CCI [redacted]													

Abbreviations: →= ongoing/continuous event; ECG = electrocardiogram; CCI [redacted]; EC = ethics committee; IRB = institutional review board, BFI = Brief Fatigue Inventory.

1. **Physical Examination (PE):** Includes an examination of major body systems: general appearance, as well as head, eyes, ears, nose, and throat (HEENT), neck, cardiovascular, lungs, abdomen, lymph nodes, genitourinary, extremities, neurological, skin, musculoskeletal, and weight (height at screening only).
2. **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 the 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 the conversation in the patient's medical 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 in the patient's partner.
3. **Baseline Signs and Symptoms**: Patients will be asked about any signs and symptoms experienced within the 14 days prior to randomization.
4. **Eastern Cooperative Oncology Group Performance Status (ECOG PS) at screening** (ECOG PS 0 or 1) and time points noted in schedule above and **International Prognostic Index (IPI)** Score (≤2 or ≥3) assessed at Screening.
5. **Vital Signs:** Temperature, Blood pressure (BP) and heart rate (HR) to be recorded in the seated position after the patient has been sitting quietly for at least 5 minutes on the first day of each treatment cycle.
6. **Staging and Response Assessment:** 18F-FDG PET-CT performed ≤6 weeks prior to randomization, once every 12 weeks (±1 week) from randomization and at EOT (unless performed within the prior 4 weeks). After 12 months from randomization, 18F-FDG PET-CT is performed every 24 weeks (±1 week). If a patient discontinues treatment for reasons other than disease progression, Staging and Response Assessment will be performed until disease progression regardless of initiation of subsequent anti cancer therapy. See Study Manual for details. All radiographic images must be collected.
7. **Blood Collection for Minimal Residual Disease (MRD) Assessment:** 6 mL whole blood draw for processing into plasma will be collected to align with time-points for tumor staging and response assessment by PET-CT prior to randomization then once every 12 weeks and at EOT (unless performed ≤6 weeks before EOT). After 12-months from randomization, performed every 24 weeks (±1 week) until PD. See 7.4 and Laboratory Manual for additional details.

8. **12-Lead ECG:** All patients require a single ECG measurement at screening or prior to the first day of the first treatment cycle in the study to confirm eligibility. On treatment ECGs will be performed pre- and post-infusion/SC dose on the first dosing days (Day 1 and 2) of Cycles 1 and 2 for the second dose of avelumab in Cycle 1 (Day 16) and EOT/early withdrawal. At each time point, three (3) consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTcF (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. If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke) triplicate ECGs should be obtained at time of the event. If the mean QTcF is prolonged (>500 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated. Clinically significant findings observed on any 12-lead ECGs should be recorded as adverse events.
9. **ECHO/MUGA for LVEF (**multiple gated acquisition (MUGA) or echocardiogram (ECHO)**:** An ECHO/MUGA must be performed for patients within 60-days of the first dose at Cycle 1 (and as clinically warranted) and EOT. Same methold throughout study for each individual patient, if possible.
10. **Laboratory Tests**: Please refer to Laboratory Manual for detailed instructions and Table 19.
11. **Hematology:** No need to repeat for Cycle 1 if screening assessment performed within 3 days prior to that date.
12. **Blood Chemistry:** Includes all tests indicated on the Chemistry Panel. No need to repeat for Cycle 1 if screening assessment performed within 3 days prior to that date.
13. **ACTH, FT4, and TSH:** ACTH, Free T4 and TSH will be measured prior to study enrollment, every 8 weeks from first dose of treatment for 2 additional measurements, then every 12 weeks thereafter while on treatment, End of Treatment, at the 30-day post-treatment visits, and as clinically indicated.
14. **HBV Serology and HCV Serology**: measured prior to study enrollment and then every 6 months from first dose of treatment, End of Treatment, and as clinically indicated.
15. **Urinalysis:** Dipstick is acceptable. Microscopic analyses should be performed if dipstick abnormal. No need to repeat prior to Cycle 1 if screening assessment performed within 3 days prior to Cycle 1.
16. **Pregnancy Test (serum/urine):** For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on two occasions prior to starting study therapy, once at the start of screening and once at the baseline visit immediately before investigational product administration. Urine pregnancy tests with sensitivity of at least 25 mIU/mL will also be routinely repeated at every treatment cycle during the active treatment period, at the end of study therapy, at 30, 60 and 90 days during safety follow up period, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Urine test kits with sensitivity of at least 25 mIU/mL may be utilized at every treatment cycle during the study in accordance with instructions provided in its package insert. Patients of childbearing potential who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative qualitative serum pregnancy test conducted at a certified laboratory). Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations.
17. **Randomization:** Allocation of patients to treatment groups will proceed through the use of an Interactive Response Technology (IRT) System. Study treatment must start within 7 days after patient randomization.
18. **Premedications:** In regimen with: **avelumab** 5.4.1; **utomilumab** 5.4.2; **rituximab** 5.4.3; **azacitidine** 5.4.4; **bendamustine** 5.4.5; **gemcitabine** 5.4.6; **oxaliplatin** 5.4.7.
19. **Selected Regimen from Phase 1b Treatment Arm D**: Refer to Table 1 for dose/administration schedule of selected regimen advancing to Phase 3.

20. **Rituximab Administration**, **Investigator's Choice Option Treatment Arm E:** Dosed at 375 mg/m^2 every 28 days on Day 1. Patients may continue treatment with rituximab for up to 8 cycles maximum.
21. **Bendamustine Administration, Investigator's Choice Option Arm E:** dosed 120 mg/m^2 Days 1 and 2 every 28 days for up to 6 cycles maximum. Refer to Sections 3.1.3 and 5.4.5.
22. **Investigators Choice Option Treatment Arm E Gemcitabine:** Dosed at 1000 mg/m^2 Day 2 and -17 every 28 days. Up to 6 cycles maximum. Refer to Sections 3.1.3 and 5.4.6.
23. **Investigators Choice Option Treatment Arm E Oxaliplatin**: Dosed at 100 mg/m^2 Day 2 and -17 every 28 days. Up to 6 cycles maximum. Refer to Sections 3.1.3 and 5.4.7.
24. **Adverse Events:** The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the patient provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), during each patient clinic visit, and including a minimum of 90 days after the last administration of the investigational product. For patients who are screen failures, the active collection period ends when screen failure status is determined. If a patient begins a new anti-cancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.
25. **Concomitant Medications:** Concomitant medications and treatments including herbal supplements will be recorded from 28 days prior to the start of study treatment, during each patient clinic visit, and up to 90 days after the last dose of study treatment (at Days 30, 60, and 90 post-treatment ±3 days). 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).
26. **Subsequent anti-cancer treatments:** To be collected.
27. **Survival Update:** After discontinuation of study treatment, post study survival status will be collected every 2 months until death or withdrawal of consent for survival follow-up. This includes the collection of information on subsequent anti-cancer therapies. Telephone communication is acceptable.
28. **Mandatory Provision of FFPE Tumor Tissue:** A biopsy (archived or Screening) will be collected at Screening. Archival samples can be provided as an FFPE block containing tumor tissue or as a minimum of 15 (preferably 25) unstained FFPE tumor slides suitable for PD-L1 expression and other tissue/molecular profiling assessments (blocks are preferable; see Section 7.4 and Laboratory Manual for details). Note that a *de novo* tumor biopsy must be obtained Screening if an archival sample is not available (see #30 below).
29. **Optional Provision of *De Novo* Tumor Biopsy:** An optional baseline *de novo* (ie, fresh) biopsy of an accessible tumor lesion may be obtained during screening and/or at EOT (note that a *de novo* tumor biopsy must be obtained at Screening if an archival specimen is not available to satisfy the requirement for the mandatory FFPE tumor tissue. The *de novo* biopsy or biopsies should be processed as FFPE (see Central Laboratory Manual), and the resulting FFPE tissue block(s) [one per time point] should be submitted to the Central Laboratory.

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36. **Blood for Avelumab PK: (Treatment Arm D only):** Blood samples (3.5 mL whole blood at each time point) will be collected from all patients at pre-dose and 1 hour (at the end of infusion) following the first dose on Day 2 of Cycle 1, and an additional sample will be collected on Day 8 and 16 of Cycle 1. Pre-dose samples will also be collected on Day 1 of Cycles 4 and 6.
37. **Blood for Rituximab PK (Treatment Arm D only):** Blood samples (4 mL whole blood at each time point) will be collected from all patients at pre-dose and at the end of infusion on Cycle 1, and then on Days 7, 15 and 22 of Cycle 1. Pre-dose samples will also be collected on Day 1 of Cycles 4 and 6.
38. **Blood for Utomilumab Pharmacokinetics:** Blood samples (4 mL whole blood at each time point) will be collected from all patients at pre-dose, and 1 hour (at the end of infusion) following the first dose on Day 2 of Cycle 1 in the study, and then on Day 16 of Cycle 1. Pre-dose samples will also be collected on Day 1 of Cycles 4 and 6.
39. **Blood for Azacitidine Pharmacokinetics:** Blood samples (2 mL whole blood at each time point) will be collected from all patients at pre-dose, 0.5, 1, 2, 4 hours on Day 1 and 5 of Cycle 1. Samples pre-dose and at 0.5 hour will also be collected on Day 1 of Cycles 4 and 6.
40. **Blood for Bendamustine (and M3 metabolite) Pharmacokinetics (Treatment Arm D only):** Blood samples (2 mL whole blood at each time point) will be collected from all patients at pre-dose and 1 hour (at the end of infusion),2, and 4 hours following the first dose in the first cycle. Samples at pre-dose and 1 hour will also be collected following the first dose of Cycles 4 and 6.
41. **Blood for Avelumab ADA (Immunogenicity) Testing:** All samples (3.5 mL) should be drawn within 2 hours prior to the start of dosing. Blood samples (3.5 mL whole blood at each time point) for avelumab immunogenicity testing will be collected pre-dose on Day 2 of Cycle 1 and pre-dose on Day 1 of Cycles 4 and 6. Additional samples for ADAs will be collected at 30 (±3) days after the end of therapy in Treatment Arm D only. A sample for ADA analysis will be drawn at the time of early withdrawal.
42. **Blood for Rituximab ADA (Immunogenicity) Testing (Treatment Arm D only):** All samples (4 mL) should be drawn within 2 hours prior to the start of dosing. Blood samples (3.5 mL whole blood at each time point) for rituximab immunogenicity testing will be collected pre-dose on the first day of Cycle 1 and pre-dose on Day 1 of Cycles 4 and 6. Additional samples for ADAs will be collected at 30 (±3) days after EOT only if Treatment Arm D contains rituximab. A sample for ADA analysis will be drawn at the time of early withdrawal.
43. **Blood for Utomilumab ADA (Immunogenicity) Testing:** All samples (4 mL) should be drawn within 2 hours before the start of treatment. Blood samples (3.5 mL whole blood at each time point) for utomilumab immunogenicity testing will be collected pre-dose on Day 2 of Cycle 1 and pre-dose on Day 1 of Cycles 4 and 6. Additional samples for ADAs will be collected at 30 (±3) days after the end of therapy only if Treatment Arm D contains utomilumab. A sample for ADA analysis will be drawn at the time of early withdrawal.
44. **Patient Reported Outcomes (PRO)**: The Brief Fatigue Inventory (BFI) and EQ-5D-5L questionnaires will be administered. An electronic PRO (ePRO) device will be given to each patient for first day of the first cycle. The ePRO device will prompt the patient to complete the questionnaires on the first day of the first visit. After completing the questionnaires on the first day of the first visit, the device will prompt the patient to complete the questionnaires every 7 days. If a patient does not complete the questionnaires on the day the patient is prompted, the device will prompt the patient to complete the questionnaires each subsequent day of the week until the questionnaires are completed. At the 90-day follow-up visit the device will be collected from the patient.

45. **Patient Reported Outcomes (PRO):** The NCCN-FACT FLymSI-18 questionnaire will be administered. An electronic PRO (ePRO) device will be given to each patient for first day of the first cycle. The ePRO device will prompt the patient to complete the questionnaire on the first day of the first visit. After completing the questionnaire on the first day of the first visit, the device will prompt the patient to complete the questionnaire every 28 days. If a patient does not complete the questionnaire on the day the patient is prompted, the device will prompt the patient to complete the questionnaire each subsequent day of the week until the questionnaire is completed. At the 90-day follow-up visit the device will be collected from the patient.

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1. INTRODUCTION

Study B9991011 is a multi-center, international, randomized, open-label, 2-component (Phase 1b followed by Phase 3), parallel-arm study of avelumab in various combinations for the treatment of Relapsed or Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL). Agents that will be tested in combination with avelumab include:

(i) Utomilumab, a novel, fully human, IgG2 monoclonal antibody agonist of 4-1BB,

(ii) Azacitidine, a DNA methyltransferase inhibitor (DNMTi), which has been shown to have the potential to prime immune activity through various mechanisms that include: (a) the induction of Programmed Death 1 (PD-1) on tumor infiltrating lymphocytes (TILs) and (b) PD-L1 on tumor cells, (c) the induction of tumor neoantigen expression, and (d) the inhibition of myeloid derived suppressor cells (MDSCs),

(iii) Rituximab, a CD20 antagonist antibody,

(iv) Bendamustine, an alkylating chemotherapy agent, which is one of the National Comprehensive Cancer Network[1] recommended agents for the salvage therapy of patients with DLBCL who are ineligible for high-dose chemotherapy and autologous stem cell transplant (ASCT).

The treatment regimens tested in the study include avelumab in combination with:

(i) Rituximab and utomilumab,

(ii) Azacitidine and utomilumab,

(iii) Rituximab and bendamustine.

Based on the safety and efficacy observed in the Phase 1b component of the study, a single avelumab-based combination regimen will potentially be selected to be further investigated in the randomized Phase 3 component of the study. In the Phase 3 component, patients will be randomized (1:1) to the avelumab-based treatment regimen selected in the Phase 1b component or to Investigator's Choice treatment to determine whether the selected treatment regimen is superior to the Investigator's Choice treatment in prolonging progression-free survival (PFS).

The target study population of this Phase 1b/3 registrational study is patients with R/R DLBCL who have completed at least 2 (but not more than 4) lines of prior rituximab-containing multi-agent chemotherapy, and/or in whom ASCT has failed, or who are not candidates for ASCT or who are not eligible for intensive chemotherapy. The study will assess the safety, efficacy, pharmacokinetics (PK), immunogenicity of the 3 avelumab-based combination regimens tested, and collect patient reported outcome (PRO) data.

The primary objective of the Phase 1b component of the study will be to make a preliminary assessment of safety and efficacy for each combination regimen. In order to help select a treatment regimen suitable for testing in the Phase 3 component of the study, each treatment arm without a safety signal in the first 6 and/or 12 patients tested will be expanded to a total of 28 patients per arm. The decision to advance a specific treatment arm into the Phase 3 part will be based upon a hierarchical assessment of (a) the investigator-observed objective response rate (ORR), (b) the 6 month durable response rate (DRR) and (c) the PFS rate at 6 months. The overall safety profile of each combination regimen will also be taken into consideration. The treatment combination regimens that will be assessed in the Phase 1b component of the study include:

Arm A: Avelumab/Utomilumab/Rituximab

(i) Rituximab 375 mg/m^2 (IV) will be administered on the morning of Day 1 of each 28-day cycle for a maximum of 8 cycles.

(ii) Utomilumab 100 mg fixed dose (IV) will be administered on the morning of Day 2 of each 28-day cycle in Cycles 1 and 2 (or if well-tolerated in Cycles 1 and 2, then again on Day 1 in Cycle 3 and in all subsequent cycles) until the patient no longer receives clinical benefit.

Utomilumab must have completed administration at least 1 hour prior to avelumab in Cycles 1 and 2. If well-tolerated in Cycles 1 and 2, then in Cycle 3 and in all subsequent cycles, the time window of dose administration between utomilumab and avelumab may be decreased from ≥1 hour to 30-60 minutes apart.

(iii) Avelumab 10 mg/kg (IV) will be administered every 2 weeks on Day 2 and Day 16 of each 28-day cycle in Cycle 1 and Cycle 2 (or if well tolerated in Cycle 1 and Cycle 2, on Day 1 and Day 15 in Cycle 3 and in all subsequent cycles) until the patient no longer receives clinical benefit.

Avelumab must be administered at least 1 hour after the end of the utomilumab infusion in Cycle 1 and Cycle 2. If well-tolerated in Cycle 1 and Cycle 2, then in all subsequent cycles, the time window of dose administration between avelumab and utomilumab may be decreased from ≥1 hour to 30-60 minutes apart.

Arm B: Avelumab/Utomilumab/Azacitidine

(i) Azacitidine 40 mg/m^2 (SC) will be administered in the morning on Days 1 - 5 of each 28-day cycle, until the patient is no longer achieving clinical benefit.

Azacitidine must have completed administration at least 1 hour prior to utomilumab when dosed on the same day.

(ii) Utomilumab 100 mg fixed dose (IV) will be administered on the morning of Day 2 of each 28-day cycle in Cycles 1 and 2 (or if well-tolerated in Cycles 1 and 2, then again on Day 1 in Cycle 3 and in all subsequent cycles) until the patient no longer receives clinical benefit.

Utomilumab must have completed administration at least 1 hour prior to avelumab in Cycle 1 and Cycle 2. If well-tolerated in Cycle 1 and Cycle 2, then in Cycle 3 and in all subsequent cycles, the time window of dose administration between utomilumab and avelumab may be decreased from ≥1 hour to 30-60 minutes apart.

(iii) Avelumab 10 mg/kg (IV) will be administered every 2 weeks on Day 2 and Day 16 of each 28-day cycle in Cycle 1 and Cycle 2 (or if well tolerated in Cycle 1 and 2, then on Day 1 and Day 15 in Cycle 3 and in all subsequent cycles) until the patient no longer receives clinical benefit.

Avelumab must be administered at least 1 hour after the end of utomilumab infusion in Cycle 1 and Cycle 2. If well-tolerated in Cycle 1 and Cycle 2, then in all subsequent cycles, the time window of dose administration between utomilumab and avelumab may be decreased from ≥1 hour to 30-60 minutes apart.

Arm C: Avelumab/Bendamustine/Rituximab

(i) Rituximab 375 mg/m^2 (IV) will be administered on the morning of Day 1 of each 28-day cycle for a maximum of 8 cycles.

(ii) Bendamustine 90 mg/m^2 (IV) will be administered on Days 2 and 3 of each 28-day cycle in Cycle 1 and Cycle 2. If bendamustine is well-tolerated in Cycle 1 and 2, then bendamustine may be administered on Day 1 and Day 2 in Cycle 3 (and all subsequent cycles). Bendamustine is administered for a maximum of 6 cycles.

(iii) Avelumab 10 mg/kg (IV) will be administered every 2 weeks on Day 2 and Day 16 of each 28-day cycle in Cycle 1 and Cycle 2 (or if well tolerated in Cycle 1 and 2, then on Day 1 and Day 15 in Cycle 3 and in all subsequent cycles) until the patient no longer receives clinical benefit. Avelumab administration should be at least 1 hour after the end of the bendamustine infusion.

Continued Treatment with Avelumab and/or Utomilumab

Per Investigator clinical judgment and following discussion between the Investigator and the Sponsor, if a patient with documented progressive disease (PD) continues to receive clinical benefit, treatment with avelumab and/or utomilumab may be continued. The Investigator's judgment must be based on the overall benefit-risk assessment, and on the patient's clinical condition, including performance status (PS), clinical symptoms, adverse events (AEs), and laboratory data. Other agents in the regimen combination with avelumab and/or utomilumab may also be considered for continuation if in the Investigator's clinical judgment the patient may achieve clinical benefit. See Section 5.4 for treatment duration limits for agents other than avelumab and utomilumab.

1.1. Indication

Patients with R/R DLBCL who have completed at least 2 (but not more than 4) lines of prior rituximab-containing multi-agent chemotherapy, and/or in whom autologous SCT (ASCT) has failed or who are not candidates for ASCT, or who are not eligible for intensive chemotherapy.

1.2. Mechanism of Action

The investigational product common to each treatment arm in the Phase 1b is avelumab (MSB0010718C), a fully-human monoclonal antibody of the immunoglobulin (Ig) G1 isotype directed against the PD-L1 cell surface antigen that is expressed by tumor cells, as well as by various immune cells. MSB0010718C has a calculated molecular weight of 143,832 Daltons.

PD-L1 (B7-H1 or CD274) and its receptor, PD-1, have an established role in the suppression of T cell responses. The PD-1 receptor is expressed on activated $CD4^+$ and $CD8^+$ T cells. Through interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals that inhibit T cell function.[2,3,4]

Avelumab selectively binds PD- L1 and competitively blocks its interaction with PD-1. As compared with anti PD-1 antibodies that target T cells, avelumab targets tumor cells and therefore is expected to have potentially 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.[5] For additional details on the relevant in vitro and nonclinical studies, see the avelumab Investigator's Brochure.[6]

1.3. Background and Rationale

1.3.1. Diffuse Large B-Cell Lymphoma

Diffuse Large B-Cell Lymphoma (DLBCL) is a heterogeneous disease with subtypes distinguished by various clinical, pathologic, and molecular characteristics.[7]

It is the most common type of lymphoma, accounting for 30-40% of all newly diagnosed cases of non-Hodgkin Lymphoma (NHL), and more than 80% of all aggressive lymphomas. The median age at the time of diagnosis is ~70 years.[8,9,10]

The World Health Organization (WHO) classification of lymphoid malignancies acknowledges the heterogeneity of DLBCL by recognizing a broad category termed 'DLBCL not otherwise specified' (DLBCL-NOS) as well as a variety of DLBCL subtypes.[11]

Within the DLBCL-NOS category, gene expression profiling studies have identified two principal molecular subtypes: (i) germinal center B-cell (GCB) and (ii) activated B-cell (ABC). These subtypes represent lymphomas arising from different stages of lymphoid differentiation. The GCB subtype arises from centroblasts and expresses genes usually active in germinal center B cells, whereas the ABC subtype arises from B-cells at a plasmatic stage, just prior to germinal center exit, and expresses genes frequently expressed in mature plasma cells. This molecular distinction has prognostic implications in treatment-naïve

DLBCL patients, with the GCB subtype being associated with a more favorable prognosis.[8] The prognostic significance of the cell of origin beyond first line has not, however, been established. A significant advance in recent years has been the better understanding of MYC alterations. MYC is rearranged in 5% to 15% of DLBCL-NOS (Diffuse Large B-cell Lymphoma, not otherwise specified), and is frequently associated with BCL2 or, to a lesser extent, BCL6 translocation, in the so-called "double-hit" or "triple-hit" lymphomas that are included in the updated 2016 WHO classification in the new category of high-grade B-cell lymphoma (HGBCL), with rearrangements of MYC and BCL2 and/or BCL6.[11]

Approximately 75% of patients with DLBCL present with advanced stage disease. The established frontline standard of care (SOC) is R-CHOP comprised of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (5-year OS 58%). The majority (~60%) of patients with DLBCL may be cured with this regimen, but patients who have treatment failure with R-CHOP have a very poor outcome. Ten to fifteen percent of patients have primary refractory disease (no response, or relapse within 3 months of therapy), and an additional 20-25% relapse following an initial response to therapy. Most relapses occur within the first 2 years following treatment.[7,8]

Patients who are refractory to induction therapy or who relapse after achieving a complete response may be considered for salvage chemotherapy. If their disease is chemosensitive, they may be considered for high-dose chemotherapy followed by autologous stem cell transplant (ASCT).[7]

High-dose chemotherapy and ASCT have been shown to provide the best chance of cure for patients with chemotherapy-sensitive relapse. However, due to advanced age and comorbidities, only approximately half of all patients are eligible for this intensive treatment approach, and, of the transplant-eligible patients, only half are chemosensitive to salvage therapy and proceed to transplant, of which less than half will be cured.[8]

The development of more effective salvage strategies consequently remains an area of significant clinical importance, and a very high unmet medical need, especially in patients who are not candidates for high-dose chemotherapy. Patients with primary refractory disease following R-CHOP present the greatest clinical challenge, with less than 10% achieving durable remissions with salvage therapy.[8]

1.3.2. Pharmaceutical and Therapeutic Background

1.3.2.1. Avelumab (MSB0010718C)

Avelumab (MSB0010718C) is a fully human monoclonal antibody (mAb) of the immunoglobulin (Ig) G1 isotype.

Avelumab selectively binds to programmed death ligand 1 (PD-L1) and competitively blocks its interaction with programmed death protein 1 (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 programmed death ligand 2 (PD-L2)/PD-1 pathway intact to promote peripheral self-tolerance.[1]

1.3.2.2. Avelumab Safety

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%), 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 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 renal cell carcinoma (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.

1.3.2.3. Avelumab Pharmacokinetics

Available PK data from EMR100070-001 show that the concentration at the end of the dosing interval (C_{trough}) increased more than proportionally to dose between 1 to 10 mg/kg and proportionally to dose for doses above 10 mg/kg. The terminal half-life ($t_{1/2}$) also increased with dose; however, the geometric mean values for $t_{1/2}$ were similar for the 10 mg/kg and 20 mg/kg dose levels, at 94.6 hours (3.96 days) and 99.1 hours (4.1 days), respectively. This PK characteristic suggests that target mediated drug disposition is involved in the clearance of avelumab and that high PD-L1 target receptor occupancy (TO) is likely achieved throughout the dosing interval at doses of 10 mg/kg and 20 mg/kg given every 2 weeks.

The 10 mg/kg dose Q2W achieved high TO (mean TO >90%) of PD-L1 in peripheral blood mononuclear cells (PBMC) during the entire dosing interval, as determined from ex vivo studies. Based on the in vitro TO data and the observed trough serum avelumab levels in the dose escalation cohorts of Study EMR100070-001, TO was predicted to reach or exceed 95% throughout the entire dosing interval in more subjects in the 10 mg/kg dose group than in the 3 mg/kg dose group.

Avelumab is eliminated by intracellular lysosomal proteolytic degradation throughout the entire body and therefore is not expected to be affected by small molecule drugs that are cytochrome P450 (CYP) enzyme modulators or by transporter modulators. Population PK analysis did not show any meaningful effects on clearance of avelumab from premedication with acetaminophen (paracetamol) or diphenhydramine, nor from concomitant medication with ibuprofen, acetylsalicylic acid, opioids, corticosteroids, and biological therapies evaluated to date.

1.3.2.4. Immunogenicity of Avelumab in Humans

Immunogenicity assessment included all subjects from Studies EMR100070-001 and EMR100070-003 treated with 10 mg/kg of avelumab once every 2 weeks (Q2W) who had at least one valid anti-drug antibody (ADA) result as of the data cut-off date of 09 June 2016. Of the 1738 patients treated with avelumab, 1558 were evaluable for treatment-emergent ADAs and 64 (4.1%) tested positive. Titers were generally low across ADA ever-positive subjects, with no clear relationship between the duration of immunogenicity response and the

maximum observed titer. Current data suggest there is no clinically meaningful impact of ADA positivity on PK, efficacy, or safety.

Additional information for avelumab may be found in the SRSD, which for this study is the avelumab Investigator's Brochure.[6]

1.3.2.5. Rituximab

Rituximab is a CD20-directed cytolytic monoclonal antibody that is approved in the following lymphoma indications: (i) as a single agent in relapsed or refractory, low-grade or follicular, $CD20^+$, B-cell NHL, (ii) in previously untreated follicular, $CD20^+$, B-cell NHL in combination with cyclophosphamide/vincristine/ prednisone (CVP) chemotherapy, (iii) as a single agent in non-progressing (including stable disease), low-grade, $CD20^+$, B-cell NHL, (iv) after first-line CVP chemotherapy, and (v) in previously untreated diffuse large B-cell, $CD20^+$ NHL in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens. The other registered indications are $CD20^+$ chronic lymphocytic leukemia (CLL) and rheumatoid arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.

The CHOP chemotherapy regimen has remained the mainstay frontline therapy for DLBCL patients. The addition of rituximab to this chemotherapy backbone dramatically improved outcomes, with a complete response rate of 76% vs. 63%, p=0.005, and a reduced risk of treatment failure and death (risk ratios, 0.58 [95 percent confidence interval, 0.44 to 0.77] and 0.64 [0.45 to 0.89], respectively), establishing R-CHOP as the standard of care in DLBCL, with approximately 60% of patients being cured.[1,7,8] The most common (≥25%) adverse reactions of rituximab observed in clinical trials of patients with NHL are infusion reactions, fever, lymphopenia, chills, infection, and asthenia. Further information about rituximab may be found in the Rituxan® United States package insert (USPI).[12]

Rituximab and any concomitant therapy must be discontinued in patients who develop viral hepatitis, and appropriate treatment including anti-viral therapy must be instituted.

Additional information for rituximab may be found in the SRSD, which for this study is the Rituxan® USPI.[12]

1.3.2.6. Utomilumab (PF-05082566)

4-1BB (CD137, TNFRSF9), first identified as an inducible co-stimulatory receptor expressed on activated T cells, is a membrane-spanning glycoprotein of the Tumor Necrosis Factor receptor superfamily (TNFRSF). 4-1BB expression is generally activation dependent and encompasses a broad subset of immune cells including activated NK and natural killer T (NKT) cells, regulatory T cells, dendritic cells (DC) including follicular DC, stimulated mast cells, differentiating myeloid cells, monocytes, neutrophils, and eosinophils.[13,14]

Following 4-1BB activation, TRAF -1 and -2, pro-survival members of the TNFR-associated factor (TRAF) family, are recruited to the 4-1BB cytoplasmic tail resulting in downstream activation of NFkB and the Mitogen Activated Protein (MAP) Kinase cascade including Erk, Jnk, and p38 MAP kinases. NFkB activation leads to up-regulation of Bfl-1 and Bcl-XL, pro-survival members of the Bcl-2 family. The pro-apoptotic protein Bim is down-regulated in a TRAF1 and Erk-dependent manner.[15]

Numerous studies of murine and human T cells have indicated that 4-1BB promotes enhanced cellular proliferation, survival, and cytokine production.[16] Reports have shown that 4-1BB agonist monoclonal antibodies (mAbs) increase co-stimulatory molecule expression and markedly enhance cytolytic T lymphocyte responses, resulting in anti-tumor efficacy in various models. 4-1BB agonist mAbs have demonstrated efficacy in prophylactic and therapeutic settings in both monotherapy and combination therapy tumor models, and have established durable anti-tumor protective T-cell memory responses.[17] 4-1BB agonists also inhibit autoimmune reactions in a variety of autoimmunity models.[18] The dual activity of 4-1BB has the potential to convey anti-tumor activity while at the same time dampening autoimmune side effects that have been associated with immunotherapeutic agents that break immune tolerance.

1.3.2.7. Utomilumab Safety

In Study B1641001, utomilumab was given as a single agent in patients with solid tumors or R/R B-cell lymphoma (Portion A), and was given in combination with rituximab in patients with R/R $CD20^+$ NHL (Portion B). The administered dose levels were 0.006 mg/kg to 10 mg/kg once every 4 weeks (Q4W) for Portion A, and 0.03 mg/kg to 10 mg/kg Q4W for Portion B. The maximum tolerated dose (MTD) for utomilumab was not reached as a single agent or in combination with rituximab. Rituximab was administered only in Cycle 1 at a fixed dose of 375 mg/m^2, once per week for a total of 4 weeks. The first dose of rituximab was administered on Cycle 1 Day (-7) followed by the second dose a week later on Day (0) followed by utomilumab on C1D1. No DLT or Grade 4 or 5 treatment-related AEs were observed in either study portion.

Based on a data cutoff date of 06-Jun-2016, 61 patients in Portion A (54 male, 32 female, mean age of 61.8) and 47 patients in Portion B (26 male, 21 female, mean age of 58) were treated.

The most frequently observed (≥10% of patients; all grades) treatment-related TEAEs in Portion A with 86 patients was fatigue (11.6%). Treatment-related TEAEs were mostly Grade 1 or Grade 2 with only three treatment-related Grade 3 TEAEs reported (fatigue, ALT elevation, and hyponatremia). Note: After the data cut-off date, causality of the Grade 3 ALT elevation was re-assessed as not related to utomilumab by the investigator. Only 1 patient permanently discontinued treatment with utomilumab for a Grade 2 treatment-related TEAE of enterocolitis. Only 3 treatment-related serious AEs (SAEs) were reported in 2 patients: enterocolitis, decreased appetite and pneumonitis.

The most frequently observed (≥10% of patients; all grades) treatment-related TEAEs in Portion B with 47 patients were fatigue (23.4%) and infusion-related reaction (21.3%). Treatment-related TEAEs were either Grade 1 or Grade 2 in severity. There were no reported TEAEs leading to permanent treatment discontinuation. There were no DLTs, study related deaths, clinically significant ECG, or vital sign changes reported in either Portion A or Portion B.

Additional information for utomilumab may be found in the SRSD, which for this study is the utomilumab Investigator's Brochure (IB).[19]

1.3.2.8. Utomilumab Efficacy

The anti-tumor activity of single agent utomilumab in patients with advanced malignancies and utomilumab in combination with rituximab in patients with CD20 positive NHL is being assessed in Study B1641001. This study does not have a control arm, and tumor responses are reported by Investigators per Response Evaluation Criteria in Solid Tumors (RECIST 1.1)[20] and irRECIST for patients enrolled in the expansion cohort of Portion A[93] or International Working Group (IWG) criteria[21] for Portion B. Forty-seven patients in Portion A and 40 patients in Portion B (24 male, 16 female, mean age 60.8 years) have been treated.[19]

As of the data cut-off date 06 June 2016, in Portion A of the study, best objective responses observed have been 1 confirmed CR(Complete Response) and 1 confirmed PR (Partial Response) in MCC were reported in patients who were treated at 0.24 mg/kg and 0.6 mg/kg, respectively. In addition, 1 patient with anti-PD-1 refractory melanoma treated at 0.24 mg/kg had a PR that was not yet confirmed at the time of data cut-off date; however, the response was confirmed at a subsequent assessment. In addition, 1 patient with anti-PD-1 refractory melanoma treated at 0.24 mg/kg had a greater than 30% reduction in the diameters of multiple target tumors but was considered to have stable disease (irSD) per Immune-related Response Criteria Derived from RECIST 1.1.

In Portion B, 8 patients with follicular lymphoma (7 patients were refractory to prior rituximab-containing regimen) achieved an objective response: 4 patients achieved a CR (2 treated at1.2 mg/kg, 1 at 0.12 mg/kg, and 1 at 0.03 mg/kg) and 4 patients achieved PR (2 treated at 0.18 mg/kg, 1 treated at 1.2 mg/kg, and 1 treated at 5.0 mg/kg). One (1) patient with $CD20^+$ Hodgkin's lymphoma treated at 1.2 mg/kg achieved a PR and 1 patient with Mantle Cell Lymphoma (MCL) treated at a utomilumab dose of 2.4 mg/kg achieved a PR.

1.3.2.9. Utomilumab Pharmacokinetics

Preliminary PK data following single dose of treatments are available for 81 patients (46 in Portion A (utomilumab monotherapy) and 35 in Portion B (utomilumab + rituximab) in Study B1641001. Following the attainment of C_{max}, utomilumab serum concentrations showed a bi-exponential decline with a mean terminal elimination half-life of 208-349 hrs, a low systemic clearance (CL = 0.265 to 0.389 mL/hr/kg) and a small volume of distribution (Vss = 83.3-231 mL/kg) in Cycle 1 of Portion A. In Portion B, utomilumab also showed a bi-exponential decline with a mean terminal elimination half-life of 274-550 hrs, a low

systemic clearance (CL = 0.175-0.335 mL/hr/kg) and a small volume of distribution (Vss = 88.4-164 mL/kg). A dose proportional increase in exposure was observed.

Simulations were performed at various dosing schedules which indicated that the exposure at dose levels higher than 0.12 mg/kg was above the assumed efficacious concentration with both once every 3 weeks (Q3W) and once Q4W schedule. Although body weight was identified as a significant covariate on CL, it accounted for only a small percentage (~<7%) of the inter-individual variability in serum utomilumab exposure. In addition, simulations indicated that utomilumab exposure is similar between body weight based and fixed dosing regimens. Therefore, this supports a fixed dosing regimen in utomilumab clinical studies.[19]

1.3.2.10. Utomilumab Immunogenicity

ADA to utomilumab in human serum were determined using a validated, quasi-quantitative bridging electro chemi-luminescence method. Preliminary analyses based on quality-controlled, non-quality-assured data are presented. In Portion A, 9 out of 61 (14.8%) patients exhibited positive ADA prior to treatment with utomilumab. Thirty-five out of 61 patients (57.4%) were positive for ADA for at least one time point regardless of baseline ADA status. Among 35 ADA-positive patients, 7 (20%) exhibited positive neutralizing antibody (Nab) against utomilumab.

In Portion B, 2 out of 41 (4.9%) patients exhibited positive ADA against utomilumab prior to treatment with utomilumab plus rituximab. Three out of 41 patients (7.3%) were positive for ADA for at least 1 time point regardless of baseline ADA status when administered in combination with rituximab. Among 3 ADA-positive patients, 1 (33.3%) exhibited positive Nab against utomilumab.[19]

The impact of ADA on PK of utomilumab was characterized. ADA negative patients were defined as those with negative antibody status for all samples collected during the study including baseline (pre-treatment). ADA positive patients were defined as those with at least positive ADA sample anytime during the study including baseline (pre-treatment). The CL was similar in ADA negative and ADA positive patients suggesting that ADA status had minimal impact on the PK of utomilumab.[19]

1.3.2.11. Combination of a 4-1BB Agonist Antibody (Utomilumab) with a PD-1 Antagonist

Tumor expression of PD-L1 may limit the ability of cytotoxic T cells to directly kill tumor cells.[22] Therefore, if a 4-1BB agonist is used to stimulate tumor-specific cytotoxic T cells, PD-L1 expressed at the tumor cell surface may down-modulate T cell activity. A 4-1BB agonist antibody resistant mouse MC38 colon cancer tumor model expressing PD-L1 was used to examine anti-tumor activity using the combination of a 4-1BB agonist antibody with PD-1 antagonist antibody compared with either agent alone. Consistent with the proposed mechanism for the combination, significant increases in $CD8^+$ effector memory cells and tumor responsive IFN-γ producing cells were found in the spleens of mice treated with the

combination. In addition, preliminary toxicology data in mice suggest that the toxicity of an anti-4-1BB agonist is not increased by the addition of an anti-PD-1 antagonist.

The combination of a 4-1BB agonist antibody with a PD-1 antagonist antibody shows significant inhibition tumor growth in a colon carcinoma model. C57BL6 mice were subcutaneously implanted with $1x10^6$ MC38 murine colon carcinoma cells. Tumor growth was monitored and animals randomized to four groups of 8 when the tumors reached an average size of 150 mm^3 and intraperitoneally dosed with vehicle (phosphate-buffered saline; PBS), 1 mg/kg anti-mouse 4-1BB agonist (MAB9371), 10 mg/kg anti-mouse PD-1 antagonist (RMP1-14), or the simultaneous combination of the two once every 5 days for a total of two doses. The study was terminated when tumor sizes of the controls reached 1000 mm^3. Combination treatment of animals with 4-1BB agonist in combination with a PD-1 antagonist resulted in 63.2% reduction in tumor growth as compared with vehicle controls (unpaired t test *p = 0.0125). Significant tumor growth inhibition by either agent dosed individually was not observed.

1.3.2.12. Preliminary Safety Summary for Study B9991004 Phase 1b Combination A (Avelumab/Utomilumab)

B9991004 is an ongoing Phase 1b/2 open-label, multi-center, multiple-dose study to evaluate the safety, pharmacokinetic (PK), pharmacodynamics, and preliminary antitumor activity of avelumab (anti-PD-L1) at 10 mg/kg Q2W in combination with other cancer immunotherapies in patients with locally advanced or metastatic solid tumors. The objective of this study is to assess the safety and early signs of efficacy of avelumab in combinations with various other cancer immunotherapies, optimizing dosing regimens as appropriate in a limited series of indications. Initially, this study is evaluating the safety and antitumor activity of avelumab in combination with utomilumab (PF-05082566, anti 4-1BB agonist); Combination A. Combinations of avelumab with other immune modulators will be added to the study via protocol amendments based on emerging preclinical and clinical data.

In the Phase 1b lead-in for combination A, 18 patients with NSCLC were randomized in a 1:1:1 across 3 cohorts to receive utomilumab at 500 mg (Cohort A1), 100 mg (Cohort A2), or 20 mg (Cohort A3) in combination with 10 mg/kg of avelumab. The DLT observation period was 2 cycles (1 cycle = 28 days). If a DLT was observed in 2 or more of 6 patients, the cohort would be stopped. Each utomilumab dose level determined as tolerable in combination with 10 mg/kg of avelumab (ie, not meeting the DLT criteria) in the Phase 1b lead-in of the study will continue enrollment in Phase 2 for up to 22 additional patients with NSCLC in each cohort. Once the Phase 1b lead-in for NSCLC is completed and safety of the utomilumab dose levels in combination with 10 mg/kg of avelumab is determined, Phase 2 cohorts, designated as A4: melanoma (N=28), A5: squamous cell carcinoma head and neck (SCCHN) (N=35) and A6: triple negative breast cancer (TNBC) (N=40) will be enrolled initially at the 100 mg dose. The dose may be modified based on emerging efficacy and safety data from NSCLC expansion cohorts.

Study B9991004 is currently ongoing; therefore, the following safety summary of combination A is considered preliminary and may be subject to change.

As of the 16 May 2016 cutoff date, the study has enrolled 18 patients, 6 patients each in Cohorts A1, A2 and A3. Patients received 10 mg/kg avelumab Q2W in combination with utomilumab at 500 mg, 100 mg, or 20 mg Q4W. The DLT observation period has been completed for Combination A. The median duration of treatment with avelumab was 12 weeks (range 4 to 17.9 weeks), and the median duration of treatment with utomilumab was 12 weeks (range 4 to 19.9 weeks). All patients received treatment at assigned doses. No treatment discontinuation due to adverse event was reported.

The most common treatment emergent, all causality Grade 3, 4 TEAEs were dyspnea (16.7%), hypoxia (16.7%) and nausea (5.6 %). There were no treatment-emergent, treatment-related Grade 3, 4 or 5 AEs reported. All three dose levels were well tolerated. There were 3 cases of fatal outcome (Grade 5) attributed to disease progression.

A total of 12 serious adverse events (SAEs) were reported in 5 patients (3 patients in the 20 mg dose cohort and 1 patient each at 100 and 500 mg dose cohorts), including 3 patients with Grade 5 events of disease progression. All SAEs were assessed as not related to study treatments (avelumab and utomilumab).

Additional information for utomilumab may be found in the SRSD, which for this study is the utomilumab IB.[19]

1.3.2.13. Azacitidine

Azacitidine is a cytosine analog and a potent DNA methyl-transferase inhibitor, which induces DNA demethylation. Azacitidine is used for the treatment of patients with higher-risk myelodysplastic syndrome (MDS), and for a subgroup of acute myeloid leukemia (AML) and chronic myelomonocytic leukemia (CMML) patients.

It is indicated for the treatment of patients with the following French-American-British (FAB) MDS subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and CMML.

Compared to conventional care regimens, treatment with azacitidine has resulted in improved outcomes in MDS, including delayed leukemic transformation, increased survival in patients with higher-risk MDS, and prolonged overall survival in patients with oligoblastic AML (20-30% bone marrow blasts).[23,24]

The most common adverse reactions (>30%) by subcutaneous route are: nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia and ecchymosis. The most common adverse reactions by intravenous route include: petechiae, rigors, weakness and hypokalemia.

Azacitidine and its metabolites are primarily excreted by the kidneys. The risk of toxic reactions may be greater in patients with impaired renal function. Azacitidine is potentially hepatotoxic in patients with severe pre existing hepatic impairment. Caution is required in

patients with known liver disease. Azacitidine is administered by the subcutaneous route in this protocol.

Additional information for azacitidine may be found in the SRSD, which for this study is the Vidaza® USPI.[25]

1.3.2.14. Bendamustine

Bendamustine is an alkylating agent indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin's lymphoma (NHL) that have progressed during or within 6 months of treatment with rituximab (or with a rituximab-containing regimen).

The most common non-hematologic adverse reactions (≥30%) are: nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%) and pyrexia (34%). The most common non-hematologic Grade 3 or 4 adverse reactions (≥5%) are fatigue (11%), febrile neutropenia (6%), and pneumonia, hypokalemia and dehydration, each reported in 5% of patients.

The most common serious adverse reactions occurring in ≥5% of patients are: febrile neutropenia and pneumonia. Other important serious adverse reactions reported in clinical trials and/or postmarketing experience are: acute renal failure, cardiac failure, hypersensitivity, skin reactions, pulmonary fibrosis, and myelodysplastic syndrome. Serious drug-related adverse reactions reported in clinical trials included myelosuppression, infection, pneumonia, tumor lysis syndrome and infusion reaction.

Patients with myelosuppression following treatment with bendamustine are more susceptible to infections. Opportunistic infection prophylaxis is recommended per local guidelines. Prophylactic use of G-CSF in all cycles for patients ≥60 years old randomized to arm C is mandatory (and arm D in Phase 3, if arm C is selected to advance to the Phase 3 component).

High-dose therapy with stem cell support is the reference treatment for relapsed lymphoma, but is not appropriate for all patients, due to advanced age and comorbidities. Conventional salvage chemotherapies have been used with limited efficacy and significant toxicity.

Bendamustine is active in indolent B-cell NHL and CLL. Clinical activity in combination with rituximab in patients with relapsed and refractory DLBCL has been evaluated with ORRs ranging from 45.8% to 62.7%.[7,27,28]

Additional information for bendamustine may be found in the SRSD, which for this study is the Treanda® USPI.[26]

1.3.2.15. Gemcitabine

Gemcitabine is a nucleoside analogue that exhibits antitumor activity. Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. The registered indications of gemcitabine are as follows:

Breast Cancer - Gemcitabine in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

Non-Small Cell Lung Cancer - Gemcitabine is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.

Pancreatic Cancer - Gemcitabine is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemcitabine is indicated for patients previously treated with 5-FU.

Myelosuppression is the principal DLT with gemcitabine therapy. Dosage adjustments for hematologic toxicity are frequently needed.

Gemcitabine is associated with transient elevations of one or both serum transaminases in approximately 70% of patients.

Additional information for gemcitabine may be found in the SRSD, which for this study is the Gemzar® USPI.[29]

1.3.2.16. Oxaliplatin

Oxaliplatin is indicated in combination with 5-fluorouracil and folinic acid in the adjuvant treatment of Stage III colon cancer after complete resection of primary tumor, and in metastatic colorectal cancer.

The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil/folonic acid are: gastrointestinal (diarrhea, nausea, vomiting and mucositis), haematological (neutropenia, thrombocytopenia), and neurological (acute and dose cumulative peripheral sensory neuropathy).

High dose therapy with stem-cell support is the reference treatment for relapsed lymphoma, but is not appropriate for all patients, due to advanced age and comorbidities. Conventional salvage chemotherapies have been used with limited efficacy and significant toxicity.

Rituximab, gemcitabine and oxaliplatin has been evaluated as a salvage regimen in relapsed or refractory lymphoma patients who are not eligible for high dose therapy, with demonstrated overall response rates ranging from 46% to 83%.[29,30,31]

Additional information for oxaliplatin may be found in the SRSD, which for this study is the Eloxatin® USPI.[32]

1.4. Study Rationale

1.4.1. High Unmet Medical Need

The current NCCN Guidelines[1] for DLBCL recommend treatment with R-CHOP or an attenuated dose of R-CHOP (mini-CHOP in patients >80 years with comorbidities) in patients with newly diagnosed DLBCL with all stages of disease. Approximately 60% of patients will be cured following R-CHOP; however, 30% to 50% of those with advanced disease will be either primary refractory (~15%) or resistant (~25%) to R-CHOP.[1,7,8]

DLBCL patients who are refractory to induction therapy or who relapse following achieving a complete response may be considered for salvage chemotherapy. If their disease is chemosensitive, they may be considered for high-dose chemotherapy and ASCT.[7]

High-dose chemotherapy followed by ASCT provides the best chance of a cure in relapsed or refractory patients in the second-line treatment setting; however, due to advanced age or co-morbidities, only ~50% of patients that fail first-line R-CHOP are fit for high dose chemotherapy, and of these, only ~50% are chemosensitive in second-line and suitable for ASCT.[8] Even if eligible for high-dose chemotherapy, patients may refuse ASCT, or be ineligible for other reasons. Even in patients who are eligible for treatment with high-dose chemotherapy followed by ASCT, only a minority are cured.

Overall, >30% of DLBCL patients ultimately relapse. According to the European Society of Medical Oncology (ESMO) guidelines, relapsed and refractory DLBCL patients who are not suitable for high-dose chemotherapy should be enrolled in clinical trials testing the activity of novel drugs.[33]

The following rituximab-containing chemotherapy regimens are currently recommended by the NCCN Guidelines (version 1.0 2016) for 2L salvage therapy and beyond in patients that are not eligible for high dose chemotherapy and ASCT: Bendamustine ± rituximab, brentuximab, CEPP, CEOP, DA-EPOCH ± rituximab, GDP ± rituximab, Gem/Ox ± rituximab, lenalidomide ± rituximab, and rituximab.[1]

In spite of these salvage therapies, the outcome of patients that fail treatment with R-CHOP, and who are not eligible for high-dose chemotherapy or ASCT is dismal, with a median PFS of only 3.6 months.[7] The treatment options for these patients remain very limited, and there is consequently a high unmet medical need in R/R DLBCL patients that meet the study eligibility criteria, with the development of more effective salvage strategies able to prolong PFS and OS being of significant interest.

1.4.2. Avelumab in DLBCL

Programmed death-ligand 1 (PD-L1) and its receptor, PD-1, have a known role in the suppression of T-cell responses. The PD-1 receptor is expressed on activated $CD4^+$ and $CD8^+$ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals to inhibit T-cell function.[2,3,4]

In lymphoma, blocking the PD-1/PD-L1 interaction is a novel immunotherapeutic approach. Preliminary data indicate that PD-1 blockade is clinically active in specific hematologic cancers, including lymphoma.[34,35,36]

The tumor microenvironment in lymphoma is highly immunosuppressive, and inhibits the anti-tumor immune response. Tumor-infiltrating lymphocytes (TILs) within the microenvironment of DLBCL express PD-L1 to varying extents, and tumor cells themselves may express PD-L1 at the cell surface with varying intensities.[37] PD-L1 expression is associated with a poor prognosis: patients with PD-L1-positive DLBCL have an inferior overall survival (OS) as compared with PD-L1-negative DLBCL.[38]

Kiyasu, et al. studied PD-L1 expression on DLBCL tumor cells and TILs in 1,253 newly diagnosed/untreated DLBCL formalin-fixed, and paraffin embedded samples from Kurume University, Japan.[38] Samples were double-stained with antibodies against PD-L1 and the B-cell surface marker Pax5. PD-L1 positivity was defined arbitrarily as ≥30% of cells with membrane/cytoplasmic staining and $Pax5^+$. By this criterion, ~11% of DLBCL B-cells were found to be $PD\text{-}L1^+$. Additionally, 15.3% of non-B-cells in the microenvironment (mPD-L1) were $PD\text{-}L1^+$ DLBCL. $PD\text{-}L1^+$ B-cells and non-B cells were found to be associated with the ABC subtype as well as Epstein-Barr Virus (EBV) positivity. The frequency of $PD\text{-}1^+$ TILs was, furthermore, found to be greater in the GCB subtype. Patients with $PD\text{-}L1^+$ DLBCL had an inferior OS as compared with $PD\text{-}L1^-$ ($p=0.0009$). No OS difference was observed between mPD-L1 positive and negative ($p=0.31$), indicating that it is B-cell surface expression of PD-L1 that impacts the disease natural history most significantly.

These results indicate that inhibition of the PD-1/PD-L1 checkpoint axis may be of therapeutic relevance to this disease, at the minimum, in those patients with B-cell PD-L1 positivity. The threshold of 30% cell surface expression has not, however, been clinically validated, and it is possible that patients with a lower percentage (<30%) of PD-L1 positive B-cells may benefit from anti-PD-L1 blockade. This issue will need to be determined empirically.

Further data relating to levels of soluble PD-L1 also suggest a prognostic role for the PD-1/PD-L1 axis in DLBCL, and the potential therapeutic relevance of PD-1/PD-L1 blockade. The clinical impact of soluble programmed cell death ligand 1 (sPD-L1), detectable in plasma, was evaluated in 288 newly diagnosed DLBCL patients. Patients with elevated sPD-L1 had a poorer prognosis than those with low levels of sPD-L1, with a 3-year OS of 76% versus 89% ($p <0.001$).[39] This further supports the potential use of PD-1/PD-L1 axis blockade in DLBCL, and the investigation of therapeutic strategies using PD-1/PD-L1 axis inhibitors.

Finally, it has been showed that TILs in DLBCL can be re-activated by the blockade of PD-L1 which can restore the autologous anti-tumor T-cell response.[40]

A study investigating PD-1/PD-L1 axis blockade using the PD-1 inhibitor nivolumab as monotherapy in DLBCL, has shown a distinct, but lackluster response, with an ORR of 36% (CR 9%, PR 27% and SD 27%). The 6-month PFS was, furthermore, 24%.[41]

The sample size in this study was, however, small with 4 responders out of a total of 11 patients.

However, the expression of PD-L1 at the cell surface of DLBCL blasts as well as tumor infiltrating T cells (TILs), and other data linking the PD-1/PD-L1 checkpoint axis to survival outcomes, suggests that it may be possible to augment the observed monotherapy signal through rational combination with other agents.

The response rate of anti-PD-1 monotherapy in DLBCL was significantly lower than that observed in classic Hodgkin's lymphoma (cHL), which gave a response rate of 87%, and a 6 month PFS of 86%. The difference in ORR and PFS between cHL and DLBCL, may be attributed to the presence of a distinct targetable molecular lesion in cHL, namely the 9p24.1 amplicon which contains both PD-1 and PD-L1 and leads to their overexpression and which is found in cHL at high frequency, but is not present in DLBCL. There are two potential ways in which to further explore the use of PD-1/PD-L1 checkpoint blockade in DLBCL. The first is to attempt to define and target a sub-population of patients based upon PD-L1 cell surface expression. This approach would, however, limit the relevance of checkpoint blockade to a small subset of patients with DLBCL. The alternative approach, explored in the current study, is to attempt to define a basis for increasing the immunogenicity of DLBCL through the rational combination of PD-1/PD-L1 checkpoint blockade with other agents.

The target population in the current study has been defined to broadly align with the nivolumab DLBCL study population, with a view to augmenting the checkpoint inhibitor signal seen in the nivolumab monotherapy study, through various triplet chemotherapy-free and chemotherapy combinations. Rather than using the anti-PD-1 monoclonal antibody nivolumab, the current study will test the anti-PD-L1 monoclonal antibody avelumab.

Agents that will be tested in combination with avelumab include: (i) utomilumab a novel fully humanized IgG2 mAb agonist of 4-1BB, (ii) the epigenetic agent azacitidine, which has been shown to have potential immune priming activity through various mechanisms including the induction of PD-1 on TILs and PD-L1 on tumor cells, as well as the induction of tumor neo-antigen expression, (iii) the CD20 antagonist mAb rituximab, and (iv) the chemotherapy agent bendamustine, which is one of the NCCN recommended agents for the salvage therapy of DLBCL patients that are ineligible for high-dose chemotherapy and ASCT.

The aim of the Phase 1b component of the study is to determine whether any of these three experimental triplet combinations can augment the efficacy signal previously observed in an R/R DLBCL target population following PD-1/PD-L1 checkpoint axis inhibition using the PD-1 inhibitor nivolumab.

1.4.3. Rationale for Treatment Arm A (Avelumab, Rituximab, and Utomilumab)

CD137 (4-1BB) is a co-stimulatory receptor belonging to the TNF receptor superfamily. It regulates the activity of a broad range of immune cells, including $CD4^+$ and $CD8^+$ T-cells, regulatory cells (Tregs), dendritic cells, and natural killer (NK) cells. Agonistic anti-CD137

mAbs have been shown to increase T-cell proliferation, differentiation to memory cells, and resistance to apoptosis in $CD8^+$ T cells. CD137 agonism can also inhibit Treg function.[42] These immunostimulatory effects of CD137 agonism provide an independent rationale for the combination of the 4-1BB agonist utomilumab with the PD-L1 inhibitor avelumab.

CD137 expression has, furthermore, been observed on T cells and TILs in DLBCL, with higher CD137 expression conferring an improved OS, independently suggesting that CD137 agonism with utomilumab may impact DLBCL natural history.[43]

CD137 is expressed at the cell surface of a variety of immune cells following activation, including NK cells. Antibody-dependent cell-mediated cytotoxicity (ADCC), largely mediated by NK cells, is thought to be an important mode of action for rituximab. NK cells mediate ADCC by binding the C region of antibodies through their Fc receptor.

CD137 agonism has been shown to enhance the ADCC activity of NK cells. R/R DLBCL patients treated with rituximab continue to express CD137, and consequently bind utomilumab. Treatment with rituximab increases cell surface CD137 expression.[44]

Anti-CD137 agonist mAbs have been shown to enhance the anti-lymphoma activity of rituximab by enhancing ADCC.[44] It is consequently possible that by enhancing NK cell activity with CD137 agonism the ADCC activity of rituximab may be restored in patients that are relapsed or refractory to rituximab. This hypothesis was first tested in vitro using lymphoma cell lines. It was shown that recognition of rituximab-coated tumor B cells induces CD137 up-regulation on human NK cells, a phenomenon that is time dependent and peaks at 24 hours. Subsequent stimulation of these NK cells with anti-CD137 mAb enhances rituximab-dependent cytotoxicity against the lymphoma cells (cytotoxic granules mobilization).[44]

These results were confirmed *in vivo* using a syngeneic immunocompetent mouse model, and a human xenotransplant model of lymphoma. This data suggests an innovative approach to enhance the efficacy of rituximab based on sequential targeting of both the tumor and immune system. Rituximab will induce up-regulation of CD-137 on NK cells involved in ADCC, and the agonistic anti-CD137 mAb can then subsequently be administered to enhance the NK-cell mediated killing of rituximab-coated tumor cells.[44] CD137 agonism may in this way potentially re-activate rituximab activity in patients that are relapsed or refractory to rituximab in the context of R-CHOP. Combination therapy of an anti-PD-1 mAb with rituximab achieved a 66% ORR in patients with relapsed follicular lymphoma previously treated with rituximab.[45]

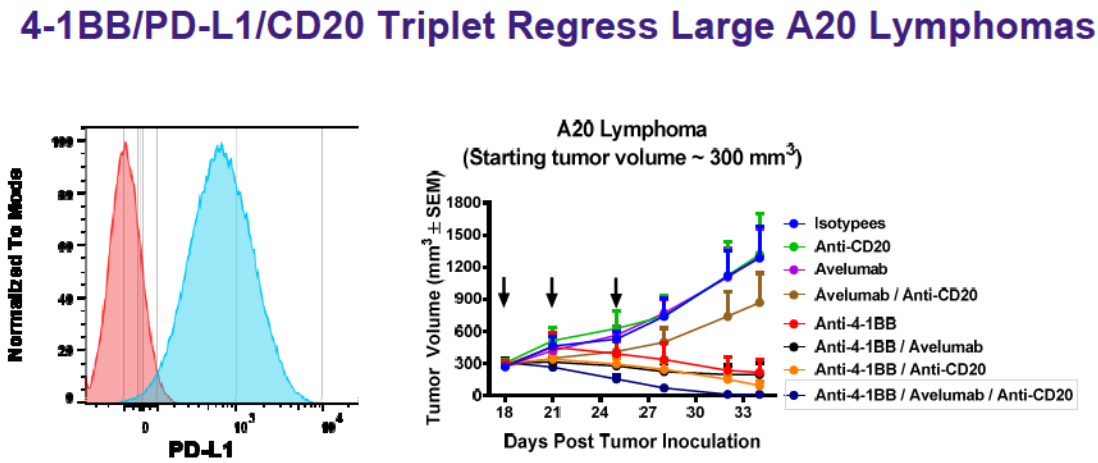
Data suggests that the combination of PD-L1 antagonism and anti-4-1BB agonism may be synergistic. In both a colon carcinoma and melanoma model, pronounced tumor inhibition was observed in animals receiving anti-PD-1 and anti-4-1BB concomitantly. They had a significantly increased reduction in tumor volume as compared with either agent alone.

Other pre-clinical studies indicated that PD-L1 expression confers resistance to therapeutic anti-CD137 antibody in mice with established tumors. The resistance is accompanied by failure of antigen specific $CD8^+$ cytotoxic TLs to destroy tumor cells without impairment of cytotoxic TL function. Blockade of PD-L1 or PD-1 using mAbs could reverse this resistance and enhance therapeutic efficacy.[46]

A mastocytoma cell line negative for PD-L1, was either mock transfected or transfected with a PD-L1 construct. The cells were then injected into the strain of mouse where the tumor cells were derived (DBA/2). Anti-PD-L1 mAbs were shown to abrogate the response to anti-4-1BB mAbs, suggesting that PD-L1 blockade might enhance the response to anti-4-1BB.

The hypothesis that a triplet comprising avelumab, rituximab and utomilumab might provide enhanced clinical activity in DLBCL has been tested in an A20 lymphoma model (Unpublished Pfizer data on file). In this model the triplet combination of avelumab, anti-4-1BB, and rituximab resulted in a higher frequency of tumor-free mice than either of the corresponding doublets or monotherapy (Figure 1).

Figure 1. A20 Lymphoma Model Data Showing Synergy of Simultaneous PD-L1, Anti-4-1BB, and Rituximab Blockade



Treatments	# Tumor-Free Mice
Isotypes	0 / 8
Anti-CD20	0 / 8
Avelumab	0 / 8
Avelumab / Anti-CD20	0 / 8
Anti-4-1BB	3 / 8
Anti-4-1BB / Avelumab	4 / 8
Anti-4-1BB / Anti-CD20	4 / 8
Anti-4-1BB / Avelumab / Anti-CD20	7 / 8

Together this data provides a compelling rationale for evaluating safety and efficacy of PD-L1 checkpoint blockade in combination with anti-4-1BB agonism and CD137 inhibition.

1.4.4. Rationale for Treatment Arm B (Avelumab, Azacitidine, and Utomilumab)

Following the observation that NSCLC patients previously treated with a combination of two epigenetic agents (entinostat and azacitidine) had a higher frequency of response to monotherapy with the anti-PD-1 inhibitor nivolumab, it was hypothesized that epigenetic priming might sensitize cancer cells to PD-1/PD-L1 axis blockade. This resulted in multiple investigations to explore potential mechanisms of action of epigenetic agents in this context. In one study, treatment with azacitidine increased the cell surface expression of PD-L1 on NSCLC cell lines.[47]

Further studies have provided evidence implicating multiple other mechanisms that support a potential immune priming role for azacitidine, and potentially also other epigenetic agents in the context of checkpoint blockade. Preclinical data demonstrated that the addition of azacitidine and entinostat to anti-PD-1 and anti-CTLA-4 mAbs, resulted in a significant decrease in tumor-infiltrating $FoxP3^+$ Tregs compared with either untreated tumors or tumors treated with anti-PD-1 and anti-CTLA-4 antibodies.[48]

PTPL1 encodes a cytoplasmic tyrosine phosphatase with roles in numerous physiological and pathological processes. Among the potential roles in carcinogenesis, the *PTPL1* gene product can impact cancer development through its capacity to counteract the activity of oncogenic tyrosine kinases or its inhibitory interaction with the death receptor Fas.

The frequency of *PTPL1* methylation I patients with DLBCL is significantly higher as compared with non-malignant lymphoid controls (59.6% of DLBCL versus 6.3% in reactive lymph node proliferation). It has been suggested that azacitidine has therapeutic potential in NHL as it may re-induce the expression of PTPL1. This suggests a tumor-suppressor role for PTPL1 in lymphoma, and suggests that azacitidine may induce growth inhibition in NHL through the demethylation of *PTPL1*.[49]

A Phase 1/2 study (N=45) of patients with advanced NSCLC examined the epigenetic effects of azacitidine administered at 40 mg/m^2 in combination with entinostat. In the Phase 1 component of the study, azacitidine was administered at a starting dose of 30 mg/m^2, and escalated to 40 mg/m^2 in an attempt to define an epigenetically targeted dose rather than a cytotoxic one. No significant dose-limiting toxicities (DLTs) were observed, and 40 mg/m^2 was selected for the Phase 2 study. Promoter methylation status in circulating DNA from patient plasma collected prior to therapy, and following 1 cycle of treatment, was assessed in 26 patients. Ten of these patients had at least 2 methylated target genes on Day 0, and were shown to have a decreased level of methylation of 2 or more of these genes by Day 29. It was notable that 80% of 'methylation signature' positive patients achieved either stable disease or objective responses (ORs).[50] A Phase 2 study combining the anti-PD-1 monoclonal antibody nivolumab, azacitidine (40 mg/m^2), and entinostat in NSCLC patients is currently ongoing (NCT01928576).

Furthermore, it was observed that chemo-resistance is associated with aberrant DNA methylation in DLBCL. Prolonged exposure to low-dose DNMTIs (decitabine or azacitidine) reprograms chemo-resistant-cells to become doxorubicin sensitive, without any major toxicity in vivo. A Phase 1 study of azacitidine followed by R-CHOP in the

treatment-naïve patients with DLBCL explored doses of azacitidine ranging from 25 mg/m^2 to 75 mg/m^2. Two of ten patients treated at 75 mg/m^2 experienced a DLT,[51] suggesting that the 75 mg/m^2 used routinely in MDS may not be well-tolerated in treatment-naïve DLBCL, and may consequently be even less well tolerated in later lines of therapy. It is notable in this context, that pre- and post-azacitidine treatment biopsies obtained from six patients confirmed SMAD1 demethylation and chemosensitization in all patients, even those treated at 25 mg/m^2 and 50 mg/m^2.[51] This raises the possibility of testing a dose less than 75 mg/m^2. Azacitidine has been shown to induce the expression of immune-related genes at doses which are lower than those necessary for the induction of cytotoxicity in vitro. This phenomenon is also observed clinically in patients with DLBCL at doses as low as 25 mg/m^2.

In light of: (i) the hematologic and non-hematologic toxicities observed at the standard cytotoxic azacitidine 75 mg/m^2 dose, (ii) the fact that DLTs have been observed in patients with DLBCL at this dose, and (iii) the fact that the cytotoxic effects of azacitidine are still observed at doses of 50 mg/m^2, the 50 mg/m^2 dose appears to define the upper limit of the azacitidine pharmacodynamic window encompassing both hypomethylation (at the lower dose end) and cytotoxicity (at the higher dose end). The 40 mg/m^2 azacitidine dose has, furthermore, been shown to be a clinically safe dose in patients with NSCLC, making this a reasonable candidate dose for testing in the epigenetic priming context. This dose is expected to minimize the cytotoxic effects of azacitidine, while at the same time preserving its hypomethylating effects. The 40 mg/m^2 dose is higher than 25 mg/m^2, a dose which has been shown to exert the full hypomethylating effects on key target genes such as SMAD1. Consequently, it is likely that 40 mg/m^2 will prove to provide an optimal combination of hypomethylation and mild and tolerable cytotoxicity.

Immunomodulatory effects of hypomethylating agents through demethylation of the tumor genome results in the increased expression of tumor antigens and neo-antigens. It has been shown that decitabine can induce specific autologous cytotoxic T lymphocytes against some mouse cancer testis antigens (CTAs) in leukemia cells both in vitro and in vivo, therefore inducing autologous immune response, and that this response may contribute to disease control.[52] It was also demonstrated that treatment with azacitidine or decitabine re-induces the expression of cancer germline (CG) antigens in myeloid cell lines, in AML and in MDS patients (in combination with decitabine). This is the result of CpG island promoter hypomethylation of CG genes following hypomethylating agent (HMA) therapy.[53]

Azacitidine sensitizes tumor cells to T-cell mediated cytotoxicity and modulates NK cell activity. It has been shown that azacitidine treatment leads to recognition of tumor cells by host T-cells and enhances direct ex vivo cytotoxicity. Cancer testis antigens are established targets for immune recognition in cancer. Azacitidine upregulates cancer testis antigens expression in tumor cells following demethylation. It is hypothesized that the combination of azacitidine with checkpoint inhibition may preferentially boost T-cell responses against cancer-testis antigens.[53]

It has been shown that azacitidine treatment increases the expression of several killer-cell immunoglobulin-like receptors (KIRs) in proliferating NK cells both in vitro and in MDS patients undergoing azacitidine treatment, and that azacitidine-exposed proliferating NK cells have a higher functionality.[54]

Proliferating NK cells exposed to azacitidine *in vitro* have considerably higher responses against K562 cells, suggesting that NK cells with an active uptake of azacitidine may mount improved responses against tumor targets.

When combined with avelumab, azacitidine may consequently lead to an enhanced anti-tumor response by increasing the expression of tumor antigens and tumor neo-antigens, by sensitizing malignant cells to cytotoxic T cells, by inhibiting Tregs and suppressing MDSCs, and by inducing tumor cell PD-L1 expression. Azacitidine may also have a synergistic effect when combined with a 4-1BB agonist by increasing NK cell activity.

The data showing the potential for synergy between anti-PD-L1 and a 4-1BB agonist, as well as the potential for azacitidine to prime the responses to anti-PD-L1, supports the testing of the azacitidine, anti-PD-L1 and the 4-1BB agonist triplet.

1.4.5. Rationale for Treatment Arm C (Avelumab, Rituximab and Bendamustine)

Emerging data support the rationale for combining immune checkpoint inhibitors with chemotherapy.[56,57] Chemotherapy has been shown to have immune-stimulatory properties through the release of neoantigens and adjuvants by dying cells, increasing susceptibility to immune attack, and preferentially reducing immunosuppressive cells such as T regulatory cells.[58,59 59] Most conventional chemotherapy agents, such as platinum-based agents, are mutagenic.[60] Therefore, treatment with chemotherapy may result in the expression of neoepitopes, which may enhance checkpoint inhibitor activity. In preclinical studies, the combination of avelumab with chemotherapy (gemcitabine, oxaliplatin, and 5FU) showed improved anti-tumor activity over single-agent chemotherapy.[6]

Several checkpoint inhibitors have been combined with chemotherapy agents. The addition of ipilimumab to dacarbazine resulted in an improvement in OS in previously untreated melanoma compared with dacarbazine alone.[61] Ipilimumab was combined with platinum-doublet chemotherapy in SCLC as well as NSCLC with encouraging results.[63] Combinations of the PD-1 inhibitors (pembrolizumab, nivolumab) as well as a PD-L1 inhibitor (atezolizumab) with platinum-doublet chemotherapy showed acceptable safety profiles with early evidence of clinical activity that appeared to be higher than expected for platinum-doublet therapy alone, particularly for atezolizumab.[64,65,66,67]

Chemotherapy is important for reducing tumor load and shedding antigens, as well as having an inhibitory effect on regulatory cells and myeloid suppressive cells. Chemotherapy agents may also have suppressive effects on Tregs and myeloid/macrophage cells, thus allowing immunotherapy to be more effective. Shed tumor antigens are taken up by monocytes and dendritic cells and may help initiate anti-tumor T cell responses. Immunotherapy has the capacity to greatly enhance the response to chemotherapy by bolstering and activating the immune response prior to antigen release, thereby enabling the immune system to mount an

antigen specific response when tumor cells are killed.[68] In preclinical studies, the combination of avelumab with chemotherapies demonstrated improved anti-tumor activity.[6]

In a rapidly progressive disease like DLBCL, chemotherapy is expected to help gain rapid control over the disease, giving the immunotherapy time to work. The lack of such early disease control is a potential risk of chemotherapy-free drug regimens, and the incorporation of chemotherapy as an avelumab combination partner in addition to its potential immune priming role through antigen shedding and tumor debulking, should provide an adequate window of time in which the immunotherapy can demonstrate its effects. R/Benda has been chosen as the chemotherapy of choice in the Phase 1b component of the study based upon the fact that: (i) it has less hepatoxicity than R/Gem/Ox (per label), (ii) it has a well-documented safety and efficacy profile, and (iii) it is listed as one of the recommended therapies for R/R DLBCL in the NCCN guidelines.

1.4.6. Rationale for Control Arm Combinations for Phase 3 (Rituximab/Bendamustine or Rituximab/Gemcitabine/Oxaliplatin)

High-dose chemotherapy followed by autologous stem-cell transplant is the treatment of choice for relapsed lymphoma, but is not appropriate for all patients, due to age and accompanying comorbidities. Conventional salvage chemotherapy has been used, but it has limited efficacy and is associated with significant toxicity.

No standardized chemotherapy regimen is available for elderly or frail patients with relapsed or refractory DLBCL. Cardiotoxicity associated with anthracyclines limits the utility of CHOP, and there is a significant need for effective and well-tolerated chemotherapeutic approaches for patients with aggressive NHL who have limited therapeutic options following chemotherapy and ASCT failure, as well as patients with impaired cardiac function who cannot receive anthracycline-based therapy.[27]

The following rituximab-containing chemotherapy regimens are currently recommended (NCCN Guidelines version 2.2015) for 2L salvage therapy and beyond in patients that are not eligible for high dose chemotherapy followed by ASCT: bendamustine ± rituximab, brentuximab, CEPP, CEOP, DA-EPOCH ± rituximab, GDP ± rituximab, Gem/Ox ± rituximab, lenalidomide ± rituximab, and rituximab. These regimens are also used in third line salvage and beyond in younger ‘fit’ patients who fail high dose chemotherapy and ASCT, or for whom ASCT is not appropriate.[1]

None of the options listed above have become a formal standard of care in R/R DLBCL. Both R/Benda and R/Gem/Ox are used in the US and European Union (EU), and both have been extensively studied in the R/R DLBCL setting. Different EU countries and different sites within the US and EU have specific preferences for using R/Benda or R/Gem/Ox. For example, although widely used across the US and Germany, R/Benda is not frequently used in other EU regions. There are also specific preferences for R/Benda or R/Gem/Ox in different lines of therapy.

In the Phase 1 component of study B9991011, R/Benda was chosen as the preferred chemotherapy backbone over R/Gem/Ox, as the use of R/Gem/Ox is associated with transient elevations of aspartate aminotransferase/ alanine aminotransferase (AST/ALT) in ~70% of patients.[29] Note that the ESMO guidelines differ from the NCCN guidelines, in that they do not recommend the use of R/Benda in first relapse, preferring instead either a clinical trial or the use of platinum and/or gemcitabine based regimens for R/R DLBCL patients who are not eligible for transplant. Beyond first relapse, the ESMO guidelines recommend a clinical trial as the preferred therapeutic option.[33]

Bendamustine is active in indolent B cell lymphomas and chronic lymphocytic leukemia. It demonstrated clinical activity in combination with rituximab in patients with relapsed and refractory DLBCL with an overall response ranging from 45.8% to 62.7%.[7,27,28]

An ORR of 45.8% with a complete response rate of 15.3% and a partial response rate of 30.5% was demonstrated with a rituximab/bendamustine combination in 61 patients with relapsed or refractory DLBCL who were determined by their physicians not to be good candidates for ASCT or aggressive salvage regimen. The median duration of response was 17.3 months and the median PFS 3.6 months. Grade 3 or 4 hematological toxicities included: neutropenia (36%), leukopenia (29%), thrombocytopenia (22%) and anemia (12%). The majority of patients received bendamustine at 120 mg/m^2 on Days 1 and 2 and rituximab at 375 mg/m^2 on Day 1 every 28 days for up to 6 cycles.[7]

A multicenter Phase 2 study assessed the efficacy and safety of bendamustine combined with rituximab in relapsed or refractory DLBCL patients who were not eligible for ASCT or had undergone ASCT, previously treated with one to three prior chemotherapy regimens.[27]

Rituximab 375 mg/m^2 IV infusion was administered on Day 1 and bendamustine 120 mg/m^2 by IV infusion on Days 2 and 3 of each 21-day cycle for up to six cycles.

Sixty-three patients were enrolled. The ORR was 62.7% (95% CI, 49.1% to 75.0%), with a CR rate of 37.3% (95% CI, 25.0% to 50.9%). The median PFS was 6.7 months (95% CI, 3.6 to 13.7 months). The most frequently observed Grade 3 or 4 adverse events were hematologic: lymphopenia (78.0%), neutropenia (76.3%), leukopenia (72.9%), CD4 lymphopenia (66.1%), and thrombocytopenia (22.0%).[27]

Rituximab, gemcitabine, and oxaliplatin are active as a salvage regimen in relapsed or refractory lymphoma patients who are not eligible for high dose therapy, with demonstrated overall response rates ranging from 46% to 83%.[29,30]

A series of 46 patients with relapsed or refractory B-cell lymphoma (72% had Diffuse Large B-cell Lymphoma) was conducted in 2007. Patients received up to eight cycles of R/Gem/Ox (rituximab 375 mg/m^2 on Day 1, gemcitabine 1000 mg/m^2 and oxaliplatin 100 mg/m^2 on Day 2). After 4 cycles of R/Gem/Ox, the overall response rate was 83% [50% complete response (CR)/unconfirmed CR (CRu)]. In patients who had previously received rituximab, the CR/CRu rate after eight cycles was 65%. The 2-year event-free and overall survival rates (median follow-up of 28 months) were 43% and 66%, respectively. The regimen was generally well-tolerated.

R/Gem/Ox showed promising activity with acceptable toxicity in patients with relapsed/refractory B-cell lymphoma who are not eligible for high dose therapy.[30] These results compared favorably with data for conventional chemotherapy regimens, which show low response rates and few durable responses. Each component of the R/Gem/Ox regimen may contribute to the efficacy, and the results of this study support a synergistic or supra-additive action for rituximab when combined with gemcitabine and oxaliplatin.[30]

A multicenter Phase 2 study was conducted in 49 patients with refractory or relapsed DLBCL, with prior rituximab treatment in 63% of patients. Rituximab 375 mg/m^2 was administered on Day 1 and gemcitabine and oxaliplatin at doses of 1000 mg/m^2 and 100 mg/m^2 respectively on Day 2. Cycles were repeated every 15 days. After 4 cycles, the complete remission rate was 44% and the partial remission rate 17%, with an overall response rate of 61%. These multicenter study results confirmed that the R/Gem/Ox regimen provides a consistent response rate in patients with relapsed-refractory DLBCL.[69]

A patient in first relapse that received R/Benda would not generally be re-treated with R/Benda in later lines of therapy. The same is true for R/Gem/Ox. Consequently, by allowing Investigator's Choice of either R/Gem/Ox or R/Benda, the study accommodates patients previously treated with one or the other combination in an earlier line of therapy.

A review of the R/Gem/Ox and R/Benda literature does not allow for a direct comparison of the efficacy of one versus the other as the studies are small, the target populations different, and the observed ORR and PFS values variable. Although overall the literature suggests that the ORR is higher for R/Gem/Ox than for R/Benda, the apparently higher ORR does not translate into an increased PFS. Furthermore, the R/Gem/Ox studies are in an earlier line of therapy, making it hard to compare data across studies.

From the perspective of safety, both R/Benda (90 mg/m^2 and 120 mg/m^2 doses) and R/Gem/Ox have an acceptable safety profile, with neutropenia and thrombocytopenia being the most frequent toxicities for both combinations.[7,27,28,30,70]

1.4.6.1. Rituximab/Bendamustine Safety

The commonest reasons for bendamustine dose reduction are neutropenia and thrombocytopenia. Neutropenia, thrombocytopenia, and anemia, each occur in about 45 % of patients (all grades; around 30%, 16% and 15% of Grade 3, respectively).

Other common adverse events (all grades, mainly Grade 1 or 2 in severity) include nausea (41%), constipation (25 to 50%), anorexia (14 to 34%), dehydration (10%), fatigue (21%), diarrhea (18%), and fever (17). Severe (Grade 3) infections can be observed.[7,27,28]

1.4.6.2. Rituximab/Gemcitabine/Oxaliplatin Safety

The most common toxicities are hematologic, with 98% of patients developing neutropenia, (including 43% to 73% of patients developing a Grade ≥3 neutropenia on at least 1 occasion). About 90% of patients experience thrombocytopenia, including about 44% with at least one Grade 3 episode. Neurotoxicity is reported in 35% to 45% of patients, mostly Grade 1 or

Grade 2 (approximately 7% of Grade 3/4). Nausea and vomiting occur in the majority of patients, but at Grade 2 or lower.[30,70]

1.5. Summary of Benefit/Risk Assessment

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

The benefit-risk relationship has been carefully considered in the planning of the trial.

Approximately 75% of patients with DLBCL present with advanced stage disease, and the majority (~60%) of patients may be cured with R-CHOP. However, patients with refractory or relapsing disease have a poor prognosis. High-dose chemotherapy and ASCT represent the best second-line treatment option, but eligibility for such intensive treatments is often limited by advanced age and comorbidities, and in addition only a fraction of patients is eventually cured by this approach. The development of novel, safe and more effective salvage strategies remains a high clinical priority.

Avelumab has demonstrated clinical activity in patients with a variety of advanced solid tumors in the expansion cohorts of the ongoing Phase 1 Trial EMR 100070-001. The clinical safety data with single-agent avelumab in patients with advanced solid tumors available to date, suggest an acceptable safety profile of the compound. Most of the observed events were either in line with those expected in patients with advanced solid tumors or with those observed with other monoclonal antibodies blocking the PD-1/PD-L1 axis (Section 1.3.2). Infusion-related reactions including hypersensitivity and irAEs/autoimmune disorders have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this clinical trial protocol. These include guidelines for treatment interruption and discontinuation in case of irAEs, as well as mandatory pre-treatment with a histamine H1 receptor (H1) blocker and acetaminophen.

The anti-4-1BB agonist mAb, utomilumab, has also demonstrated clinical activity as monotherapy in patients with advanced solid tumors and in combination with rituximab in patients with NHL in an ongoing Phase 1 Trial B1641001. The clinical safety profile of utomilumab supports its use as both a single agent and in combination with rituximab (Section 1.3.2.6). Pyrexia, fatigue, decreased appetite, dizziness, and skin rashes represent the most common utomilumab related AEs when given as a single agent, and they were generally mild to moderate in intensity. While clinically significant irAEs have not been observed with utomilumab, risk mitigation measures have been implemented in ongoing clinical studies with utomilumab, including this clinical trial protocol. These include guidelines for treatment interruption and discontinuation in case of treatment-related irAEs.

The combination of avelumab with utomilumab is being evaluated in patients with advanced solid malignancies in the ongoing Phase 1b/2 Trial B9991004 in which avelumab 10 mg/kg every 2 weeks is administered with utomilumab at doses of 20 mg, 100 mg, or 500 mg every 4 weeks. As of 16 March 2016, preliminary safety data were available for 5 patients in each utomilumab dose level cohort. Thirty-three treatment-emergent AEs were reported overall,

with 6 (18%) being drug related. All drug-related AEs (nausea, vomiting, fatigue, diarrhea, infusion reaction) were either Grade 1 or Grade 2 and were in line with the previously reported safety profiles for the two drugs when dosed separately. The events of infusion reaction (n=2) were reported as related to avelumab in 2 patients in the avelumab plus 500 mg utomilumab cohort (utomilumab is dosed first; followed 30 minutes later by avelumab). No drug-related AEs were reported in the avelumab plus 100 mg utomilumab cohort. In addition, 4 SAEs (all unrelated) have been noted: Grade 5 pneumonia (prior to study entry), Grade 3 nausea (100 mg utomilumab cohort), Grade 2 constipation (100 mg utomilumab cohort), Grade 3 lung infection (20 mg utomilumab cohort).

With exception for fatigue, pyrexia and decreased appetite, which are usually low-grade events observed with both avelumab and utomilumab single agents, there are no additional expected overlapping toxicities between the two agents. Given their distinct mechanisms of action and toxicity profiles, additional safety concerns are not expected from this combination. Of note, the utomilumab dose to be administered in this trial (100 mg [approximately 1.2 mg/kg] once every 4 weeks) is considerably lower than the highest dose tested (10 mg/kg every 4 weeks) as a single agent and in combination with rituximab in Study B1641001 and is thereby expected to provide an adequate safety margin for evaluation in combination with avelumab. In the current study, patients will be monitored closely for toxicity and in the event of significant toxicity or if unexpected safety concerns arise from the B9991004 trial, this study protocol will be amended to include additional guidance and/or a modified dosing regimen, if applicable.

The preclinical rationale for the three triplet combination regimens are outlined in Section 1.4. A safety analysis of the three combinations did not predict any significant potential for overlapping toxicities.

Based on the above, the projected benefit/risk of the three combinations to be tested in this study is anticipated to be favorable, and supports their investigation in patients with relapsed/refractory DLBCL.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Phase 1b Primary Objective:

- To asses safety, efficacy, and potentially select the most active treatment regimen among 3 treatment arms to advance to the Phase 3 component of the study.

Phase 1b Secondary Objectives:

- To evaluate the pharmacokinetics (PK) of each treatment arm.
- To assess the immunogenicity of each treatment arm.

- To evaluate PD-L1 expression levels in tumor cells and cells of the tumor microenvironment (for example, infiltrating lymphocytes) as candidate predictive biomarkers with their relationship to selected clinical response parameters.

- To evaluate the relationship between minimal residual disease burden as assessed using serial blood samples with selected clinical response parameters.

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Phase 3 Primary Objective:

- To demonstrate superiority in PFS as assessed by the Blinded Independent Central Review (BICR) of the selected Phase 1b avelumab-based combination regimen over Investigator's Choice chemotherapy.

Phase 3 Secondary Objectives:

- To compare overall survival (OS) between the selected Phase 1b avelumab-based combination regimen to Investigator's Choice chemotherapy.

- To further evaluate the efficacy of each treatment arm.

- To evaluate the overall safety profile of each treatment arm.

- To evaluate the PK of the selected Phase 1b avelumab-based combination regimen.

- To assess the immunogenicity of the selected Phase 1b avelumab-based combination regimen.

- To evaluate patient-reported outcomes (PROs) in the selected Phase 1b avelumab-based combination regimen versus Investigator's Choice chemotherapy.

- To evaluate PD-L1 expression levels in tumor cells and cells of the tumor microenvironment (for example, infiltrating lymphocytes) as candidate predictive biomarkers with their relation to selected clinical response parameters.

- To evaluate the relationship between minimal residual disease burden as assessed using serial blood samples with selected clinical response parameters.

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2.2. Endpoints

Phase 1b Primary Endpoint:

- Dose Limiting Toxicity (DLT).
- Objective Response (OR) as assessed by the Investigator per Lugano Response Classification Criteria.[71]

Phase 1b Secondary Endpoints:

- Safety: AEs and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Critera for Adverse Events (CTCAE) v.4.03; vital signs (blood pressure, heart rate); electrocardiograms (ECGs).
- Duration of Response (DR), Time to Tumor Response (TTR), Disease Control (DC), Progression-Free Survival (PFS), as assessed by the Investigator per Lugano Response Classification Criteria and Overall Survival (OS).
- Pharmacokinetics: PK parameters of avelumab, rituximab, utomilumab, azacitidine and bendamustine as data permit: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration time curve from time 0 to τ hours post dose ($AUC_{0-\tau}$, where τ is dependent on the analyte) apparent plasma clearance (CL/F), and apparent volume of distribution (V/F) of each analyte following single and multiple dosing.
- Immunogenicity: Anti-drug antibodies (ADA); neutralizing antibodies (Nab) against avelumab, rituximab, and utomilumab.
- PD-L1 expression levels in tumor cells and cells of the tumor microenvironment at baseline.
- Minimal residual disease burden (MRD) as assessed using serial blood samples.

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Phase 3 - Primary Endpoint:

- Progression-Free Survival (PFS) as determined by Blinded Independent Central Review (BICR) per Lugano Response Classification Criteria.

Phase 3 - Secondary Endpoints:

- Overall Survival (OS).
- PFS by Investigator assessment.
- Objective Response (OR), Time to Tumor Response (TTR), Duration of Response (DR), and Disease Control (DC) by BICR and Investigator assessment.
- Safety: AEs and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Critera for Adverse Events (CTCAE) v.4.03; vital signs (blood pressure, heart rate); electrocardiogram (ECG).
- Pharmacokinetics: PK parameters of avelumab, rituximab, utomilumab, azacitidine, and bendamustine (depending on the treatment being tested in Phase 3) will be determined as data permit: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration time curve from time 0 to τ hours post dose ($AUC_{0-\tau}$, where τ is dependent on the analyte) apparent plasma clearance (CL/F), and apparent volume of distribution (V/F) of each analyte following single and multiple dosing.
- Immunogenicity: anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against avelumab, rituximab, and utomilumab.
- Patient-Reported Outcomes: Fatigue measured via Brief Fatigue Inventory (BFI) questionnaire, disease symptoms and quality of life (QoL) measured via the NCCN-FACT FLymSI-18 questionnaire, and QoL measured via the EQ-5D-5L questionnaire.
- PD-L1 expression levels in tumor cells and cells of the tumor microenvironment at baseline.
- Minimal residual disease burden as assessed using serial blood samples.

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- [redacted]

3. STUDY DESIGN

3.1. Study Overview

Study B9991011 is a multicenter, international, randomized, open-label, 2-component (Phase 1b followed by Phase 3), parallel-arm study of avelumab in combination with:

(i) rituximab (CD20 antagonist) and utomilumab (4-1BB agonist);

(ii) azacitidine (DNA methyltransferase inhibitor [DNMTi]) and utomilumab (4-1BB agonist); or

(iii) rituximab (CD20 antagonist) and bendamustine (chemotherapy).

Crossover between treatment arms will not be permitted.

The target study population of this Phase 1b/Phase 3 registrational study will comprise patients with R/R DLBCL following at least 2 (but not more than 4) lines of prior rituximab/multi-agent chemotherapy, and/or failed ASCT, or who are not eligible for intensive chemotherapy or candidates for ASCT. The study will assess safety, efficacy, PK, and immunogenicity, and patient reported outcomes (see Figure 2).

Patients for whom first-line therapy failed may be categorized into two distinct groups:
(i) any response, with progression occurring after 3 months of therapy (relapsed disease),
(ii) no response, or progression within 3 months of therapy (refractory disease).

3.1.1. Phase 1b

The primary objective of the Phase 1b component is to make a preliminary assessment of dose-limiting toxicities in each treatment arm (N=6 each), and then to potentially select a treatment regimen to be advanced to the Phase 3 component based on efficacy including the observed ORR (as assessed by the Investigator) and safety profile in each expanded treatment arm (N=28 each).

Crossover between treatment arms will not be permitted.

The following treatment regimens will be assessed in the Phase 1b component of the study, with all treatments being administered in 28-day cycles: See Figure 3 for dosing schematic.

Treatment Arm A: Avelumab/Rituximab/Utomilumab

(i) Rituximab 375 mg/m^2 (IV) will be administered on the morning of Day 1 of each 28-day cycle for a maximum of 8 cycles.

(ii) Utomilumab 100 mg fixed dose (IV) will be administered on the morning of Day 2 of each 28-day cycle in Cycles 1 and 2 (or if well-tolerated in Cycles 1 and 2, then on Day 1 in Cycle 3 and in all subsequent cycles) at least 1 hour after the rituximab infusion is complete, until the patient no longer receives clinical benefit.

Utomilumab must have completed administration at least 1 hour prior to avelumab in Cycles 1 and 2. If well-tolerated in Cycles 1 and 2, then in Cycle 3 and in all subsequent cycles, the time window of dose administration between utomilumab and avelumab may be decreased from ≥1 hour to 30-60 minutes apart.

(iii) Avelumab 10 mg/kg (IV) will be administered every 2 weeks on Day 2 and Day 16 of each 28-day cycle in Cycle 1 and Cycle 2 (or if well tolerated in Cycle 1 and 2, then on Day 1 and Day 15 in Cycle 3 and in all subsequent cycles) until the patient no longer receives clinical benefit.

Avelumab must be administered at least 1 hour after the end of the utomilumab infusion in Cycle 1 and Cycle 2. If well-tolerated in Cycle 1 and Cycle 2, then in all subsequent cycles, the time window of dose administration between avelumab and utomilumab may be decreased from ≥1 hour to 30-60 minutes apart.

Treatment Arm B: Avelumab/Azacitidine/Utomilumab

(i) Azacitidine 40 mg/m^2 (SC) will be administered at the site in the morning on Days 1-5 of each 28-day cycle until the patient is no longer receiving clinical benefit.

Azacitidine must have completed administration at least 1 hour prior to utomilumab when dosed on the same day.

(ii) Utomilumab 100 mg fixed dose (IV) will be administered on the morning of Day 2 of each 28-day cycle in Cycles 1 and 2 (or if well-tolerated in Cycles 1 and 2, then on Day 1 in Cycle 3 and in all subsequent cycles) until the patient no longer receives clinical benefit.

Utomilumab must have completed administration at least 1 hour prior to avelumab in Cycle 1 and Cycle 2. If well-tolerated in Cycle 1 and Cycle 2, then in Cycle 3 and in all subsequent cycles, the time window of dose administration between utomilumab and avelumab may be decreased from ≥1 hour to 30-60 minutes apart.

(iii) Avelumab 10 mg/kg (IV) will be administered every 2 weeks on Day 2 and Day 16 of each 28-day cycle in Cycle 1 and Cycle 2 (or if well tolerated in Cycle 1 and 2, then on Day 1 and Day 15 in Cycle 3 and in all subsequent cycles) until the patient no longer receives clinical benefit.

Avelumab must be administered at least 1 hour after the end of utomilumab infusion in Cycle 1 and Cycle 2. If well-tolerated in Cycle 1 and Cycle 2, then in all subsequent cycles, the time window of dose administration between utomilumab and avelumab may be decreased from ≥1 hour to 30-60 minutes apart.

Treatment Arm C: Avelumab/Bendamustine/Rituximab

(i) Rituximab 375 mg/m^2 (IV) will be administered on the morning of Day 1 of each 28-day cycle for a maximum of 8 cycles.

(ii) Bendamustine 90 mg/m^2 (IV) will be administered on Days 2 and 3 of each 28-day cycle in Cycle 1 and Cycle 2. If bendamustine is well-tolerated in Cycle 1 and 2, bendamustine may be administered on Day 1 and Day 2 in Cycle 3 (and all subsequent cycles). Bendamustine is administered for a maximum of 6 cycles.

(iii) Avelumab 10 mg/kg (IV) will be administered every 2 weeks on Day 2 and Day 16 of each 28-day cycle in Cycle 1 and Cycle 2 (or if well tolerated in Cycle 1 and 2, then on Day 1 and Day 15 in Cycle 3 and in all subsequent cycles) until the patient no longer receives clinical benefit. Avelumab administration should be at least 1 hour after the end of the bendamustine infusion.

A dose level -1 (3 mg/kg) to be tested only in the event of excessive toxicity attributable to avelumab at 10 mg/kg is permitted.

Continued Treatment with Avelumab and/or Utomilumab

Per Investigator clinical judgment and following discussion between the Investigator and the Sponsor, if a patient with documented progressive disease (PD) continues to receive clinical benefit, treatment with avelumab and/or utomilumab may be continued. The Investigator's judgment must be based on the overall benefit-risk assessment, and on the patient's clinical condition, including performance status (PS), clinical symptoms, adverse events (AEs), and laboratory data. Other agents in the regimen combination with avelumab and/or utomilumab may also be considered for continuation if in the Investigator's clinical judgment the patient may achieve clinical benefit. See Section 5.4 for treatment duration limits for agents other than avelumab and utomilumab.

In the Phase 1b component of the study, pre-specified Go/No-Go criteria are configured to identify with ≥95% confidence a treatment regimen that is superior to rituximab/ bendamustine benchmark data (ie, historical reference control) with respect to one or more of the following (in a hierarchical manner):

1. ORR (ie, proportion of patients achieving CR or PR).

2. Six-month DRR (ie, proportion of patients with CR or PR persisting for at least 6 months).

3. PFS rate at 6 months.

In the final analysis of the Phase 1b the decision-making process will include the following steps:

1. In each treatment arm, the null hypothesis that the ORR does not exceed 46% (H0: ORR ≤46%) will be tested against the alternative hypothesis (H1: ORR >46%) at a one-sided level of significance α=0.025 using the binomial distribution.

2. If the null hypothesis for ORR is not rejected for any of the three treatment arms, the study will not proceed to Phase 3.

3. If only 1 treatment arm meets the ORR criterion, then that arm will be evaluated in Phase 3.

4. If ≥2 treatment arms meet the ORR criterion, then the Phase 3 investigational arm may be selected based on Criterion 1, 6-month DRR. In each treatment arm, the null hypothesis that the 6-month DRR does not exceed 23% (H0:6 Mo DRR ≤23%) will be tested against the alternative (H1: 6 Mo DRR >23%) at a one-sided level of significance α=0.025 using the binomial distribution.

5. If only 1 treatment arm meets the 6-month DRR criterion, then that arm will be evaluated in Phase 3. If none, or >1 treatment arm meets the 6-month DRR criterion, then the Phase 3 investigational arm may be selected based upon PFS rate at 6 months. In each treatment arm, the null hypothesis that the proportion of paitents who are progression-free at 6 months does not exceed 31% (H0: PFS rate at 6 months ≤31%), will be tested against the alternative (H1: PFS rate at 6 months >31%) at a one-sided level of significance α=0.025 using the using the binomial distribution.

6. If only 1 treatment arm meets the PFS rate at 6 months criterion, then that arm will be evaluated in Phase 3. If none or >1 treatment arm meets the PFS rate at 6 months criterion, then the totality of safety and efficacy data will be taken into consideration when determining which arm to take forward into the Phase 3.

In addition, there will be a formal interim analysis (IA) in the Phase 1b component of the study, performed 13 weeks after 8 patients in each treatment arm have been randomized (Section 9.14). The purpose of the IA is to allow for the early stopping of any treatment arm for futility based on ORR.

3.1.2. Dose-Limiting Toxicity Definition

The severity of adverse events will be graded according to CTCAE version 4.03 (see Appendix 4).

Up to 12 DLT-evaluable (see Section 9.3.3) patients will be randomized into each treatment arm in the Phase 1b and evaluated for DLT during the first cycle of treatment as follows:

- Randomize and treat up to 6 DLT-evaluable patients in each treatment arm:
  - If ≤1 of 6 patients experience DLT, the treatment arm will be expanded to randomize up to 28 patients;
  - If ≥3 of up to 6 patients experience DLT, randomization in the specific treatment arm will be discontinued;
  - If 2 of 6 patients experience DLT, the treatment arm will be expanded to randomize to 6 additional DLT-evaluable patients;
    - If ≤3 of 12 patients experience DLT, the treatment arm will be expanded to randomize up to 28 patients;
    - If ≥4 of up to 12 patients experience DLT, randomization in the specific treatment arm will be discontinued.

A Pfizer Internal Review Committee (IRC) evaluation of the first 6 and/or 12 DLT-evaluable patients in each treatment arm will occur after the last patient has completed one cycle (4 weeks) of treatment. Enrollment will be halted while the first 6 DLT-evaluable patients in each treatment arm are evaluated for safety.

For the purpose of selecting the regimen to advance into Phase 3, any of the adverse events listed below occurring during the DLT observation period (4 weeks from the time of the first study treatment administration (Cycle 1, Day 1) that are attributable to an agent in the combination (and not incontrovertibly related to underlying disease or intercurrent illness)), will be classified as DLTs:

<u>Hematologic</u>

- Grade 4 neutropenia (absolute neutrophil count [ANC] <500 cells/mm^3) not recovering to ≤ Grade 3 lasting >7 days (despite the use of G-CSF – see Section 5.5.5.2).
- Grade ≥3 febrile neutropenia (ANC <1000/mm^3) with a single temperature of >38.3 degrees Celsius (>101.0 degrees Fahrenheit) or a sustained temperature of ≥38.0 degrees Celsius (100.4 degrees Fahrenheit) for more than 1 hour, with or without associated sepsis or that leads to a delay in the next cycle of therapy(despite the use of G-CSF – see Section 5.5.5.2).

- Grade ≥3 neutropenic infection (despite the use of G-CSF – see Section 5.5.5.2).
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with clinically significant bleeding (requiring red cell transfusion).
- Grade 4 anemia (despite red blood cell transfusion).

Non-Hematologic:

Any Grade ≥3 toxicity, except for the following:

- Transient (≤6 hours) Grade 3 flu-like symptoms or fever controlled with standard medical management.
- Transient (≤24 hours) Grade 3 fatigue, localized skin reactions, or headache that resolves to Grade ≤1.
- Grade 3 nausea or vomiting resolved to Grade ≤1 in <72 hours following the initiation of adequate medical management.
- Grade 3 diarrhea that resolved to Grade ≤1 in <72 hours following the initiation of adequate medical management.
- Grade 3 skin toxicity resolved to Grade ≤1 in <7 days.
- Tumor flare.
- Single laboratory values that are out of the normal range, that do not have any clinical correlate, and resolve to Grade ≤1 within 7 days with adequate medical management.

Abnormal laboratory tests should be repeated. While the rules for adjudicating DLTs in the context of selecting the regimen to advance to Phase 3 clinical trial are specified above, AEs not listed above, or any AE meeting the DLT criteria above but occurring outside of the DLT observation period may be defined as a DLT following consultation between the Sponsor and the Investigator, based upon the overall emerging safety profile.

3.1.3. Phase 3

In Phase 3 (N=220) the primary objective is to demonstrate superiority in PFS (as assessed by Blinded Independent Central Review (BICR) of the treatment combination identified in Phase 1b, over the control treatment, namely Investigator's Choice chemotherapy comprised of rituximab/bendamustine or rituximab/gemcitabine/oxaliplatin.

Crossover between treatment arms will not be permitted.

The following combination treatment regimens will be assessed in the Phase 3 part of the study, with all treatments being administered in 28-day cycles:

Treatment Arm D: Combination regimen selected from the Phase 1b part of the study (from Treatment Arm A, B, or C). See Figure 3 for dosing schematic.

Treatment Arm E: Investigator's Choice options:

- Rituximab/bendamustine;
  - Rituximab (375 mg/m^2 Day 1 of each 28-day each cycle);
  - Bendamustine (120 mg/m^2 Day 1 and Day 2 of each 28-day cycle).
- Rituximab/gemcitabine/oxaliplatin;
  - Rituximab (375 mg/m^2 Day 1 of each 28-day cycle);
  - Gemcitabine (1000 mg/m^2 on Day 2 and Day 17 of each 28-day cycle);
  - Oxaliplatin (100 mg/m^2 on Day 2 and Day 17 of each 28-day cycle).

  Note that the Investigator must pre-specify which chemotherapy regimen (R/Benda or R/Gem/Ox) each patient will receive in the event that they are randomized to the Investigator's Choice arm, prior to randomization.

Figure 2. Study Design

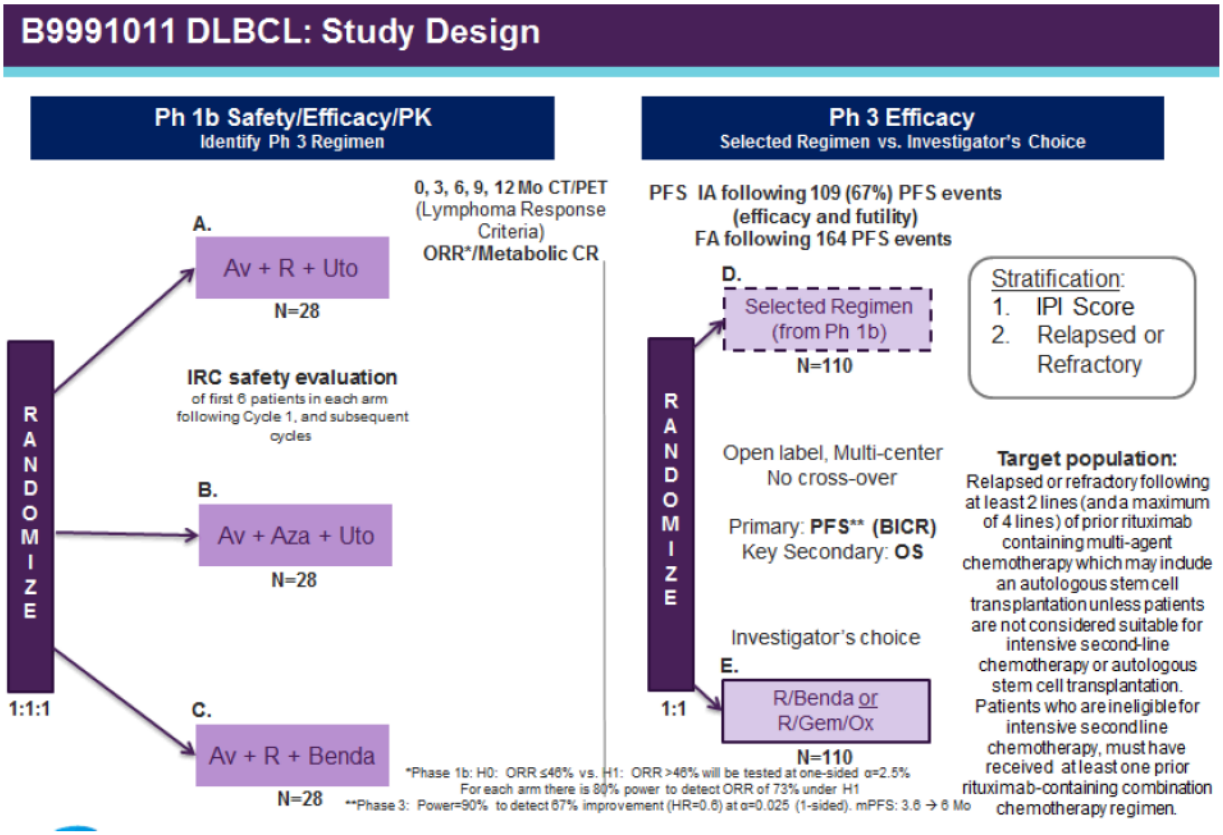
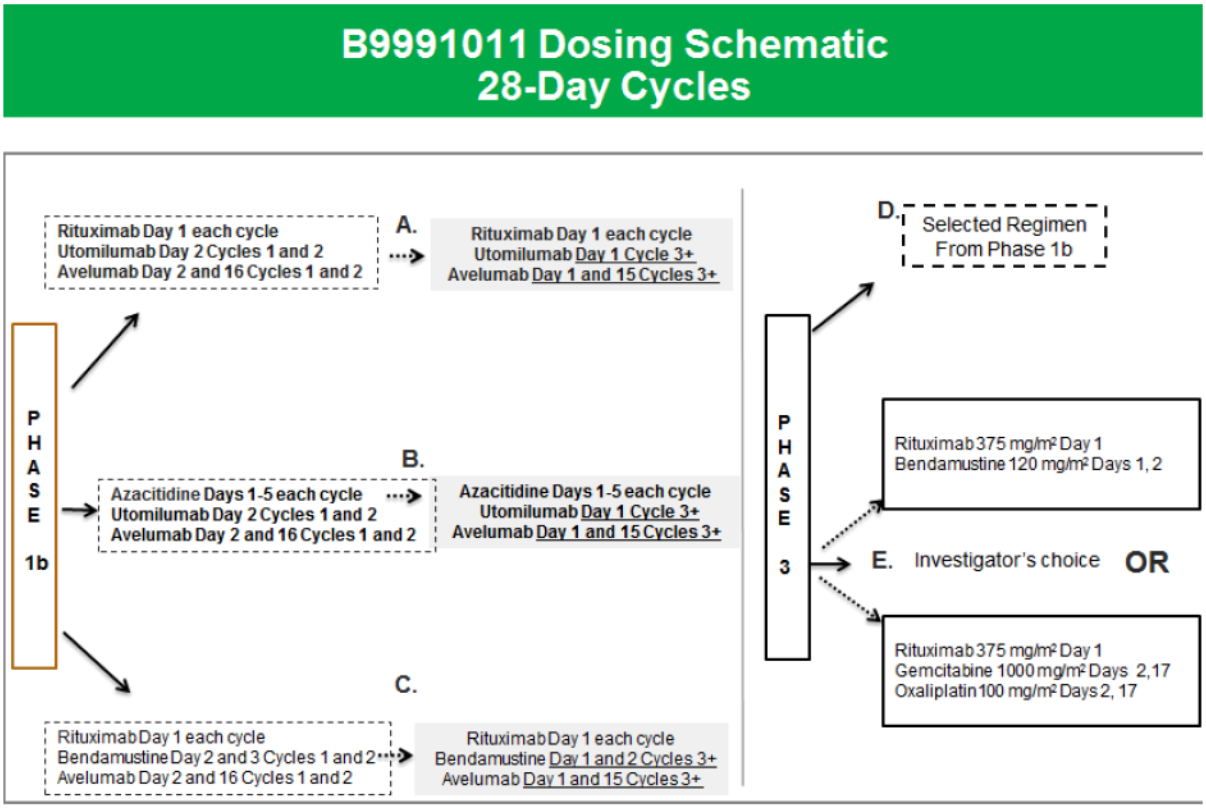


Figure 3. Dosing Schema: Phase 1b and Phase 3



4. PATIENT SELECTION

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

Patient eligibility should be reviewed and documented by an appropriate member of the Investigator's study team before patients are enrolled into the study.

4.1. Inclusion Criteria

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

1. Any of the following as defined by the WHO, 2016 lymphoid neoplasm classifications and histologically confirmed:
    - Diffuse large B-cell lymphoma (DLBCL), Not Otherwise Specified (NOS);
        - Germinal center B-cell type (GCB);
        - Activated B-cell type (ABC).

- High-grade B-cell lymphoma (HGBCL)-NOS.
- HGBCL with MYC and BCL2 and/or BCL6 rearrangements.
- T-cell histocyte-rich large B-cell lymphoma.
- EBV+ DLBCL, NOS.
- HHV8+ DLBCL, NOS.

2. Documentation that the disease is relapsed or refractory following at least 2 lines (and a maximum of 4 lines) of prior rituximab containing multi-agent chemotherapy which may include an autologous stem cell transplantation unless patients are not considered suitable for intensive second-line chemotherapy or autologous stem cell transplantation. Patients who are ineligible for intensive second line chemotherapy, must have received at least one prior rituximab-containing combination chemotherapy regimen.
3. Patients previously treated with bendamustine must have experienced a response duration ≥6 months.
4. Documentation of baseline measurable disease with at least 1 bi-dimensional lesion with longest diameter (LDi) >1.5 cm on CT scan which is fluorodeoxyglucose (FDG) avid on PET scan.
5. A biopsy (archived or Screening/recent) will be collected at Screening.
6. Estimated life expectancy ≥3 months.
7. At least 18 years of age (or ≥20 years in Japan).
8. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
9. All adverse events must have resolved to NCI CTCAE v.4.03 Grade ≤1 (with the exception of alopecia and other Grade ≤2 AEs not considered medically relevant in the judgment of the Investigator).
10. Patients must have an adequate bone marrow function, including:
    a. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L;
    b. Platelet count ≥100 x 10^9/L;
    c. Hemoglobin ≥8 g/dL.
11. Patients must have adequate liver function, including:

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

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

12. Patients must have an adequate renal function as evidenced by a creatinine clearance ≥40 mL/min as calculated using the Cockcroft-Gault equation.

13. Serum or urine pregnancy test (for females of childbearing potential) must be negative.

14. Female patients of non-childbearing potential must meet at least 1 of the following criteria:

    - 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 with a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state;
    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure.

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

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

16. Patients must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

17. Must be willing to receive prophylactic granulocyte colony stimulating factor (G-CSF) in all cycles, for patients ≥60 years old randomized to arm C (and arm D in Phase 3, if arm C is selected to advance to the Phase 3 component).

4.2. Exclusion Criteria

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

1. Active central nervous system (CNS) lymphoma.

2. Prior organ transplantation including prior allogeneic SCT.

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

4. Use of any standard or experimental anti-cancer therapy within 2 weeks prior to first dose of study treatment, including cytoreductive therapy and radiotherapy, immunotherapy, or cytokine therapy (except for erythropoietin).

5. Use of any non-drug anti-cancer therapy including chimeric antigen receptor (CAR) T-Cell (CAR-T-Cell) therapy.

6. Major surgery within 28 days prior to first dose of study treatment.

7. Diagnosis of any other malignancy ≤3 years prior to first dose of study treatment, with the exception of: (i) adequately treated basal cell or squamous cell skin cancer, (ii) carcinoma in situ of the breast or cervix, or (iii) low-grade (Gleason ≤6) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration).

8. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.

9. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen, positive HBV core antibody or HCV ribonucleic acid (RNA) if anti-HCV antibody screening test positive).

10. Active infection requiring systemic therapy.

11. Vaccination within 4 weeks prior to randomization and while on trial is prohibited except for administration of inactivated vaccines.

12. Peripheral neuropathy with functional impairment (for the Phase 3 component only due to oxaliplatin).

13. Current use of immunosuppressive medication, EXCEPT for the following: a.) intranasal, inhaled, eye drops, topical steroids, or local steroid injection (eg, intra-articular injection); b.) Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent; c.) Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

14. Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.

15. Known anaphylaxis or severe hypersensitivity to rituximab or other monoclonal antibodies, mannitol, or any of the compounds used in this study or to compounds with a similar chemical or biological composition.[72]

16. Clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke/transient ischemic attack [TIA]/symptomatic pulmonary embolism (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication, other severe acute or chronic medical (including colitis, inflammatory bowel disease, pneumonitis, uncontrolled asthma, or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or 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.

17. Known alcohol or drug abuse.

18. Pregnant female patients; breastfeeding female patients; fertile male patients and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception for a defined timeframe dependent on study treatment assigned per protocol and, where applicable, in agreement with local prescribing information for individual drugs (See Section 4.3.1).

19. 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, including their family members, directly involved in the conduct of the study.

20. Participation in other studies involving investigational drugs within 4 weeks prior to Cycle 1 Day 1 and/or during study participation.

21. Current use or anticipated need for treatment with drugs that are known strong CYP1A2 inhibitors, including their administration within 10 days prior to patient randomization (ie, ciprofloxacin, fluvoxamine, clinafloxacin, exoxacin, oltipraz, propranolol, rofecoxib, thiabendole and zafirlukast).

22. Current use or anticipated need for treatment with drugs that are known CYP1A2 inducers, including their administration within 10 days prior to patient randomization (ie, omeprazole, phenytoin).

4.3. Lifestyle Guidelines

4.3.1. Contraception

In this study, fertile male patients and female patients who are of childbearing potential will receive avelumab, which the teratogenic risk is currently unknown. Avelumab will be combined with rituximab, utomilumab, azacitidine, bendamustine, gemcitabine and/or oxaliplatin.

Patients who are, in the opinion of the Investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study. Contraception must also be continued after the last dose of study treatment is received as mandated by the relevant IB for experimental study drugs or by local prescribing information for marketed study drugs.

Table 3. Required Contraception Timeframes After Last Dose of Individual Study Drugs

Study Drug	Contraception Timeframe per Individual SRSD	
	IB	
Avelumab	60 days	
Utomilumab	90 days[a]	
	SPC	**USPI**
Rituximab	12 months	12 months
Azacitidine	90 days	Women of childbearing potential should be advised to avoid pregnancy during treatment
Bendamustine	Women of childbearing potential use effective methods of contraception both before and during treatment. Men are advised not to father a child during and for up to 6 months following cessation of treatment[b]	90 days
Gemcitabine	Women should not become pregnant during treatment	Do not become pregnant
Oxaliplatin	Women should not become pregnant during treatment	Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment

a. In France, the required timeframe for contraception following utomilumab treatment is 120 days.
b. In France, the required timeframe for contraception following bendamustine treatment is 180 days.
SPC= Summary of Product Characteristics; USPI= United States Package Insert

The Investigator or his or her designee, in consultation with the patient, will confirm that the subject has selected 2 appropriate methods of contraception for the individual patient [and his/her partner(s)] from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the patient of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the Investigator or designee will instruct the patient to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the patient or 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 hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner 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 separate spermicidal product (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. Note: The German Regulatory Authority (Paul-Ehrlich-Institut) does not recognize condoms as a highly effective contraception method even if used in conjunction with spermicide.

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).

4.4. Sponsor's Qualified Medical Personnel

To facilitate access to appropriately qualified medical personnel regarding on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product 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 the Investigator 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 Investigator 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 Investigator 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/comparator 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). All supplies will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

5.1. Allocation to Treatment

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

Once the patient has provided a signed Informed Consent Form (ICF) and has met inclusion and exclusion criteria, the Investigator or delegate will request the study treatment assignment using the Interactive Response Technology (IRT) system (interactive web-based response [IWR]/interactive voice response [IVR] system). Study treatment must start within 7 days after patient randomization.

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

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

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

Qualified patients in the Phase 1b component of the study will be randomized (1:1:1) to receive either avelumab in combination with (i) rituximab (CD20 antagonist)/utomilumab (4-1BB agonist) in Treatment Arm A, or (ii) azacitidine (DNMTi)/ utomilumab (4-1BB agonist) in Treatment Arm B, or (iii) rituximab (CD20 antagonist)/bendamustine (chemotherapy) in Treatment Arm C.

Qualified patients in the Phase 3 component of the study will be randomized (1:1) to the selected regimen from Phase 1b or Investigator's Choice chemotherapy comprised of either rituximab/bendamustine or rituximab/gemcitabine/oxaliplatin.

In Phase 1b, randomization will not be stratified.

In Phase 3, randomization will be stratified according to: (i) International Prognostic Score (IPI) ≤2 (low/low intermediate risk) or ≥3 (high intermediate/high risk) and (ii) Relapsed vs. Refractory status. The stratification will be centrally allocated across all centers via the IRT system. At the time of randomization, Investigators will be asked to provide the Investigator's Choice chemotherapy if a patient is randomized to Arm E (*a priori* selection of rituximab/bendamustine or rituximab/gemcitabine/oxaliplatin).

In Phase 3, the selection of the best control treatment for each patient must be decided by the Investigator and documented prior to randomization.

5.2. Patient Treatment Compliance

The site will complete the required dosage Preparation Record located in the Investigational Product Manual. The use of the Preparation Record is preferred, but 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 following approval from the Pfizer designated study monitor.

5.3. Investigational Product Supplies

All supplies will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

5.3.1. Dosage Form(s) 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 Practice (GMP) guidelines. Avelumab will be packed in cartons each containing one vial. The information on the labels 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.

5.3.1.2. Utomilumab

Utomilumab is a sterile, colorless solution intended for IV administration. For Phase 1b, utomilumab will be presented at a concentration of 10 mg/mL in single-use glass vials closed with a rubber stopper and sealed with an aluminum overseal. For Phase 3, utomilumab will be presented at a concentration of 25 mg/mL in single-use glass vials closed with a rubber stopped and sealed with an aluminum overseal.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines. Utomilumab will be packed in cartons each containing one vial. The information on the labels will be in accordance with approved submission documents.

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

5.3.1.3. Rituximab

Rituximab is commercially available in multiple presentations. All supplies will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements. Detailed information regarding rituximab formulation can be found in the Package Insert (PI) or Summary of Product Characteristics (SPC).

5.3.1.4. Azacitidine

Azacitadine is commercially available in multiple presentations. All supplies will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements. Detailed information regarding azacitidine formulation can be found in the PI or SPC.

5.3.1.5. Bendamustine

Bendamustine is commercially available in multiple presentations. All supplies will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements. Detailed information regarding bendamustine formulation can be found in the PI or SPC.

5.3.1.6. Gemcitabine

Gemcitabine is commercially available in multiple presentations. All supplies will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements. Detailed information regarding gemcitabine formulation can be found in the PI or SPC.

5.3.1.7. Oxaliplatin

Oxaliplatin is commercially available in multiple presentations. All supplies will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements. Detailed information regarding oxaliplatin formulation can be found in the PI or SPC.

5.3.2. Preparation and Dispensing

5.3.2.1. Avelumab Preparation

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

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

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

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

5.3.2.2. Utomilumab Preparation

Preparation instructions for utomilumab are identical to those for avelumab (Section 5.3.2.1). Specific preparation and dispensing instructions are provided in the IP Manual.

5.3.2.3. Rituximab Preparation

Refer to specific preparation and dispensing instructions provided in the IP Manual.

5.3.2.4. Azacitidine Preparation

Refer to specific preparation and dispensing instructions provided in the IP Manual.

5.3.2.5. Bendamustine Preparation

Refer to specific preparation and dispensing instructions provided in the IP Manual.

5.3.2.6. Gemcitabine Preparation

Refer to specific preparation and dispensing instructions provided in the IP Manual.

5.3.2.7. Oxaliplatin Preparation

Refer to specific preparation and dispensing instructions provided in the IP Manual.

5.4. Administration

Administration of investigational products should be performed by an appropriately qualified, Good Clinical Practice (GCP) trained, and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance. All trial treatments will be administered at the Investigational site.

A Complete Blood Count (CBC) and Chemistry panel (core chemistry required as noted by "*" in Table 19) are to be reviewed and signed off by medically qualified study personnel prior to dosing at each visit. This safety precaution is to ensure that protocol toxicity thresholds are not exceeded prior to treatment commencement at each dosing visit.

Investigational product administration details will be recorded on the CRF.

5.4.1. Avelumab

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

Avelumab will be administered as a 1 hour IV infusion, -10/+20 minutes (50-80 minutes), once every 2 weeks of each 28-day cycle. 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.

Premedication prior to rituximab is mandatory; if the avelumab is administered more than 1 hour after the rituximab infusion then the premedication must be repeated. The line should be flushed, according to local practice, between infusions, and a new administration set should be used for avelumab.

Site staff should make every effort to target the timing of avelumab infusion to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 20 minutes is permitted (ie, infusion time is 50-80 minutes). The exact duration of infusion should be recorded in both source documents and CRFs. Possible modifications of the infusion rate for the management of infusion related reactions are described in Section 5.6.6.

5.4.2. Utomilumab

Utomilumab is administered in this study as a 1 hour IV infusion, -10/+20 minutes (50-80 minutes), at 100 mg fixed dose of each 28-day cycle and must have completed administration at least 1 hour before avelumab administration until the patient is no longer achieving clinical benefit. If Cycle 1 and Cycle 2 dosing administration was well tolerated,

Cycle 3 and subsequent cycles may decrease administration of utomilumab and avelumab from at least 1 hour apart to 30-60 minutes apart. Utomilumab is administered for as long as the patient is continuing to achieve clinical benefit.

5.4.3. Rituximab

Rituximab is administered in this study at the dose of 375 mg/m^2 up to 8 cycles maximum as an IV infusion in the morning of each 28 day cycle on Day 1. Rituximab infusion must have completed at least 1 hour prior to utomilumab and bendamustine.

Rituximab should not be administered as an IV push or bolus. Premedication with acetaminophen and an antihistamine should be administered 30 minutes before each IV infusion.

Premedication prior to rituximab is mandatory; if the avelumab is administered more than 1 hour after the rituximab then the premedication must be repeated. The line should be flushed, according to local practice, between infusions, and a new administration set should be used for avelumab.

The first infusion should be initiated at a rate of 50 mg/hr. In the absence of infusion toxicity, the rate of infusion may be increased by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Subsequent infusions should be initiated at a rate of 100 mg/hr. In the absence of infusion toxicity, the rate of infusion may be increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr.

The infusion should be interrupted or slowed for infusion reactions. Upon improvement of symptoms, continue the infusion at one-half the previous rate. Medical management should be instituted (glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue rituximab.

In the event that dosing with rituximab in Cycle 1 is interrupted and the full dose of rituximab cannot be administered within 24 hours, repeat dosing for a maximum of one repeated rituximab infusion may in some instances be acceptable following discussion with the Sponsor stating that in the opinion of the Investigator the patient is suitable for re-treatment. This will only be allowed if the patient received less than half of the planned rituximab doses, and if the reason for dose interruption does not include a Grade ≥3 toxicity attributed to rituximab. Any patient requiring two dose interruptions, each of which prevent administration of the full rituximab dose within 24 hours will be withdrawn from the study.

5.4.4. Azacitidine

Azacitidine is administered at a dose of 40 mg/m^2 until the patient is no longer receiving clinical benefit as a SC injection at the site (not IV infusion), on Day 1 to Day 5 in the morning of each 28-day cycle. Intra-patient dose escalation is not permitted. Azacitidine must have completed administration at least 1 hour prior to utomilumab.

Patients should be premedicated for nausea and vomiting (as per local practice). The site should be rotated for each injection (thigh, abdomen, or upper arm). New injections should be administered at least one inch from an old site, and never to areas where the site is tender, bruised, red, or hard.

5.4.5. Bendamustine

Bendamustine is administered in the Phase 1b (Treatment Arm C) and in the Phase 3 investigational arm (in the event that Treatment Arm C advances to the Phase 3 part of the study) at 90 mg/m^2 IV infusion up to 6 cycles maximum. Intra-patient dose escalation is not permitted.

Note that in the Phase 3 Investigator's Choice option (Arm E), bendamustine is administered at a higher dose of 120 mg/m^2 on Days 1 and 2 of each 28-day cycle, for up to 6 cycles.

Measures to prevent infusion reactions and anaphylaxis including antihistamines, antipyretics, and corticosteroids should be considered in subsequent cycles in patients who have previously experienced Grade 1 or Grade 2 infusion reactions. Bendamustine is infused intravenously over 60 minutes. Patients with myelosuppression following treatment with bendamustine are more susceptible to infections. Opportunistic infection prophylaxis is consequently recommended per local guidelines. Prophylactic use of G-CSF in all cycles for patients ≥60 years old randomized to arm C is mandatory (and arm D in Phase 3, if arm C is selected to advance to the Phase 3 component).

5.4.6. Gemcitabine

Gemcitabine is administered at 1000 mg/m^2 IV infusion up to 6 cycles maximum on Day 2 and Day 17 of each 28 day cycle as part of the Investigator's Choice option (Arm E) in Phase 3.

Gemcitabine must be administered at a fixed dose rate of 16.7 mg/m^2/minute over 60 minutes. This prolonged administration schedule has been shown to achieve superior intracellular drug concentration as compared with the 30 minute IV schedule.[29]

5.4.7. Oxaliplatin

Oxaliplatin is administered at 100 mg/m^2 IV infusion up to 6 cycles maximum on Day 2 and Day 17 of each 28-day cycle as part of the Investigator's Choice option (Arm E) in Phase 3.

Gastro-intestinal toxicity related to oxaliplatin may manifest as nausea and vomiting, and may be managed with prophylactic and/or therapeutic anti-emetic therapy. Oxaliplatin is administered over 2 hours on Day 2 following gemcitabine.

5.4.8. Treatment Following Evidence of Radiological Disease Progression

If a patient with documented PD continues to experience clinical benefit, per Investigator's clinical judgment and following discussion between the Investigator and the Sponsor, the patient may be eligible for continued treatment with avelumab and/or utomilumab. The Investigator's judgment should be based on the overall benefit-risk assessment and on the

patient's clinical condition, including: performance status, clinical symptoms, adverse events, and laboratory data. Other agents in the regimen combination with avelumab and/or utomilumab may also be considered for continuation if in the Investigator's clinical judgment the patient may achieve clinical benefit. See Section 5.4 for treatment duration limits for agents other than avelumab and utomilumab.

The criteria that must be met are as follows: (i) No decline in ECOG performance status, (ii) Absence of rapid progression of disease by radiographic imaging, (iii) Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention, and (iv) Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression.

Before continuation of treatment, the patient must be re-consented and informed that by continuing receiving the investigational products on study, they may be foregoing treatment with approved therapies with possible clinical benefits.

5.4.9. Food Requirements

All investigational products may be administered without regard for food.

5.5. Recommended Dose Modifications

Every effort should be made to administer investigational products using the planned dose and schedule.

Dose modifications may occur in one of three ways during study conduct:

- Within a cycle, dosing may be interrupted until adequate recovery from toxicities;
- Next cycle administration may be delayed due to persisting toxicity when a new cycle is due to commence;
- Dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Patients whose treatment is delayed due to adverse events should be evaluated at intervals of one week or less until adequate recovery has been documented. Dose reductions are only allowed for bendamustine and oxaliplatin. No dose reductions are allowed for avelumab, utomilumab, rituximab, or gemcitabine. Intra-patient dose escalation is not allowed for any of the study drugs at any time.

Any suspected immune-related adverse event should be managed according to the Management of Immune Related Adverse Events (irAEs) guidance (see Table 5).

In Treatment Arms A and B, the same irAEs management guidelines will apply to both avelumab and utomilumab. In addition, in the event of an irAE, dosing with rituximab (Arms A and C), azacitidine (Arm B), and/or bendamustine (Arm C) should continue per

protocol, but may be interrupted for the same duration as avelumab or utomilumab, or for longer at the discretion of the Investigator, following prior discussion with the Sponsor.

In the event that it is necessary to permanently discontinue treatment with avelumab, all other study drugs must also be discontinued. In the event that it becomes necessary to stop dosing with one or more of the other drugs in the combination, avelumab dosing may continue per protocol.

In the event of significant toxicity; dosing may be delayed and/or reduced as outlined below. In the event of multiple toxicities, dose modifications should be based on the worst observed toxicity. Patients must be instructed to notify Investigators at the first occurrence of any adverse symptom/s.

Additional Recommended Treatment Modifications relevant to each of the three treatment arms in the Phase 1b component of the study may also be found in Section 5.5.3, and for the Investigator's Choice options in the control treatment arm of the randomized Phase 3 component are in Section 5.6.2.

All treatment modification recommendations must be followed unless previously discussed with and agreed by the Sponsor. All dose modifications/adjustments must be clearly documented in the patient's notes and in the CRF.

5.5.1. Special Precautions for Avelumab Administration

As with all monoclonal antibody therapies, there is a risk of allergic reaction including anaphylactic shock.

In order to mitigate the risk of avelumab related infusion-related reactions, a pre-medication regimen comprising 25 to 50 mg IV (or oral equivalent) diphenhydramine, and 650 mg IV (or oral equivalent) acetaminophen/paracetamol (per local practice) is mandatory, and should be administered approximately 30 to 60 minutes prior to each dose of avelumab. This may be modified, as appropriate, according to local treatment practice and guidelines.

Premedication prior to rituximab is mandatory; if the avelumab is administered more than 1 hour after the rituximab infusion then the premedication must be repeated. The line should be flushed, according to local practice, between infusions, and a new administration set should be used for avelumab.

Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators or equivalents and oxygen should be available for immediate access. Infusion of avelumab will be stopped in case of Grade ≥2 infusion-related, allergic, or anaphylactic reactions. Following avelumab infusion, patients must be observed for 2 hours for potential infusion-related reactions. If an allergic reaction occurs, the patient should be

treated according to the best available medical practice. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Investigators should additionally monitor patients closely for potential irAEs, which may become manifest at any time after the first dose of treatment of treatment. Immune-related adverse events described with this class of drugs include pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, hypophysitis, and diabetes mellitus, renal dysfunction, encephalitis, eye disorders (uveitis, iritis), myositis and myocarditis. However, potential irAEs can occur in any organ or tissue. Treatment recommendations for the management of irAEs are outlined in Section 5.5.2 and Table 5.

5.5.2. Management of Avelumab Infusion-Related Reactions

Symptoms may include one or more of the following: fever, chills, rigors, diaphoresis, and headache.

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

Table 4. Avelumab Treatment Modifications for Symptoms of Infusion Related Reactions

NCI-CTCAE Grade	Treatment Modifications
Grade 1 - Mild Mild and transient reaction; infusion interruption not indicated; interventions not indicated.	• Decrease avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 - Moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	• Temporarily discontinue avelumab infusion. • Resume infusion at 50% of the previous rate once the infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 - Severe or Life-threatening (a) Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. (b) Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion tubing from the subject. • Subject have to be withdrawn immediately from avelumab treatment, and must not receive any further avelumab treatment.

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

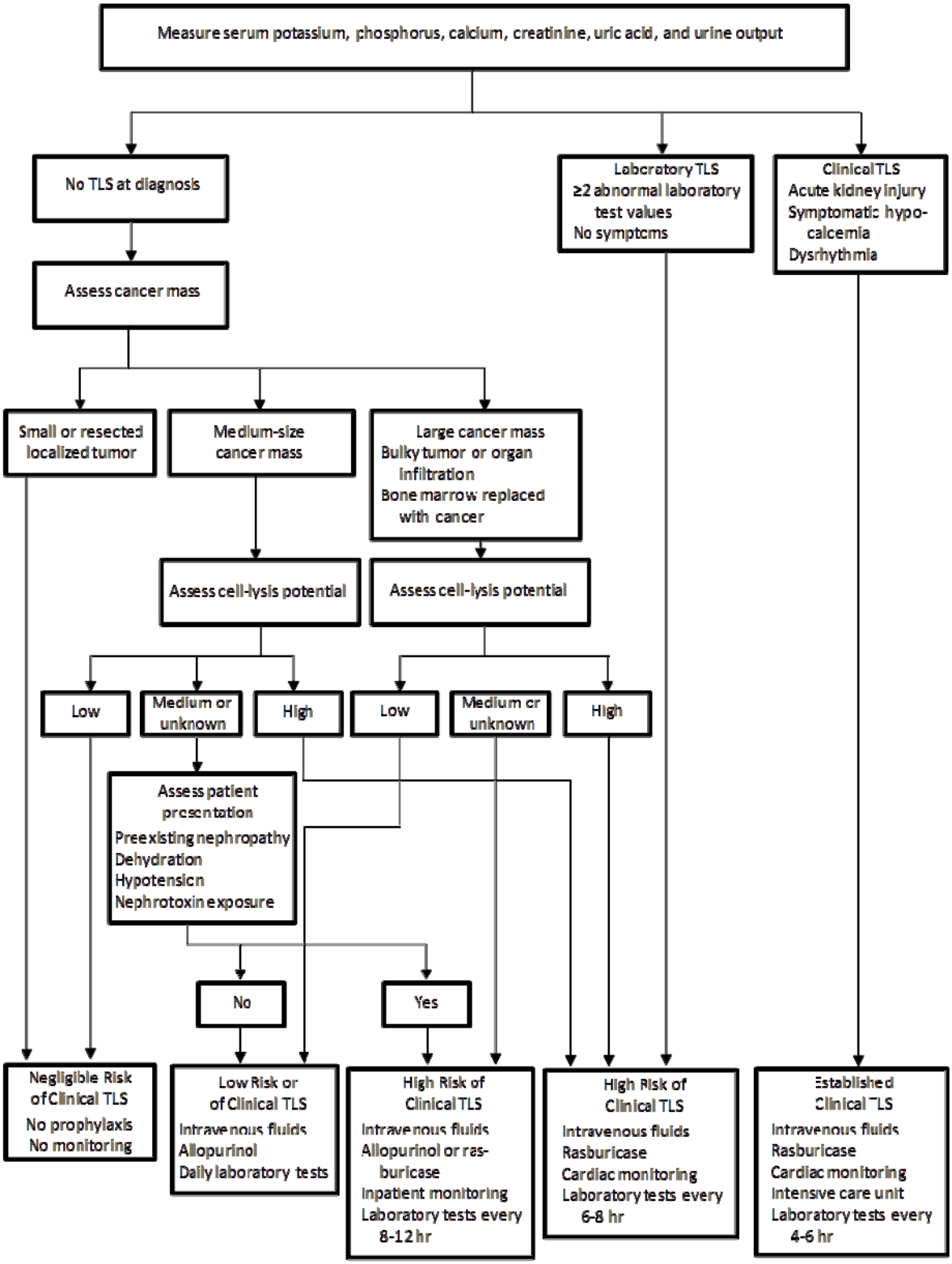
In the event of a Grade 2 infusion-related reaction that does not improve or that worsens following implementation of the modifications indicated in Table 4 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed. At the next dose, the Investigator may consider the addition

of H2-blocker antihistamines (eg, famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids are NOT permitted.

5.5.2.1. Tumor Lysis Syndrome

Since avelumab can induce antibody-dependent cell-mediated cytotoxicity (ADCC), there is a potential risk of syndrome, especially when used in combination with other ADCC-inducing agents. In the event that this occurs, patients should be treated per local guidelines, and the management algorithm (see Figure 4) published by Howard et al. should be followed.

Figure 4. Assessment and Initial Management of Tumor Lysis Syndrome



5.5.2.2. Immune-Related Adverse Events

NOTE: for Treatment Arms A and B, the same immune-related adverse events (irAEs) management guidelines apply to both avelumab and utomilumab.

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

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, and more frequent monitoring;
- Grade 1 to 2 (persistent): manage as per high-grade (ie, Grade 3 to 4) AEs;
- Grade 3 to 4: treat with high-dose corticosteroids.

Any event suspected to be immune-related should be managed according to the guidance for management of immune-related adverse events in this section and in Table 5.

In the event of an irAE, the dose of avelumab should be modified in accordance with Table 5 (see below).

Immune-related adverse events described with this class of drugs include: pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, hypophysitis, and diabetes mellitus or hyperglycemia, rash, nephritis and renal dysfunction, encephalitis, eye disorders (including uveitis, iritis), and other immune-mediated reactions including myositis and myocarditis.

Any adverse event which may have an underlying immune-mediated mechanism including those described above, and without other confirmed etiologies, should be considered immune-related and managed according to guidelines described in this section.

Table 5. Management of Immune Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4.03)	**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 subject to report worsening immediately If worsens: Treat as per 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 to 7 days or recurs: Treat as per Grade 3 to 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (Grade 3): Severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day methlyprednisolone IV or equivalent. Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy.	If improves: Continue steroids until Grade 1, then taper over at least 1 month; 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 v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area	Continue avelumab therapy. Symptomatic therapy (for example, antihistamines, topical steroids).	If persists >1 to 2 weeks or recurs: Withold 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 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 v4.03)	**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 per 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. 1.0-2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, and 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 following steroids taper If not improving after 2 weeks or worsening: Treat as per Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New / worsening hypoxia; Grade 4: Life-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, and 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 (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4.03)	**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 worsens: 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 of prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically indicated.	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 immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4.03)	**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 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 Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	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 immunosuppressants per local guidelines.

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetesmellitus)	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.	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.

	Guideline based supportive treatment as appropriate per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	
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. If no improvement or worsening, consider additional immunosuppressions (eg, azathioprine, cyclosporine A).
*Local guidelines, or eg, ESC guidelines (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines) or AHA guidelines (http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001)		
Other irAEs (not described above)		
Other irAEs (not described above) (NCI-CTCAE v4.03)	**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.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold 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 and resume avelumab therapy following steroids taper.
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 1.0 to 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	

Abbreviations: 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; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

5.5.3. Recommended Treatment Modifications for Phase 1b Treatment Arm A

Dose modifications for drug-related toxicities related to avelumab, utomilumab, and rituximab are detailed in Table 6 and Table 7. If a toxicity can be attributed just to one of the drugs in the combination, dose modifications can be implemented independently for each drug. In instances where it is not possible to attribute the toxicity to only one of the three drugs, the avelumab treatment modifications detailed in Table 6 and Table 7 should be followed for all 3 drugs.

5.5.3.1. Treatment Delays

A new treatment cannot start unless the ANC is $\geq 1.0 \times 10^9$/L, the platelet count is $\geq 75 \times 10^9$/L, and non -hematologic toxicities have returned to baseline or Grade ≤ 1 severity.

A new treatment may be delayed for a maximum duration of 4 weeks to allow for ANC and platelet count recovery. In the event that recovery does not occur within 4 weeks, all study drugs must be permanently discontinued. The 4 weeks recovery window commences on the day of the planned treatment.

If avelumab treatment is delayed due to toxicities attributable to avelumab and/or utomilumab (eg, pneumonitis or hypothyroidism), rituximab administration does not need to be delayed. If the start of rituximab administration is delayed due to toxicities attributable to rituximab, administration of utomilumab and avelumab does not need to be delayed delayed.

5.5.3.2. Dose Reductions for Avelumab, Utomilumab, and Rituximab

No dose reductions are permitted for avelumab, utomilumab, or rituximab.

5.5.3.3. Management of Immune-Related Adverse Events

The irAE management guidelines outlined in Section 5.5.2.2 apply to both avelumab and utomilumab. Any event suspected to be immune related should be managed according to the guidance for management of immune related adverse event in Table 5.

In case of a potential irAE, besides the management related to avelumab and utomilumab therapy, rituximab doses may also be modified or interrupted based on the guidance provided for avelumab-utomilumab-rituximab combination toxicity management Table 6 and Table 7, product labeling and institutional guidelines according to Investigator's best medical judgment.

5.5.3.4. Management of Infusion-Related Reactions

5.5.3.5. Avelumab and Utomilumab

Guidelines for the management of avelumab infusion-related reactions are outlined in Section 5.5.2.2. The same management guidelines are applicable to utomilumab infusion-related reactions.

5.5.3.6. Rituximab

Rituximab may cause severe, including fatal, infusion reactions. Severe reactions typically occur during the first infusion, with time to onset typically being 30-120 minutes.

Patients with pre-existing cardiac or pulmonary conditions, those who have experienced prior cardio-pulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq$25,000/mm^3) should be closely monitored. 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.

5.5.3.7. Management of Tumor Lysis Syndrome

Avelumab, utomilumab, and rituximab are associated with a potential risk of tumor lysis syndrome. Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia resulting from tumor lysis, which may be fatal, can occur within 12-24 hours after the first infusion of rituximab. A high number of circulating malignant cells ($\geq$25,000/mm^3) or high tumor burden confers a greater risk of Tumor Lysis Syndrome (TLS).

In the event that tumor lysis syndrome occurs, patients should be treated per local guidelines, and the recommended management algorithm published by Howard et al. followed (see Figure 4).

Table 6. Treatment Arm A (Avelumab, Rituximab, and Utomilumab) Treatment Modifications for Investigational Product Related Hematologic Toxicities

Hematologic Toxicity (NCI CTCAE version 4.03)	Avelumab	Rituximab	Utomilumab
Grade 1	Continue per schedule	Continue per schedule	Continue per schedule
Grade 2	Continue per schedule	Continue per schedule	Continue per schedule
Grade 3	Hold treatment up to 4 weeks until Grade ≤1, or baseline, then rechallenge. Permanent discontinuation if recurrence to Grade 3. (Unless resolve to Grade ≤1 or baseline within 7 days following appropriate medical management).	Hold treatment up to 4 weeks until Grade ≤1, or baseline then rechallenge. Permanent discontinuation if recurrence to Grade 3. (Unless resolve to Grade ≤1 or baseline within 7 days following appropriate medical management).	Hold treatment up to 4 weeks until Grade ≤1, or baseline then rechallenge. Permanent discontinuation if recurrence to Grade 3 (Unless resolve to Grade ≤1 or baseline within 7 days following appropriate medical management).
Grade 4	Permanent discontinuation (Unless resolve to Grade ≤1, or baseline within 7 days following appropriate medical management).	Permanent discontinuation (Unless resolve to Grade ≤1 or baseline within 7 days following appropriate medical management).	Permanent discontinuation. (Unless resolved to Grade ≤1 or baseline within 7 days following appropriate medical management).

Table 7. Treatment Arm A (Avelumab, Rituximab, and Utomilumab) Treatment Modifications for Investigational Product-Related Non-Hematologic Toxicities

Non-Hematologic Toxicity (NCI CTCAE v. 4.03)	Avelumab	Rituximab	Utomilumab
Progressive multi-focal leuco-encephalopathy (PML) - any grade	Permanently discontinue	Permanently discontinue	Permanently discontinue
Viral Hepatitis B – any grade	Permanently discontinue	Permanently discontinue	Permanently discontinue.
Grade ≥3 infection	Permanently discontinue	Permanently discontinue	Permanently discontinue.
Grade ≥3 cardiac arrhythmia	Permanently discontinue	Permanently discontinue	Permanently discontinue
Grade ≥3 renal toxicity (eg, acute kidney injury, urine output decreased)	Permanently discontinue	Permanently discontinue	Permanently discontinue
Grade ≥3 muco-cutaneous reactions including paraneoplastic pemphigus, Steven-Johnson syndrome, lichenoid dermatitis, vesciculobullous dermatitis, and toxic epidermal necrolysis	Permanently discontinue	Permanently discontinue	Permanently discontinue
See irAEs management guidelines for dermatologic toxicity (Table 5), which are applicable to both avelumab and Utomilumab			
Any Grade ≥3 liver function test abnormality	Permanently discontinue	Permanently discontinue	Permanently discontinue
See irAEs management guidelines for hepatic toxicity (Table 5), which are applicable to both avelumab and Utomilumab			
Other - Grade 1	Continue per schedule.	Continue per schedule.	Continue per schedule.

Non-Hematologic Toxicity (NCI CTCAE v. 4.03)	Avelumab	Rituximab	Utomilumab
Other Grade 2	Hold treatment until the toxicity resolves to Grade ≤1 up to 4 weeks. Exceptions: • Transient flu-like symptoms or fever, which are controlled by medical management. • Transient fatigue, local reactions, or headache, that resolve to Grade ≤1. • Nausea or vomiting controlled by medical management. • Amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. • Tumor flare. • Single non-hematologic laboratory values that do not have any clinical correlates, and resolve to ≤ Gr 1 within 7 days following appropriate medical management. • Endocrine deficiencies that are manageable by hormone replacement therapy.	As per as avelumab.	As per avelumab.
Other - Grade 3	Hold treatment up to 4 weeks until the toxicity resolves to Grade ≤1 If Grade 3 recurs: permanently discontinue Exceptions: • Transient flu-like symptoms or fever, which are controlled by medical management.	As per avelumab.	As per avelumab.

Non-Hematologic Toxicity (NCI CTCAE v. 4.03)	Avelumab	Rituximab	Utomilumab
	• Transient fatigue, local reactions, or headache, that resolve to Grade ≤1. • Nausea or vomiting resolved to Grade ≤1 in <72 hours following the initiation of adequate medical management. • Tumor flare. • Single non-hematologic laboratory values that are out of the normal range, that do not have any clinical correlates, and resolve to Grade ≤1 within 7 days following appropriate medical management. • Endocrine deficiencies that are manageable by hormone replacement therapy.		
• Other - Grade 4	Permanent discontinuation. Exceptions: • Single non- hematological laboratory values that do not have clinical correlates, and resolve within 7 days following appropriate medical management.	As per avelumab.	As per avelumab.

Non-Hematologic Toxicity (NCI CTCAE v. 4.03)	Avelumab	Rituximab	Utomilumab
irAEs	See Table 5.	Continue dosing if Grade ≤2, however, dosing may be withheld until irAE resolution and the time of avelumab and utomilumab dosing recommence according to Investigator judgment. For Grade ≥3 irAEs, permanently discontinue.	See Table 5.
Infusion-related reactions	See Section 5.5.4.5.	Medical management (eg, glucocorticoids, epinephrine, bronchodilators, and oxygen) for infusion reactions as clinically indicated. Depending on the severity of the infusion reaction and the required interventions, rituximab should be temporarily or permanently discontinued. The infusion must re-commenced at a minimum of a 50% reduction in rate following symptoms resolution.	See Section 5.5.4.5.

5.5.4. Recommended Treatment Modifications for Phase 1b Treatment Arm B

The recommended utomilumab, and avelumab dose modifications for drug-related toxicities are detailed in Section 5.5.3.2. If a toxicity can be attributed to just one of the drugs in the combination, dose modifications may be implemented independently for each drug. In instances where it is not possible to attribute a specific toxicity to just one of the three drugs, the guidelines for avelumab should be followed for all 3 drugs.

5.5.4.1. Treatment Delays

A new treatment cannot start unless ANC $\geq 1.0 \times 10^9$/L, platelets $\geq 75 \times 10^9$/L, and non-hematologic toxicities have returned to baseline or Grade ≤ 1 severity.

The start of a new treatment may be delayed for 4 weeks to allow for ANC and platelet count recovery. In the event that recovery does not occur within 4 weeks, all study drugs should be permanently discontinued. The 4-week recovery time window commences on the day of the planned treatment (see Table 8 and Table 9).

If avelumab treatment is delayed due to toxicities potentially attributable to avelumab and/or utomilumab (eg, pneumonitis or hypothyroidism), azacitidine administration does not need to be delayed. If azacitidine treatment is delayed due to toxicities potentially attributable to azacitidine, administration of avelumab and utomilumab does not need to be delayed.

5.5.4.2. Dose Reductions for Avelumab and Utomilumab

Dose reductions are not permitted for avelumab and utomilumab.

5.5.4.3. Dose Interruptions for Azacitidine

Azacitidine dosing interruption is not allowed within a cycle unless an unacceptable or unexpected azacitidine related toxicity occurs (eg, renal failure). In this case, azacitidine dosing may be resumed following the implementation of the dose interruption guidelines detailed in this section.

If, for unforeseen circumstances, (for reasons other than toxicity, eg, emergency surgery) the patient omits a dose of azacitidine within a cycle, the dose may be given in the same cycle if no more than a 2-day delay has occurred, and the patient remains likely to obtain clinical benefit.

The recommended azacitidine, utomilumab, and avelumab treatment modifications for treatment-related hematologic toxicities are described in Table 8.

5.5.4.4. Management of Immune-Related Adverse Events

The same irAEs management guidelines outlined in Section 5.5.3.3 and Table 5 apply to avelumab and utomilumab.

Any adverse event suspected to be immune-related should be managed according to the guidance for management of irAEs (see Table 5).

In the case of potential irAEs, in addition to the management related to avelumab and utomilumab therapy, azacitidine doses may also be modified or interrupted based on the guidance provided for avelumab/utomilumab/azacitidine combination toxicity management, product labeling, and institutional guidelines according to the Investigator's best medical judgment.

5.5.4.5. Management of Infusion-Related Reactions

5.5.4.6. Avelumab and Utomilumab

Guidelines for the management of avelumab infusion-related reactions are outlined in Section 5.5.2. The same management guidelines for avelumab infusion-related reactions are also applicable to utomilumab.

5.5.4.7. Management of Tumor Lysis Syndrome

Avelumab and utomilumab are both associated with a potential risk of tumor lysis syndrome. In the event that this occurs patients should be treated per local guidelines, referencing the recommended management algorithm published by Howard et al. (see Figure 4).

Table 8. Treatment Arm B (Azacitidine, Avelumab, and Utomilumab) Treatment Modifications for Investigational Product-Related Hematologic Toxicities

Hematologic Toxicity (Platelets and Neutrophils only) (NCI CTCAE v. 4.03)	Azacitidine	Avelumab	Utomilumab
Grade 1	Continue per schedule.	Continue per schedule.	Continue per schedule.
Grade 2	Continue per schedule.	Continue per schedule.	Continue per schedule.
Grade 3	Hold treatment up to 4 weeks until Grade ≤1, or baseline then rechallenge. Permanent discontinuation if recurrence of Grade 3 (Unless recovers to Grade ≤1, or baseline within 7 days following appropriate medical management).	Hold treatment up to 4 weeks until Grade ≤1, or baseline then rechallenge. Permanent discontinuation if recurrence of Grade 3 (Unless recovers to Grade ≤1, or baseline within 7 days following appropriate medical management).	Hold treatment up to 4 weeks until Grade ≤1 or baseline, then rechallenge. Permanent discontinuation if recurrence of Grade 3 (Unless recovers to Grade ≤1 or baseline within 7 days following appropriate medical management).
Grade 4	Permanent discontinuation. (Unless resolve to Grade ≤1 or baseline within 7 days following appropriate medical management).	Permanent discontinuation. (Unless resolve to Grade ≤1, or baseline within 7 days following appropriate medical management).	Permanent discontinuation. (Unless resolved to Grade ≤1 or baseline within 7 days following appropriate medical management).

Table 9. Treatment Arm B (Azacitidine, Avelumab, and Utomilumab) Treatment Modifications for Investigational Product-Related Non-Hematologic Toxicities

Non-Hematologic Toxicity (NCI CTCAE v. 4.03)	Azacitidine	Avelumab	Utomilumab
Renal Toxicity - Serum creatinine or BUN ≥2x baseline value or serum bicarbonate level <20 mmol/L.	Grade 2: Hold dosing up to 4 weeks. If laboratory tests return to baseline or to Grade ≤1, resume treatment If Grade 2 recurs or worsen to Grade 3 or Grade 4, permanently discontinue If Grade 3 or Grade 4, permanently discontinue	See "Other - Grade 2" in this table.	See "Other - Grade 2" in this table.
Other - Grade 1	Continue per schedule.	Continue per schedule.	Continue per schedule.
Other - Grade 2	As per avelumab.	Hold treatment up to 4 weeks until the toxicity resolves to Grade ≤1 Exceptions: • Transient flu-like symptoms or fever, which are controlled by medical management. • Transient fatigue, local reactions, or headache, that resolve to ≤ Grade 1. • Nausea or vomiting controlled by adequate medical management. Amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. • Tumor flare. • Single non-hematologic laboratory values that do not have any clinical correlates, and resolve to ≤ Gr 1 within 7 days following appropriate medical management. • Endocrine deficiencies that are manageable by hormone replacement therapy.	As per avelumab.
Other - Grade 3	As per avelumab.	Hold treatment up to 4 weeks until the toxicity resolves to Grade ≤1.	As per avelumab.

Non-Hematologic Toxicity (NCI CTCAE v. 4.03)	Azacitidine	Avelumab	Utomilumab
		If Grade 3 recurs: permanently discontinue. Exceptions: • Transient flu-like symptoms or fever, which are controlled by adequate medical management. • Transient fatigue, local reactions, or headache, that resolve to ≤ Grade 1. • Nausea or vomiting resolve to Grade ≤1 in <72 hours following the initiation of adequate medical management. • Tumor flare. • Single non-hematologic laboratory values that are out of the normal range that do not have any clinical correlates, and resolve to ≤ Grade 1 within 7 days following appropriate medical management. • Endocrine deficiencies that are manageable by hormone replacement therapy.	
Other - Grade 4	As per avelumab.	Permanent discontinuation. Exceptions: Single non- hematological laboratory values that do not have clinical correlates, and resolve within ≤7 days following appropriate medical management.	As per avelumab.
irAEs	Continue dosing if Grade ≤2, however, dosing may be withheld until irAE resolution, and the time of avelumab and utomilumab dosing recommence according to the Investigator's judgment. For Grade ≥3 permanently discontinue.	See Section 5.5.2.2.	See Section 5.5.2.2.

5.5.5. Recommended Treatment Modifications for Phase 1b Treatment Arm C

5.5.5.1. Dose Modifications for Avelumab, Bendamustine, and Rituximab

Dose modifications for avelumab, bendamustine, and rituximab in the case of drug-related toxicities are detailed in Table 11 and Table 12. If a toxicity can be attributed to just one of the drugs in the combination, dose modifications may be performed independently for each drug. In instances where it is not possible to attribute a toxicity to just one of the three drugs, the avelumab treatment modifications detailed in Table 11 and Table 12 (see below) must be followed for all 3 drugs.

5.5.5.2. Treatment Delays

Treatment cannot be administered until ANC $\geq 1.0 \times 10^9$/L, platelets $\geq 75 \times 10^9$/L, and non-hematologic toxicities have returned to baseline or Grade ≤ 1 severity.

The administration of the study drug treatments at the beginning of each cycle may be delayed for a maximum duration of 4 weeks to allow for ANC and platelet count recovery. In the event that recovery does not occur within two weeks, all study drugs must be permanently discontinued. The 4 weeks recovery window commences on the day of the planned treatment

Myelosuppression is a known side effect of bendamustine therapy. Prophylactic use of G-CSF in all cycles for patients ≥60 years old randomized to arm C is mandatory (and arm D in Phase 3, if arm C is selected to advance to the Phase 3 component). The use of colony stimulating factor for the treatment of neutropenia is allowed in any cycle, according to NCCN guidelines.[1] In addition, patients may receive erythropoietin, iron supplements, and/or transfusions as clinically indicated for the management of anemia.

If avelumab treatment in the next cycle is delayed due to toxicities potentially attributable to avelumab (eg, pneumonitis or thyroid disease), bendamustine administration and rituximab administration does not need to be delayed. If the start of rituximab administration in the next cycle is delayed due to toxicities attributable to rituximab, administration of bendamustine and avelumab does not need to be delayed. If the start of bendamustine administration in the next cycle is delayed due to toxicities attributable to bendamustine, avelumab and rituximab administration does not need to be delayed.

5.5.5.3. Dose Reductions for Rituximab and Avelumab

No dose reductions are permitted for rituximab or avelumab.

5.5.5.4. Dose Reductions for Bendamustine

Following dose interruption or cycle delay due to toxicity, the bendamustine dose may need to be reduced when treatment is resumed according to the grade of the toxicity.

Dose reduction of bendamustine by 1 dose level is allowed depending on the nature and grade of the toxicity (see Table 10).

Once the bendamustine dose has been reduced, it should be administered at the same reduced dose level in all subsequent cycles. No dose re-escalation of bendamustine is allowed following dose reduction.

Table 10. Bendamustine Dose Reduction

Bendamustine (mg/m^2)
90
60

Patients requiring more than 1 dose reduction of bendamustine should permanently discontinue treatment, but may continue treatment with avelumab and rituximab.

5.5.5.5. Management of Immune-Related Adverse Events

The irAE management guidelines in Table 5 apply to both avelumab and utomilumab.

Any event suspected to be immune-related should be managed according to the guidance for management of irAEs (see Table 5). In the case of a potential irAE, in addition to the management related to avelumab and utomilumab therapy, rituximab doses may also be modified or interrupted based on the guidance for the avelumab/utomilumab/rituximab combination toxicity management section, product labeling, and institutional guidelines according to Investigator's clinical judgment.

5.5.5.6. Management of Infusion-Related Reactions

5.5.5.7. Avelumab

Guidelines for the management of avelumab infusion-related reactions are detailed in Section 5.5.2.

5.5.5.8. Rituximab

Rituximab can cause severe, including fatal, infusion reactions. Severe reactions typically occur during the first infusion, with a time of onset of 30-120 minutes.

Patients with pre-existing cardiac or pulmonary conditions, those who have experienced prior cardio-pulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq 25{,}000/mm^3$), should be closely monitored.

5.5.5.9. Bendamustine

Infusion reactions to bendamustine are common. Symptoms include: fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, especially in the second and subsequent cycles of therapy. Patients should be asked about symptoms suggestive of infusion reactions following their first cycle of therapy. As per the bendamustine label, in order to mitigate bendamustine infusion-related reactions a pre-medication regimen including antihistamines, antipyretics and corticosteroids should be considered in subsequent cycles in patients who have previously experienced Gr 1 or Gr 2

infusion reactions. Discontinuation should be considered in patients with ≥Gr 3 infusion reactions.

5.5.5.10. Management of Tumor Lysis Syndrome

Avelumab and rituximab are associated with a potential risk of tumor lysis syndrome. See Figure 4.

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12-24 hours after the first infusion of rituximab. A high number of circulating malignant cells (≥25,000/mm^3) or high tumor burden confers a greater risk of TLS.

Tumor lysis syndrome associated with bendamustine treatment has occurred in patients in clinical trials and in post-marketing reports. The onset tends to be within the first treatment cycle of bendamustine and, without intervention, may lead to acute renal failure and death. Preventive measures include vigorous hydration and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of bendamustine therapy. However, there may be an increased risk of severe skin toxicity when bendamustine and allopurinol are administered concomitantly.

In the event of Tumor Lysis Syndrome, patients should be treated per local guidelines, referencing the recommended management algorithm published by Howard et al. (see Figure 4).

Table 11. Treatment Arm C (Bendamustine, Rituximab, and Avelumab) Treatment Modifications for Investigational Product-Related Hematologic Toxicities

Hematologic Toxicity (Platelets and Neutrophils only) (NCI CTCAE v. 4.03)	Bendamustine	Rituximab	Avelumab
Grade 1	Continue per schedule.	Continue per schedule.	Continue per schedule.
Grade 2	If ANC Grade 2 ($\geq$1.0 x10^9/L), continue per schedule, if platelets Grade 2 hold until $\leq$ Grade 1 ($\geq$75 x10^9/L).	If ANC Grade 2 ($\geq$1.0 x10^9/L), continue per schedule, if platelets Grade 2 hold until $\leq$ Grade 1 ($\geq$75 x10^9/L).	If ANC Grade 2 ($\geq$1.0 x10^9/L), continue per schedule, if platelets Grade 2 hold until $\leq$ Grade 1 ($\geq$75 x10^9/L).
Grade 3	Hold treatment until Grade $\leq$2 following appropriate medical management then rechallenge at the same dose level	Hold treatment until Grade $\leq$2 following appropriate medical management then rechallenge	Hold treatment until Grade $\leq$2 following appropriate medical management then rechallenge
Grade 4	Hold treatment until Grade $\leq$2 following appropriate medical management then rechallenge at the next lower dose level	Hold treatment until Grade $\leq$2 following appropriate medical management then rechallenge	Hold treatment until Grade $\leq$2 following appropriate medical management then rechallenge

Table 12. Treatment Arm C (Bendamustine, Rituximab, and Avelumab) Treatment Modifications for Investigational Product-Related Non-Hematologic Toxicities

Non-Hematologic Toxicity (NCI CTCAE v. 4.03)	Bendamustine	Rituximab	Avelumab
Progressive multi-focal leuco-encephalopathy (PML) - any Grade	Permanently discontinue	Permanently discontinue	Permanently discontinue
Viral Hepatitis - any Grade	Permanently discontinue	Permanently discontinue	Permanently discontinue
Grade $\geq$3 infection	Permanently discontinue	Permanently discontinue	Permanently discontinue
Grade $\geq$3 muco-cutaneous reactions including paraneoplastic pemphigus, Steven-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis	Permanently discontinue	Permanently discontinue	Permanently discontinue For dermatologic toxicity see irAEs management guidelines (Table 5).
Any Grade $\geq$3 liver function test abnormality	Permanently discontinue	Permanently discontinue	Permanently discontinue. See irAEs management guidelines (Table 5).
Grade $\geq$3 cardiac arythmia	Permanently discontinue	Permanently discontinue	Permanently discontinue
Grade $\geq$3 renal toxicity (eg, acute kidney injury,	Permanently discontinue	Permanently discontinue	Permanently discontinue

Non-Hematologic Toxicity (NCI CTCAE v. 4.03)	Bendamustine	Rituximab	Avelumab
urine output decreased)			
Other - Grade 1	Continue per schedule	Continue per schedule	Continue per schedule
Other - Grade 2	Hold treatment until the toxicity resolves to Grade ≤1 then rechallenge at the same dose level. If skin reactions occur and are progressive, bendamustine should be discontinued.	As per avelumab.	Hold treatment until the toxicity resolves to Grade ≤1. Exceptions: • Transient flu-like symptoms or fever, which are controlled by medical management. • Transient fatigue, local reactions, or headache, that resolve to ≤ Gr 1 • Nausea or vomiting controlled by medical management. • Amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. • Tumor flare. • Single non-hematologic laboratory values that do not have any clinical correlates, and resolve to ≤ Gr 1 within 7 days following appropriate medical management. • Endocrine deficiencies that are manageable by hormone replacement therapy.
Other - Grade 3	Hold treatment up to 4 weeks until the toxicity resolves to Grade ≤1 then rechallenge. Rechallenge after the First episode: same dose level. <u>Rechallenge after the Second episode</u>: decrease bendamustine by 1 dose level. <u>Third episode</u>: permanently discontinue. If skin reaction occur and are progressive, bendamustine should be discontinued.	As per avelumab.	Hold treatment up to 4 weeks until the toxicity resolves to Grade ≤1. If Grade 3 recurs, permanently discontinue. Exceptions: • Transient flu-like symptoms or fever, which are controlled by medical management. • Transient fatigue, local reactions, or headache, that resolve to ≤ Grade 1. • Nausea or vomiting resolved to Grade ≤1 in <72 hours following the initiation of adequate medical management. • Tumor flare. • Single non-hematologic laboratory values that are out of the normal range, that do not have any clinical

Non-Hematologic Toxicity (NCI CTCAE v. 4.03)	Bendamustine	Rituximab	Avelumab
			correlate, and resolve to ≤ Grade 1 within 7 days following appropriate medical management. • Endocrine deficiencies that are manageable by hormone replacement therapy.
Other - Grade 4	Permanently discontinue for skin reaction For other toxicities: Hold treatment up to 4 weeks until the toxicity resolves to Grade ≤1 then rechallenge. Rechallenge after the First episode: decrease bendamustine by 1 dose level. Second episode: permanently discontinue.	As per Avelumab.	Permanent discontinuation. Exceptions: Single non-hematological laboratory values that do not have clinical correlates, and resolve within 7 days following appropriate medical management.
irAEs	Continue dosing if Grade ≤2, however, dosing may be withheld until irAE resolution and the time of avelumab dosing recommence according to Investigator judgment. For Grade ≥3 permanently discontinue.	See Section 5.5.2.2.	See Section 5.5.2.2.
Infusion-related reactions	See Section 5.5.5.6.	Medical management (eg, glucocorticoids, epinephrine, bronchodilators, and oxygen) for infusion reactions may be given as clinically indicated. Depending on the severity of the infusion reaction and the required interventions, rituximab should be temporarily or permanently discontinued. The infusion must be continued at a minimum of 50% reduction in rate following symptoms resolution.	See Section 5.5.5.6.

5.6. Recommended Treatment Modifications for Phase 3

5.6.1. Experimental Treatment Arm D

The experimental treatment arm to be tested in the Phase 3 will be selected at the end of the Phase 1b. The same treatment modification guidelines will apply to the experimental treatment arms in both the Phase 1b and 3. For the relevant treatment modification guidelines see Section 5.5.

5.6.2. Control Treatment Arm E (Rituximab/Bendamustine)

Dose modifications for bendamustine and rituximab for drug-related toxicities are detailed in Table 14 and Table 15. If a toxicity may be attributed to just one of the drugs in the combination, dose modifications can be performed independently for each drug.

5.6.3. Cycle Delays for Bendamustine and Rituximab Drug-Related Toxicities

A new treatment cycle cannot start until ANC $\geq 1.0 \times 10^9$/L, platelets $\geq 75 \times 10^9$/L, and non-hematologic toxicities have returned to baseline or Grade ≤ 1 severity.

The administration of the study drug treatments at the beginning of each cycle may be delayed for a maximum duration of 4 weeks to allow for ANC and platelet count recovery. In the event that recovery does not occur within 4 weeks, all study drugs will be permanently discontinued. The 4 weeks recovery window commences on Day 1 of the planned cycle.

Myelosuppression is a known side effect of bendamustine therapy. Prophylactic use of G-CSF in all cycles for patients ≥60 years old randomized to arm C is mandatory (and arm D in Phase 3, if arm C is selected to advance to the Phase 3 component). The use of colony-stimulating factor for the treatment of neutropenia is allowed in any cycle, per NCCN guidelines.[1] Additionally, patients may receive erythropoietin, iron supplements, and/or transfusions (as clinically indicated) for the management of anemia.

If the start of rituximab administration in the next cycle is delayed due to toxicities attributable to rituximab, administration of bendamustine should not be delayed. If the start of bendamustine administration in the next cycle is delayed due to toxicities attributable to bendamustine, rituximab administration should not be delayed.

5.6.4. Dose Reductions for Rituximab

Dose reductions are not permitted for rituximab.

5.6.5. Dose Reductions for Bendamustine

Following dose interruption or cycle delay due to toxicity, the bendamustine dose may need to be reduced when treatment is resumed, depending on the grade of the toxicity.

Once the bendamustine dose has been reduced, it should be administered at the reduced dose level in all subsequent cycles. No dose re-escalation of bendamustine is allowed.

Table 13. Bendamustine Dose Reduction Levels

Bendamustine (mg/m^2)
120
90
60

Patients requiring more than 2 dose reductions of bendamustine should permanently discontinue treatment with bendamustine, and rituximab.

5.6.6. Management of Infusion-Related Reactions

5.6.7. Rituximab

Rituximab can cause severe, including fatal, infusion reactions.

Severe reactions typically occur during the first infusion, with a time of onset of 30-120 mins.

Patients with pre-existing cardiac or pulmonary conditions, those who have experienced prior cardio-pulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq$25,000/mm^3) should be closely monitored.

5.6.8. Bendamustine

Infusion reactions to bendamustine are common. Symptoms include: fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, especially in the second and subsequent cycles of therapy. Patients should be asked about symptoms suggestive of infusion reactions following their first cycle of therapy. As per the bendamustine label, in order to mitigate bendamustine infusion-related reactions a pre-medication regimen including antihistamines, antipyretics and corticosteroids should be considered in subsequent cycles in patients who have previously experienced Gr 1 or -2 infusion reactions. Discontinuation should be considered in patients with $\geq$ Gr 3 infusion reactions.

5.6.9. Management of Tumor Lysis Syndrome

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12-24 hours after the first infusion of rituximab. A high number of circulating malignant cells ($\geq$25,000/mm^3) or high tumor burden confers a greater risk of TLS. A high number of circulating malignant cells ($\geq$25,000/mm^3) or high tumor burden confers a greater risk of TLS. Tumor lysis syndrome associated with bendamustine treatment has occurred in patients in clinical trials, and in post-marketing reports. The onset tends to be within the first treatment cycle of bendamustine and, without intervention, may lead to acute renal failure and death. Preventive measures include: vigorous hydration and close monitoring of blood chemistry (particularly potassium and uric acid levels). Allopurinol has also been used during the initiation of bendamustine therapy. However, there may be an increased risk of severe skin toxicity when bendamustine and allopurinol are administered concomitantly.

In the event that Tumor Lysis Syndrome occurs, patients should be treated per local guidelines, and the recommended management algorithm published by Howard et al. (see Section 5.5.2.1 and Figure 4).

Table 14. Treatment Arm E: (Bendamustine and Rituximab) Treatment Modifications for Drug-Related Hematologic Toxicities

Toxicity (Platelets and Neutrophils only)	Bendamustine Dosing at Start of the Next Cycle	Rituximab Dosing at Start of the Next Cycle
Grade 1	Continue per schedule.	Continue per schedule.
Grade 2	If ANC Grade 2 (≥1.0 x10^9/L), continue per schedule, if platelets Grade 2 hold until ≤ Grade 1 (≥75 x10^9/L).	If ANC Grade 2 (≥1.0 x10^9/L), continue per schedule, if platelets Grade 2 hold until ≤ Grade 1 (≥75 x10^9/L).
Grade 3	Delay dosing until ANC ≥1.0 x 10^9/L and platelets ≥75 x 10^9/L.	Delay dosing until ANC ≥1.0 x 10^9/L and platelets ≥75 x 10^9/L.
Grade 4	Delay dosing until ANC ≥1.0 x 10^9/L and platelets ≥75 x 10^9/L. Once blood counts have improved, bendamustine can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. First episode: decrease by 1 dose level. Second episode: decrease by 1 additional dose level.	Delay dosing until ANC ≥1.0 x 10^9/L and platelets ≥75 x 10^9/L. Once blood counts have improved, Rituximab can be reinitiated at the discretion of the treating physician.

Table 15. Treatment Arm E: Treatment Modifications for Treatment-Related Non-Hematologic Toxicities

Non-HematologicToxicity (NCI CTCAE v. 4.03)	Bendamustine	Rituximab
Progressive multi-focal leuco-encephalopathy (PML) - any grade	Permanently discontinue.	Permanently discontinue.
Viral Hepatitis – any Grade	Permanently discontinue.	Permanently discontinue.
Grade ≥3 infection	Permanently discontinue.	Permanently discontinue.
Grade ≥3 muco-cutaneous reactions including paraneoplastic pemphigus, Steven-Johnson Syndrome, lichenoid dermatitis, vesciculobullous dermatitis, and toxic epidermal necrolysis	Permanently discontinue.	Permanently discontinue.
Grade ≥3 renal toxicity (rising serum creatinine acute kidney injury, urine output decreased (oliguria)	Permanently discontinue.	Permanently discontinue.
Any Grade ≥3 liver function test abnormality	Withold bendamustine. Once toxicity has recovered to	Rituximab dosing must be withheld for any liver function test AEs Grade ≥3 (even if

Non-HematologicToxicity (NCI CTCAE v. 4.03)	Bendamustine	Rituximab
	≤ Gr ≤1, bendamustine can be re-initiated at the lower dose level. If Gr 3 toxicity recurs, once toxicity has recovered to ≤ Gr ≤ 1 bendamustine should be decreased by 1 dose level. Bendamustine should be discontinued at the third recurrence.	asymptomatic) until the values return to baseline or to Gr ≤1. In cases of potential liver injury, a consultation with a hepatologist is mandatory in the event that a decision be made to initiate treatment with anti-inflammatory medications.
Other - Grade 1	Continue per schedule.	Continue per schedule.
Other - Grade 2	Withold bendamustine. Once toxicity has recovered to Gr ≤1, bendamustine can be re-initiated at the same dose level. If skin reactions occur and are progressive, bendamustine should be discontinued.	If the toxicity resolves to Gr ≤1 by the time of the next administration, treatment may continue. If the toxicity does not resolve to Gr ≤1 by the time of the next administration despite appropriate medical management, the next infusion should be omitted. Once the toxicity has recovered to Gr ≤1, rituximab can be re-initiated. If skin reactions occur and are progressive, both bendamustine and rituximab should be discontinued.
Other - Grade 3	Withold bendamustine. Once the toxicity has recovered to Gr ≤1, bendamustine can be reinitiated at a lower dose level. If Gr 3 toxicity recurs, once non-hematological toxicity has recovered to Gr ≤1, bendamustine should be decreased by 1 dose level. Bendamustine should be discontinued at third recurrence. If skin reactions occur and are progressive, bendamustine should be discontinued.	If the toxicity resolves to Grade ≤1 by the time of the next administration, treatment may continue. If the toxicity does not resolve to Grade ≤1 by the time of the next administration (despite appropriate medical management), the next infusion should be omitted. Once the toxicity has recovered to Grade ≤1, rituximab can be re-commenced. Rituximab should be discontinued at the third recurrence.

Non-HematologicToxicity (NCI CTCAE v. 4.03)	Bendamustine	Rituximab
Other - Grade 4	Permanently discontinue for skin reactions. For other non-hematologic toxicities, withold bendamustine. Once toxicity has recovered to Gr ≤1, bendamustine can be reinitiated at a lower dose level. If Gr 4 toxicity recurs, once toxicity has recovered to Gr ≤1, bendamustine should be decreased by 1 dose level. Bendamustine should be discontinued following a third recurrence.	If the toxicity resolves to Gr ≤1 by the time of the next administration, treatment may continue. If the toxicity does not resolve to Gr ≤1 by the time of the next administration (despite appropriate medical management), the next infusion should be omitted. Once it has recovered to Gr ≤1, rituximab may be re-initiated. Rituximab should be discontinued following a third recurrence. Rituximab dosing must be withheld for any liver function test AEs Gr ≥3, even if asymptomatic, until the values return to baseline or to Gr ≤1. In cases of potential liver injury, a consultation with a hepatologist is mandatory should a decision be made to initiate treatment with anti-inflammatory medications.
Infusion-related reactions	See Section 5.6.6.	Medical management (eg, administration of glucocorticoids, epinephrine, bronchodilators, and oxygen) for infusion reactions may be given as clinically indicated. Depending on the severity of the infusion reaction and the required interventions, rituximab should be temporarily or permanently discontinued. The infusion must be continued at a minimum of 50% reduction in rate following symptoms resolution.

5.7. Investigator's Choice Treatment Arm E (Rituximab/Gemcitabine/Oxaliplatin)

The recommended dose modifications for gemcitabine, oxaliplatin and rituximab in the event of drug-related toxicities are detailed in Table 17 and Table 18.

5.7.1. Cycle Delays

A new cycle cannot start until ANC $\geq 1.0 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and non-hematologic toxicities have returned to baseline or Grade ≤ 1 severity.

The administration of the study drug treatments may be delayed for a maximum duration of 4 weeks to allow for ANC and platelet count recovery. In the event that count recovery does not occur within two weeks, all three study drugs will be permanently discontinued. The 4 weeks recovery window commences on Day 1 of the planned cycle.

If the start of rituximab administration in the next cycle is delayed due to toxicities attributable to rituximab, the administration of gemcitabine and oxaliplatin should not be delayed.

If the start of gemcitabine administration in the next cycle is delayed due to toxicities attributable to gemcitabine, administration of rituximab and oxaliplatin should not be delayed.

If the start of oxaliplatin administration in the next cycle is delayed due to toxicities attributable to oxaliplatin, administration of rituximab and gemcitabine should not be delayed.

5.7.2. Dose Reductions for Oxaliplatin

Following dose interruption or cycle delay due to non-hematological toxicities, the oxaliplatin dose may need to be reduced when treatment is resumed.

Dose reduction of oxaliplatin by 1 dose level will be allowed depending on the nature and grade of the toxicity encountered (see Table 16).

Once the oxaliplatin dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level. No dose re-escalation of oxaliplatin is allowed following a dose reduction.

Patients requiring more than 2 dose reductions of oxaliplatin should permanently discontinue treatment with oxaliplatin, but may continue treatment with rituximab and gemcitabine.

Table 16. Oxaliplatin Dose Reduction Levels

Oxaliplatin (mg/m^2)
100
75

5.7.3. Dose Reductions for Gemcitabine

No dose reductions for gemcitabine are permitted, however delays are permitted as indicated in Section 5.7.9.

5.7.4. Dose Reductions for Rituximab

No dose reductions for rituximab are permitted.

5.7.5. Management of Infusion-Related Reactions

5.7.6. Rituximab

Rituximab can cause severe, including fatal, infusion reactions.

Severe reactions typically occur during the first infusion with a time of onset of 30-120 minutes.

Patients with pre-existing cardiac or pulmonary conditions, those who have experienced prior cardio-pulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq$25,000/mm^3) should be closely monitored.

5.7.7. Oxaliplatin

Special surveillance should be ensured for patients with a history of allergic manifestations to other platinum-containing products. In case of anaphylactic manifestations, the infusion should be interrupted immediately, and appropriate symptomatic treatment commenced. Re-administration of oxaliplatin in such patients is contra-indicated. Cross-reactions, which may be fatal, have been reported with all platinum compounds. In case of oxaliplatin extravasation, the infusion must be stopped immediately, and the usual institutional guidelines for symptomatic treatment initiated.

5.7.8. Tumor Lysis Syndrome

See Section 5.6.9.

5.7.9. Treatment Modifications for Hematologic Toxicities

Dose reduction is not anticipated in the event of hematologic toxicity, however, dosing of the 3 drugs should be delayed until neutrophil and platelet counts have fully recovered (as indicated above).

Table 17. Treatment Arm E (Gemcitabine, Oxaliplatin, and Rituximab). Treatment Modifications for Drug-Related Hematologic Toxicities

HematologicToxicity (Platelets and Neutrophils only) (NCI CTCAE v.4.03)	**Gemcitabine**	**Oxaliplatin**	**Rituximab**
Grade 1	Continue per schedule.	Continue per schedule.	Continue per schedule.
Grade 2 Neutrophils	Continue per schedule.	Continue per schedule.	Continue per schedule.
Grade 2 (platelets only)	Delay administration until the platelet counts have recovered to $\geq$100 x 10^9/L.	Delay administration until the platelet counts have recovered to $\geq$100 x 10^9/L.	Delay administration until the platelet counts have recovered to $\geq$100 x 10^9/L.
Grade 3 or Grade 4	Delay administration until counts have recovered to ANC $\geq$1000 x 10^9/L and platelet counts have recovered $\geq$100 x 10^9/L. <u>First episode</u>: Resume at same dose level. <u>Second episode</u>: Resume at same dose level. <u>Third episode</u>: Permanently discontinue.	Delay administration until counts have recovered to ANC $\geq$1000 x 10^9/L and platelet counts have recovered $\geq$100 x 10^9/L. <u>First episode</u>: Resume at same dose level. <u>Second episode</u>: Resume at same dose level. <u>Third episode</u>: Permanently discontinue.	Delay administration until counts have recovered to ANC $\geq$1000 x 10^9/L and platelet counts have recovered $\geq$100 x 10^9/L. <u>First episode</u>: Resume at same dose level. <u>Second episode</u>: Resume at same dose level. <u>Third episode</u>: Permanently discontinue.

Table 18. Treatment Arm E (Gemcitabine, Oxaliplatin, and Rituximab). Treatment Modifications for Drug-Related Non-Hematologic Toxicities

Non-HematologicToxicity (NCI CTCAE v. 4.03)	**Gemcitabine**	**Oxaliplatin**	**Rituximab**
Progressive multi-focal leuco-encephalopathy (PML) - any Grade	Permanently discontinue.	Permanently discontinue.	Permanently discontinue.
Hemolytic uremic syndrome (HUS) - any grade	Permanently discontinue.	Permanently discontinue.	Permanently discontinue.
Viral hepatitis - any grade	Permanently discontinue.	Permanently discontinue.	Permanently discontinue.
Grade $\geq$3 infection	See below recommendations for 'Other - Grade 3, Grade 4'	See below recommendations for 'Other - Grade 3, Grade 4'	Permanently discontinue.
Mucositis/stomatitis (with or without neutropenia)	See below recommendations for 'Other' according to	Delay next oxaliplatin treatment until recovery to Grade 1 or less and/or	See below recommendations for 'Other'

Non-HematologicToxicity (NCI CTCAE v. 4.03)	Gemcitabine	Oxaliplatin	Rituximab
	grade	the neutrophil count is ≥1.5 x 10^9/L. Then oxaliplatin dosing may be resumed at the same dose.	according to grade.
Grade ≥3 renal toxicity (eg, acute kidney injury, urine output decreased)	See below recommendations for 'Other - Grade 3, Grade 4'	See below recommendations for 'Other - Grade 3, Grade 4'	Permanently discontinue.
Any Grade ≥3 liver function test abnormality	See below recommendations for 'Other - Grade 3, Grade 4'	See below recommendations for 'Other - Grade 3, Grade 4'	Rituximab dosing must be withheld, even if the patient is asymptomatic, until the values return to baseline or to Gr ≤1, then rituximab dosing may be resumed at the same dose. In cases of potential liver injury, a consultation with a hepatologist is mandatory should a decision be made to initiate treatment with anti-inflammatory medications.
Grade ≥3 muco-cutaneous reactions including paraneoplastic pemphigus, Steven-Johnson syndrome, lichenoid dermatitis, vesciculobullous dermatitis, and toxic epidermal necrolysis	See below recommendations for "Other - Grade 3, Grade 4"	See below recommendations for "Other - Grade 3, Grade 4"	Permanently discontinue
Respiratory symptoms	In case of severe dyspnea, permanently discontinue	In case of unexplained respiratory symptom, any grade, such as non-productive cough, dyspnea, crepitations or pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigations exclude interstitial lung disease. If it is excluded, oxaliplatin dosing may be resumed at the same dose. If it is confirmed,	See below recommendations for "Other" according to grade

Non-HematologicToxicity (NCI CTCAE v. 4.03)	Gemcitabine	Oxaliplatin	Rituximab
		oxaliplatin must be permanently discontinued.	
Grade ≥3 cardiac arrhythmia	See below recommendations for "Other - Grade 3, Grade 4"	See below recommendations for "Other - Grade 3, Grade 4"	Permanently discontinue
Significant paresthesia lasting between 7 and 13 days after each administration of oxaliplatin	See below recommendations for "Other" according to grade	Dose must be reduced to 75 mg/m^2.	See below recommendations for "Other" according to grade
Abnormal neurological examination, or significant paresthesia lasting for ≥14 days	See below recommendations for "Other" according to grade	Oxaliplatin must be stopped until the symptoms improve and then restarted at a dose of 75 mg/m^2.	See below recommendations for "Other" according to grade
Pharyngeal dysesthesia	See below recommendations for "Other" according to grade	Increase duration of the oxaliplatin infusion from 2 hours to 6 hours.	See below recommendations for "Other" according to grade
Other - Grade 1	Continue per schedule.	Continue per schedule.	Continue per schedule.
Other - Grade 2	Delay administration in case of a clinically significant Grade ≥2 non-hematological toxicity. Once it has recovered to Grade ≤1, gemcitabine can be re-initiated at same dose level.	Delay administration in case of a clinically significant Grade ≥2 non-hematological toxicity. Once it has recovered to Grade ≤1, oxaliplatin can be re-initiated at same dose level.	If the toxicity resolves to Grade ≤1 by the time of the next administration, treatment may continue. If the toxicity does not resolve to Grade ≤1 by the time of the next administration despite appropriate medical treatment, the next infusion should be omitted. Once it has recovered to Grade ≤1, rituximab can be re-initiated.
Other - Grade 3, Grade 4	Delay administration in case of a clinically significant Grade ≥2 non-hematological toxicity. Once the toxicity has recovered to Grade ≤1, gemcitabine may be	Delay administration in case of a clinically significant Grade ≥2 non-hematological toxicity. Once the toxicity has recovered to Grade ≤1, oxaliplatin may be	If the toxicity resolves to Grade ≤1 by the time of the next administration, treatment may continue. If the toxicity does not resolve to

Non-HematologicToxicity (NCI CTCAE v. 4.03)	Gemcitabine	Oxaliplatin	Rituximab
	reinitiated at the same dose level. If toxicity recurs, once the toxicity has recovered to Grade ≤1 gemcitabine may be reinitiated at the same dose level. Gemcitabine should be discontinued following a third recurrence.	reinitiated at the same dose level. If toxicity recurs, once the toxicity has recovered to Grade ≤1 oxaliplatin may be reinitiated at the same dose level. Oxaliplatin should be discontinued following a third recurrence.	Grade ≤1 by the time of the next administration despite appropriate medical treatment, the next infusion should be omitted. Once it has recovered to Grade ≤1, rituximab can be re-commenced. Rituximab should be discontinued following a third recurrence.
Infusion-related reactions	As per institutional guidelines	See Section 5.7.5.	Medical management (eg, glucocorticoids, epinephrine, bronchodilators, and oxygen) for infusion reactions may be given as clinically indicated. Depending on the severity of the infusion reaction and the required interventions, rituximab should be temporarily or permanently discontinued. The infusion must be continued at a minimum of 50% reduction in rate following symptoms resolution.

5.8. Investigational Product Storage

The Investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparators and/or marketed products, are stored in a secured area with controlled access under required 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 IP Manual, package insert, or equivalent for storage conditions of the product once reconstituted and/or diluted.

Storage conditions stated in the SRSD (eg, investigator's brochure [IB], core data sheet [CDS], United States package insert [USPI], summary of product characteristics [SPC], or local product document [LPD]) 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 available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. 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 to Pfizer 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 Pfizer. Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation.

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

Site staff will instruct patients on the proper storage requirements for take home investigational products.

5.9. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.9.1. 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 Investigator 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.

5.10. Concomitant Treatments

Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period, except for administration of inactivated vaccines (for example, inactivated influenza vaccine). If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, permanent discontinuation from study therapy may be required. The Investigator should consult with the Sponsor about individual cases. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the patient.

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

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment (at Days 30, 60, and 90 post-treatment +3 days). All concomitant medications and Non Drug Supportive Interventions should be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non drug supportive interventions (eg, transfusions).

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

5.10.1. Concomitant Radiotherapy

Local radiotherapy of isolated lesions with palliative intent (eg, bleeding, pain, compression) is acceptable; however, all attempts should be made to rule in or out disease progression. Palliative radiotherapy is permitted if considered medically necessary by the treating physician. If palliative radiotherapy is needed to control pain, the site(s) of disease causing pain should also be present at baseline; otherwise, painful lesions requiring radiotherapy will be considered as a sign of disease progression.

5.10.2. Supportive Care Guidelines

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

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 5 Avelumab Management of Immune related Adverse Events;

- Anti inflammatory or narcotic analgesics may be offered as needed.

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

5.10.3. Concomitant Surgery

In case of surgical procedure, study treatment should be delayed. All attempts should be made to rule in or out disease progression. Re initiation should be discussed with the Sponsor.

5.10.4. Other Prohibited Concomitant Medications and Treatments

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 and utomilumab.

- Radiation therapy (with the exception noted above in Section 5.10.1).

- Immunosuppressive drugs, unless otherwise indicated for the treatment of irAEs (see Table 5 above and Clarification about Steroid Use below).

- Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period; however, the administration of inactivated vaccines (eg, influenza vaccine) is allowed during the study.
- Herbal remedies or vitamins used as anti-cancer treatments.
- Herbal remedies with immunostimulating properties (eg, mistle toe extract) or known to potentially interfere with major organ function (eg, hypericin).
- Daily intake over 2 grams acetaminophen/paracetamol.

Clarifications About Steroid Use with Avelumab: Data have indicated that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[86,87] Furthermore, as with all immunotherapies intended to augment cell mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA-4 compounds have indicated that short-term use of steroids may be employed without compromising clinical outcomes.[88] Therefore, the use of steroids during this trial is restricted as follows:

- Premedication: steroid inclusion in the premedication regimen for bendamustine is allowed as described in the Schedule of Activities.
- Therapeutic use: for the treatment of infusion related reactions and irAEs, steroids are permitted according to the modalities indicated in Table 5: Avelumab Management of Immune-Related Adverse Events.
- Physiologic use: steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.
- Prophylactic use prior to CT (Computerized Tomography) or MRI (Medical Resonance Imaging).
- Intranasal, inhaled topical steroids, eye drops, or local steroid injection (eg, intra-articular injection) are allowed.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures in the Phase 1b and Phase 3 components of the study, see Table 1 and Table 2. All patients must sign an informed consent document prior to undergoing any study-specific procedures.

To allow for additional flexibility in scheduling patient visits and procedures, Screening and first day of the first study cycle procedures may be completed on the same day. See the Schedule of Activities. However, screening assessments for *eligibility* MUST have already been completed before the patient is randomized.

6.2. Treatment Period

For treatment period procedures, see Schedule of Activities.

Treatment schedules are comprised of 28-day cycles. To allow for patient and Investigator schedules, holidays, and weather or other emergencies requiring clinical facilities to be closed, all patient visits may be performed as noted in Schedule of Activities. For details of on-treatment procedures and visit time window schedules, see Phase 1b (Table 1) and Phase 3 (Table 2) Schedule of Activities.

6.3. Follow-Up Visits

For follow-up procedures, see Schedule of Activities.

6.4. Patient Withdrawal

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

Reasons for withdrawal of study treatment may include:

1. Objective disease progression. However, patients with disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue study treatment, provided that the treating physician, after discussion with the Sponsor, has determined that the benefit/risk for doing so is favorable (See Section 5.4.8 for details and exceptions);

2. Global deterioration of health status requiring discontinuation;

3. Unacceptable toxicity. If the unacceptable toxicity is attributed to one of the two study treatments, the investigator (in discussion with the Sponsor) may continue treatment with the other study treatment;

4. Pregnancy;

5. Significant protocol violation;

6. Lost to follow-up;

7. Patient refused further treatment;

8. Study terminated by Sponsor;

9. Death.

Reasons for withdrawal from study follow-up may include:

1. Study terminated by Sponsor;
2. Lost to follow-up;
3. Refused further follow-up;
4. Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request 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 the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the 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. Patients in the Phase 3 component of the study who have disease progression per Investigator's assessment, should remain on treatment until PD is confirmed by BICR. For details, refer to Table 1 and Table 2.

7.1. Safety Assessment

Safety assessment will include collection of AEs, Serious Adverse Events (SAEs), vital signs, and physical examinations, ECG (12-Lead), echocardiogram (ECHO) or multiple gated acquisition (MUGA) scans, laboratory assessments, including pregnancy tests and verification of concurrent medications.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum pregnancy test with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting administration of study

treatment, once at the start of screening and once at the baseline visit immediately before starting the investigational product. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will then be required at the baseline visit before the patient may receive the investigational product. Urine pregnancy tests with sensitivity of at least 25 mIU/mL, will also be routinely repeated at every treatment cycle during the active treatment period, at the end of study treatment, at 30, 60 and 90 days during safety follow up period, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Urine test kits with sensitivity of at least 25 mIU/mL may be utilized at every treatment cycle during the study in accordance with instructions provided in its package insert. Patients of childbearing potential who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, A negative qualitative serum pregnancy test conducted at a certified laboratory). Additional pregnancy tests may also be undertaken if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product but may remain in the study.

7.1.2. Laboratory Safety Assessments

Hematology, blood chemistry, and urinalysis will be collected at time points described in the Schedule of Activities and analyzed at local laboratories. They may also be performed when clinically indicated. The required laboratory tests are listed in Table 19.

Table 19. Required Laboratory Tests

Hematology	Chemistry Panel (* denotes core chemistry test)	Urinalysis	Coagulation Tests	Pregnancy Tests
Hemoglobin	ALT*	Urine dipstick for protein, glucose, and blood	PT or INR	For female patients of childbearing potential, serum or urine
Platelets	AST*		aPTT	
WBC	Alkaline Phosphatase*			
Absolute Neutrophils	Sodium*			
Absolute Lymphocytes	Potassium*			
Absolute Monocytes	Magnesium*			
Absolute Eosinophils	Chloride*			
Absolute Basophils	Calcium*			
	Total Bilirubin*			
	BUN or Urea*			
	Creatinine*			
	Glucose (non-fasted)*			
	Phosphorus or Phosphate*			
	Albumin			
	Total Protein			
	Uric Acid			
	Amylase*			

	Gamma glutamyl transferase (GGT)			
	Cholesterol			
	Creatine kinase			
	C-reactive protein (CRP)			
	Lactate dehydrogenase (LDH)			
	Lipase*			
	Triglycerides			
	Hepatitis Tests: HBV, HCV testing			
	Thyroid Function Tests: TSH, free T4			
	Other Tests: ACTH			

For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, 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, HBV=hepatitis B virus, HCV=hepatitis C virus, INR=international normalized ratio, LDH=lactate dehydrogenase,TSH=thyroid-stimulating hormone, WBC=white blood cell

7.1.3. Electrocardiograms

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

All patients require a single ECG measurement at screening. On treatment ECGs will be performed pre- and post-infusion/SC dose on Day 1 of Cycles 1 and 2 and also on Day 16 of Cycle 1 (See Schedule of Activities). Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all other ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. For triplicate ECGs, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTcF interval. If the mean QTcF interval 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 QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below 500 msec. If the QTcF 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 as clinically indicated. If in that timeframe the QTcF intervals rise above 500 msec the investigational product will be held until the QTcF interval decreases to ≤500 msec. Patients will then restart the investigational product at the next lowest dose level or dose delayed as appropriate for specific investigational product. If the QTcF interval has still not decreased to <500 msec after 2 weeks, or if at any time a patient has a QTcF interval >515 msec or becomes

symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

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 a specialist.

If a patient experiences any cardiac or neurologic AEs (especially syncope, dizziness, seizures, or stroke), an ECG in triplicate should be obtained at the time of the event.

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

7.1.4. Disease Response Assessment (Lugano Criteria)

18F-fluorodeoxyglucose (18F-FDG) Positron Emission Tomography (PET) imaging will be used in conjunction with Computerized Tomography (CT) imaging. It will be performed ≤6 weeks prior to randomization then once every 12 weeks (±1 week) from randomization and at EOT (unless performed ≤6 weeks before EOT). After 12-months from randomization, 18F-FDG PET-CT is performed every 24 weeks (±1 week) until PD. If a patient discontinues treatment for reasons other than disease progression, Staging and Response Assessment will be performed until disease progression regardless of initiation of subsequent anti cancer therapy. See Study Manual for more details.

The baseline 18F-FDG PET-CT imaging will be used to determine evaluable target lesions for each patient. For 18F-FDG PET-CT, tumor background ratios and development of new sites of abnormality will be recorded.

Results of the 18F-FDG PET studies will be scored according to methods developed by the American College of Radiology Imaging Network. All centers participating in the study will use the same 18F-FDG PET methodologies and measures, to the extent possible, and for Phase 3, one center will be designated as the central vendor for response evaluation to be used for final interpretation of 18F-FDG PET data.

Anti-cancer activity will be assessed at baseline, during treatment as specified in the Schedule of Activities, whenever disease progression is suspected (eg, symptomatic deterioration), at the time of withdrawal from treatment (if not performed in the previous 4 weeks) and at follow-up visits until disease progression regardless of initiation of subsequent anti-cancer therapy.

Assessment of response will be made using the Response Criteria for Malignant Lymphoma (Appendix 2).

All patients' files and radiologic images and pathology samples must be available for source verification and for potential peer review.

7.1.4.1. Expedited Blinded Independent Central Review for Disease Progression

Tumor assessments must continue until confirmation of disease progression by BICR, regardless of the Investigator's assessment of PD.

To mitigate the potential for bias in determining disease progression, expedited BICR will be performed for Investigator-assessed disease progression. Upon investigator-assessed disease progression, all radiographic images collected for a patient from screening onwards will be submitted to the BICR for expedited review. See Study Manual for process details.

Every effort should be made to keep the patient on study treatment until the BICR has completed the radiographic image review, unless contraindicated by the Investigator.

7.2. Pharmacokinetics Assessments

Blood samples will be collected for PK analysis collected into an appropriately labeled tubes as outlined in the Schedule of Activities. PK sampling schedule may be modified based on emerging PK data. Blood for PK samples will be drawn from the contralateral arm of the drug infusion.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and Sponsor.

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site prior to initiation of the trial.
- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
- The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

[redacted]

7.2.1. Blood for PK Analysis of Avelumab

Blood samples (3.5 mL whole blood) for PK analysis of avelumab will be collected into appropriately labeled tubes as outlined in the Schedule of Activities. PK sampling schedule may be modified based on emerging PK data. Blood for PK samples will be drawn from the contralateral arm of the drug infusion.

7.2.2. Blood for PK Analysis of Utomilumab

Blood samples (4 mL whole blood at each time point) will be collected into appropriately labeled tubes for PK analysis of utomilumab as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the contralateral arm of the drug infusion.

7.2.3. Blood for PK Analysis of Rituximab

Blood samples (4 mL whole blood at each time point) will be collected into appropriately labeled tubes for PK analysis of rituximab as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the contralateral arm of the drug infusion.

7.2.4. Blood for PK Analysis of Azacitidine

Blood samples (2 mL whole blood at each time point) will be collected into appropriately labeled tubes for PK analysis of azacitidine as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the contralateral arm of the drug infusion.

7.2.5. Blood for PK Analysis of Bendamustine and metabolite (M3)

Blood for PK samples will be drawn from the contralateral arm of the drug infusion. Blood samples (2 mL whole blood at each time point) will be collected into appropriately labeled tubes for PK analysis of bendamustine and M3 as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the contralateral arm of the drug infusion.

7.3. Immunogenicity Assessments

Blood samples will be collected for development of Anti-Drug Antibodies (ADAs) and Neutralizing Antibodies (NAbs) into appropriately labeled tubes. This monitoring will take place at regular intervals during the treatment and follow up periods as described in the Schedule of Activities.

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site prior to initiation of the trial.

- Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures. Samples determined to be positive for ADA may be further characterized for NAb.

- The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may

make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

- As part of understanding the immunogenicity of the study drug, samples may be used for further characterization and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, will be destroyed.

7.3.1. Blood for Analysis of Anti-Avelumab Antibodies (ADA) and Neutralizing Anti-Avelumab Antibodies (NAb)

Blood samples (approximately 3.5 mL of whole blood) will be collected for determination of Anti-Avelumab Antibodies (ADA) and Neutralizing Anti-Avelumab Antibodies (NAb) into appropriately labeled tubes at visits specified in the Schedule of Activities. Blood for ADA/NAB samples will be drawn from the contralateral arm of the drug infusion.

7.3.2. Blood for Analysis of Anti-Utomilumab Antibodies (ADA) and Neutralizing Anti-Utomilumab Antibodies (NAb)

Blood samples (approximately 4 mL of whole blood) will be collected for determination of Anti-Utomilumab Antibodies (ADA) and Neutralizing Anti- Utomilumab Antibodies (NAb) into appropriately labeled tubes at visits specified in the Schedule of Activities. Blood for ADA/NAB samples will be drawn from the contralateral arm of the drug infusion.

7.3.3. Blood for Analysis of Anti-Rituximab Antibodies (ADA) and Neutralizing Anti-Rituximab Antibodies (NAb)

Blood samples (approximately 4 mL of whole blood) will be collected for determination of Anti-Rituximab Antibodies (ADA) and Neutralizing Anti-Rituximab Antibodies (NAb) into appropriately labeled tubes at visits specified in the Schedule of Activities. Blood for ADA/NAB samples will be drawn from the contralateral arm of the drug infusion.

7.4. Biomarkers

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PD-L1 expression in tumor cells will be retrospectively assessed and may be used to determine PD-L1 positivity (as determined with a validated PD-L1 central lab IHC test) using an algorithm and cut-off which will be specified prior to analysis).

PD-L1 expression in cells of the tumor microenvironment (for example, immune cells/infiltrating lymphocytes) may also be determined to explore possible correlations with outcome to treatment and other biomarker assessments.

Monitoring of minimal residual disease (MRD) will be performed using next-generation sequencing. This will entail analysis of archival/fresh baseline tumor tissue for immunoglobulin gene rearrangement signature(s), with MRD then monitored in serial blood draws collected at baseline and at time-points which align with tumor staging and response assessment by PET-CT or CT alone through EOT (see Laboratory Manual for details).

Details of time points and sampling are provided in the Schedules of Activities Table 1 and Table 2.

In order to complete all the assessments on tumor materials and blood and fecal samples, the Sponsor or the designated Contract Research Organization (CRO) will provide instructions and necessary supplies to the site, including shipping materials and prepaid mailers. Please refer to the Central Laboratory Manual for detailed information.

Collection and storage of samples will be detailed in the Central Laboratory Manual. The panel of biomarkers might be adjusted based on results from ongoing research related to anti-PD-1/PD-L1 therapies and/or safety; therefore, each patient will also be asked whether any remaining tumor tissue and/or blood-derived samples can be stored at a central repository (until such time as these samples cannot support any further analysis) and can be used for future exploratory research on the drug(s) and / or disease-related aspects. A patient's consent to the use of any remaining samples for such future exploratory research shall be optional and shall not affect the patient's participation in the current trial. Biomarker

analyses may be conducted after the conclusion of this study and may be based on samples derived from multiple studies.

Tissue collection: A biopsy (archived or Screening) will be collected at Screening. Archived tissue samples can be provided as either blocks or slides (see "provision of samples" paragraph immediately below). Endoscopic biopsies, core needle biopsies, excisional biopsies, punch biopsies, and surgical specimens are suitable. Fine needle aspiration biopsies are not suitable. Biopsies are only to be obtained from safely accessible tumor tissue sites.

Provision of archival samples: 1) Priority: tumor containing formalin-fixed, paraffin-embedded (FFPE) tissue block; 2) Priority: if the tumor containing FFPE tissue block cannot be provided in total, sections from this block should be provided that are freshly cut and mounted on positively-charged glass slides (SuperFrost Plus are recommended). Preferably, 25 slides should be provided; if not possible, a minimum of 15 slides is required for PD-L1 expression analysis and other tissue/molecular profiling assessments.

Tissue processing: The cancer tissues should be fixed in 10% neutral buffered formalin, paraffin embedded, and routinely processed for histological evaluation. Formalin substitutes are not suitable as fixatives. See Laboratory Manual for additional details on sample provisioning and tissue processing. Sample and tissue repository: Biomarker samples may be stored beyond the end of the trial and utilized at a later time jointly with samples from other studies in order to investigate actions of the investigational drug(s) or aspects of the disease under study and/or to support the development of an IHC-based investigational PD-L1 assay.

Optional *De Novo* Tumor Biopsy: An optional baseline *de novo* (ie, fresh) biopsy of an accessible tumor lesion may be obtained during screening and/or at EOT (note that a *de novo* tumor biopsy must be obtained at Screening if an archival specimen is not available to satisfy the requirement for the mandatory FFPE tumor tissue). All *de novo* biopsy or biopsies should be processed as FFPE (see Central Lab Manual), and the resulting FFPE tissue block(s) [one per time-point] should be submitted to the Central Laboratory.

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7.4.2.1. Additional Research

Unless prohibited by local regulations or IRB/EC decision, subjects will be asked to indicate on the consent form whether they will allow banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Banked Biospecimens section will be used. Subjects may still participate in the study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.5. Patient-Reported Outcomes

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During the Phase 3 component of the study, the NCCN-FACT FLymSI-18 (FlymSI-18), Brief BFI and EQ-5D-5L questionnaires will be administered via a hand-held electronic device designed to administer patient reported outcome questionnaires (ePRO). Each patient will be given the ePRO device at the first day of the first cycle. The ePRO device will prompt the patient to complete the questionnaires at on the first day of the first visit. After completing the questionnaires on the first day of the first visit, the device will prompt the patient to complete the BFI and EQ-5D-5L every 7 days and the FlymSI-18 every 28 days. If a patient does not complete the questionnaires on the day the patient is prompted, the device will prompt the patient to complete the questionnaires each subsequent day of the week until the questionnaires are completed. At the 90-day follow-up visit the device will be collected from the patient (see Table 2).

NCCN-FACT FLymSI-18:

The FlymSI 18, which is a revised, more symptom focused version of the FACT-Lym, was developed to be part of the Functional Assessment of Chronic Illness Therapy (FACIT) system. Unlike the FACT-Lym, the FlymSI-18 was developed following the 2009 Food and Drug Administration (FDA) guidance on patient reported outcomes measures with the input from the Food and Drug Administration (FDA).[74] The FlymSI-18 questionnaire is specifically designed to be a stand alone instrument to measure disease symptoms, treatment side effects and overall quality of life in patients with advanced lymphoma.[74]

The FlymSI-18 questionnaire was validated using a sample of patients with advanced lymphoma (stage III or IV).[74]

Responses on the 18 items of the FlymSI-18 questionnaire are used to calculate a total score and scores for four subscales; Treatment Side Effect (TSE), Disease Related Symptoms Physical subscale (FLymSI DRS P), Disease Related Symptoms Emotional subscale (FlymSI DRS E), and Function/Well-being subscale. The FlymSI DRS-P and FlymSI-DRS-E can be used to calculate an overall disease related symptom score, the

FlymSI-DRS. The questionnaire contains 18 Likert items. The expected completion time for a patient is 4 to 6 minutes.[75]

Brief Fatigue Inventory (BFI):

The BFI contains 9 items and it was developed to be MD Anderson to assess fatigue and the impact of fatigue on the patient. The BFI was validation work was based on a sample of 305 patients with cancer, some of whom were under in-patients care and some were under out-patient care at the time. The questionnaire contains 3 items related to the severity of fatigue and 6 items assessing the degree to which fatigue interferes with different aspects of quality of life. Response on each item will be based on a 0-10 Likert scale. Although the developers of the BFI suggest using the using all three fatigue severity items when estimating the level of fatigue, as per precedence found in FDA label claims, only item 3, (the "worst level of fatigue in the last 24-hours" item) will be used for estimating fatigue intensity. The level of fatigue interference will be based on all interferes items a per the user manual for the questionnaire. The expected completion time for a patient is 3 to 5 minutes.

EQ-5D-5L:

The EuroQol EQ-5D-5L is a patient-completed questionnaire designed to assess health status in terms of a single index value or utility score.[82] There are two components to the EuroQol EQ-5D-5L: a Likert scale system in which individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self- care, usual activities, pain/discomfort, and anxiety/depression) and a Visual Analogue Scale (VAS) in which patients rate their overall health status from 0 (worst imaginable) to 100 (best imaginable). Published weights are available that allow for the creation of a single summary score.

The responses to the 5 Likert scale items are used to calculate a utility score. The response on the visual analogue scale item is used as a self-reported health status score. The expected questionnaire completion time for a patient is estimated to be about 12 minutes.[75]

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8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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.

8.1.1. Additional Details on Recording Adverse Events on the CRFs

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Patient Withdrawal section)

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

When a patient withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the patient provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 90 days after the last administration of the investigational product. For patients who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a patient after the active collection period has ended are reported to Pfizer Safety 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 must be reported to Pfizer Safety. Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. If a patient begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

8.1.4.2. Recording Non-Serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF. 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. If a patient begins a new anti-cancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.1.5. 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 on the CRF, 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. 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, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. 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.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject 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 signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;

- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded 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.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- 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 any protocol-specified 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 recording as an AE.

8.2.3. 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.

Or that is considered to be:

- An important medical event.

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 subject 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.

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 active collection 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 active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment Section 8.3).

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

  Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;

- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.2.4. 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 is 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 a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject 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 subject;
- Admission exclusively for the administration of blood products.

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the Investigator as described in previous sections, and will be handled as SAEs in the safety database. See Section 8.1.4.1, Serious Adverse Event Reporting Requirements.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator 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.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

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

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the 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).

- 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 subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT 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 subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety 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 Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

Additional information about pregnancy outcomes that are reported to Pfizer Safety 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 sponsor. 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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. 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 Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject 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 subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

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

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

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 (SAP), which will be maintained by Pfizer. This document may modify the plans outlined in the protocol; however, any major

modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

Phase 1b

It is expected that up to ~84 patients will be randomized among 3 treatment arms (28 patients each) in Phase 1b. The null hypothesis that the ORR for one arm does not exceed 46% (H_0: ORR≤46%) will be tested against the alternative hypothesis (H_1: ORR>46%) at a one-sided level of significance α=0.025 using the binomial distribution. 28 patients in each treatment arm will provide at least 79.7% power to reject the null hypothesis if the true ORR is at least 73% (ORR ≥73%).

If there are ≤18 objective responders out of 28 patients treated in a given treatment arm, then it will be declared that for that treatment arm the null hypothesis cannot be rejected. If there are ≥19 objective responders out of 28 patients treated in a given treatment arm, the null hypothesis will be rejected for that treatment arm and clinically meaningful activity has been demonstrated.

Phase 3

The primary objective of this component of the study is to demonstrate that the selected Phase 1b avelumab-based combination regimen is superior to Investigator's Choice chemotherapy in prolonging PFS (as assessed by BICR).

The Phase 3 component of the study is designed to test the null hypothesis that the true PFS hazard rate for the selected Phase 1b combination regimen is greater than or equal to the one for Investigator's choice chemotherapy (hazard ratio [HR] ≥1) versus the alternative hypothesis that the true hazard rate is smaller in the selected Phase 1b combination regimen (HR<1).

The study will randomize (1:1) a total of approximately 220 patients stratified by IPI score (≤2 vs. ≥3) and primary disease (refractory vs. relapsed). The sample size for the study is based on the assumptions that the median PFS for patients receiving Investigator's choice chemotherapy is 3.6 months[1] and that treatment with the selected Phase 1b combination regimen is expected to increase the median to PFS ≥6 months, corresponding to a HR of ≤0.60 under the exponential model assumption.

If the true HR is 0.6 under the alternative hypothesis, a total of 164 PFS events will be required to have 90% power to demonstrate superiority using a stratified one-sided log-rank test at a one-sided significance level of 0.025, and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma spending function (γ = -10) to determine the non-binding futility boundary.

Assuming a 15% drop-out rate for PFS within each treatment arm, a non-uniform accrual accomplished over a 9-month period and a minimum follow-up of approximately 12 months after the last patient is randomized, a total of approximately 220 patients will need to be randomized in a 1:1 ratio to the selected Phase 1b combination regimen or Investigator's Choice chemotherapy. The data cutoff for the primary PFS analysis will occur after the target number of events has been reached in both comparisons and the last patient randomized in the study has been followed for at least 12 months after randomization.

The key secondary efficacy objective for this component of the study is to compare the selected Phase 1b combination to Investigator's Choice and demonstrate that the selected Phase 1b combination regimen is superior to Investigator's choice chemotherapy in prolonging OS. The sample size of 220 patients will also allow the assessment of the effect on OS of the selected Phase 1b combination regimen versus Investigator's Choice chemotherapy. OS will be tested if superiority with respect to PFS has been demonstrated. This hierarchical testing approach will allow control of the overall probability of Type 1 error at 0.025 (1-sided). The median OS for patients receiving Investigator's Choice chemotherapy is assumed to be 8 months,[69] and treatment with the selected Phase 1b avelumab-based combination regimen is expected to increase median OS to ≥12.3 months, corresponding to an HR of ≤0.65 under the exponential model assumption. If the true HR is 0.65 under the alternative hypothesis, a total of 174 deaths will be required to have 80% power to detect a HR of 0.65 for OS at the one-sided significance level of 0.025 using a stratified log-rank test and a 3-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary. These calculations further assume a 5% drop-out rate for OS within each treatment arm and a follow-up of approximately 20 months after the last patient is randomized. The data cutoff for the final OS analysis will occur after the target number of events has been reached.

9.2. Statistical Methods and Properties

An IRC evaluation of the first 6 and/or 12 DLT evaluable patients in each treatment arm will occur after the last patient has completed one cycle of treatment. Enrollment will be halted while the first 6 DLT evaluable patients in each treatment arm are being evaluated for safety.

Table 20 shows the probability of confirming the safety in the first 6 or 12 DLT evaluable patients for a range of true DLT rates. For example, for a DLT that occurs in 10% of patients, there is 97.3% probability of confirming safety and expanding the corresponding treatment arm. Conversely, for a DLT that occurs with a rate of 70%, the probability of treatment arm expansion is 1.2%.

Table 20. Probability of Confirming Safety in the First 6 or 12 DLT Evaluable Patients

True underlying DLT rate	5%	10%	20%	30%	40%	50%	60%	70%
Probability of expanding dose	0.997	0.973	0.816	0.556	0.306	0.135	0.047	0.012

9.3. Analysis Population

9.3.1. Full Analysis Sets

The Full Analysis Set will include all randomized patients. Patients will be classified according to the treatment assigned at randomization. The Full Analysis Set will be the primary analysis set for evaluating all efficacy endpoints and patient characteristics.

9.3.2. Per Protocol Analysis Set

The Per-Protocol Analysis Set is a subset of the Full Analysis Set and will include patients who receive at least 1 dose of study treatment and do not meet specific criteria expected to impact the primary objective of the study. The criteria used to exclude patients from the per-protocol analysis set will be pre-specified in the SAP. The Per-Protocol Analysis Set will be used for sensitivity analyses for the primary efficacy endpoint.

9.3.3. Evaluable for DLT Analysis Set

The DLT Analysis Set is the analysis set for the safety confirmation and includes randomized patients in each arm who are eligible for the study, receive at least 1 dose of study treatment, and either experience DLT during the first cycle, or complete the primary DLT observation period for 4 weeks. Patients without DLTs who withdraw from study before completing the 4 week DLT observation period for reasons other than dose limiting toxicity (eg, missed appointments or development of rapidly progressing disease) are not evaluable for DLT.

9.3.4. Safety Analysis Set

The Safety Analysis Set will include all patients who receive at least 1 dose of investigational drug. Patients will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) are received throughout the dosing period in which case patients will be classified according to the first treatment received. The Safety Analysis Set will be the primary population for evaluating treatment administration/compliance and safety.

9.3.5. PK Analysis Set

The PK Concentration Analysis Set is a subset of the safety analysis set and will include patients who have at least 1 concentration above the lower limit of quantitation (LLQ) for avelumab, utomilumab, rituximab, bendamustine, or azacitidine.

The PK Parameter Analysis Set is a subset of the safety analysis set and will include patients who have at least 1 of the PK parameters of interest for avelumab, utomilumab, rituximab, bendamustine, or azacitidine.

9.3.6. Immunogenicity Analysis Set

The Immunogenicity Analysis Set is a subset of the Safety Analysis Set and will include patients who have at least one ADA/Nab sample collected for either avelumab, utomilumab or rituximab.

9.3.7. Biomarker Analysis Set

The Biomarker Analysis Set is a subset of the Safety Analysis Set and will include all patients who have at least 1 baseline biomarker assessment. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

CCI [redacted]

9.3.9. PRO Analysis Set

The PRO analysis set is a subset of the efficacy set and will include patients with at least one baseline (Day 1 of Cycle 1 data) assessment and one post-baseline assessement from either the BFI, the NCCN-FACT-FLymSI-18, or the EQ-5D-5L questionnaire.

CCI [redacted]

9.4. Efficacy Analysis

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

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

All primary and secondary endpoints based on radiological assessments of tumor burden (ie, PFS, OR, TTR, DR, DC) will be derived using the local radiologist's/investigator's assessment. In addition, radiographic images and clinical information collected on Phase 3 component of the study will also be reviewed by BICR to verify investigator reported tumor assessments. Review by BICR will be used for the primary analyses.

In the Phase 3 component, the primary analyses of PFS by BICR assessment will be repeated on the Per-Protocol Analysis Set as sensitivity analyses. All planned sensitivity analyses will be described in the Statistical Analysis Plan (SAP).

9.4.1. Analysis of the Primary Endpoint

Phase 1b

DLTs will be graded according to NCI-CTCAE version 4.03 and coded using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

DLTs will be summarized by number and percentage of patients with DLTs, by treatment group, primary SOC and PT.

OR is defined as a CR or PR per Lugano response classification criteria from randomization until disease progression or death due to any cause. A patient will be considered to have achieved an OR if the patient has a sustained CR or PR as per Lugano response classification criteria definitions. Otherwise, the patient will be considered as a non-responder in the OR rate (ORR) analysis. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow up assessments) will be considered as non-responders in the ORR analysis.

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

Phase 3

PFS is defined as the time from randomization to the date of the first documentation of objective 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 following two or more missing tumor assessments. Patients who do not have a baseline tumor assessment or who do not have any post baseline tumor assessments will be censored on the day of randomization, with a duration of 1 day, unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered as an event.

A stratified log-rank test (one sided) will be used within each comparison at the interim and/or final analyses with the overall significance level preserved at 0.025 (one sided). PFS times associated with each treatment arm will be summarized using the Kaplan Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25^{th}, 50^{th}, and 75^{th} percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratios and the corresponding 95% CIs.

PFS by BICR assessment will also be evaluated based on the Per-Protocol Analysis Set as a sensitivity analyses, using the stratified log-rank test (one sided, α=0.025).

A sensitivity analysis for PFS by BICR assessment will also be performed counting all PD and deaths as events regardless of missing assessments or timing of the event.

Proportional Hazards Assumption Evaluation

Schoenfeld residuals for the stratified Cox proportional regression model will be plotted to investigate graphically violations from the proportional hazards (PH) assumption; a non-zero slope is evidence of departure from proportional hazards (PH). The PH assumption will be formally tested using Schoenfeld's residual test.[91] Large departures from PH will be evidenced by a p-value <0.05.

In addition, the PH assumption will be checked visually by plotting

log(-log(S(t)) versus log(t),

where S(t) is the estimated survival function (for PFS) at time t.

If these show large departures from proportional hazards, then PFS by BICR assessment will also be analyzed based on restricted mean survival time (RMST) differences.[92]

The RMST up to time t* can then be interpreted as the expected survival time restricted to the common follow-up time t* among all patients. Here t* = min of (largest observed survival time for the experimental arm, largest observed survival time for control arm) in months. RMST can be estimated consistently by the area under the Kaplan-Meier curve over [0, t*].

The associated 95% CI for the difference in means and one-sided p-value will be generated. RMST as a function of t* and the associated treatment effect between the selected Phase 1b combination regimen and Investigator's Choice chemotherapy will be plotted against time t*.

9.4.2. Analysis of Secondary Endpoints

9.4.2.1. Overall Survival

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

In the Phase 3 component of the study, OS will be hierarchically tested for significance at the time of PFS analysis, provided the primary PFS endpoint is statistically significant at the interim or final analyses of PFS. A stratified log-rank test (one sided) will be used at the interim and/or final analyses with the overall significance level preserved at 0.025 (one sided).

In both components, OS time associated with each treatment arm will be summarized using the Kaplan Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25^{th}, 50^{th}, and 75^{th} percentiles will be reported. In the Phase 3 component, the Cox proportional hazards model will be fitted to compute the treatment hazard ratios and the corresponding 95% CIs.

9.4.2.2. Progression-Free Survival at 6 Months

A patient will be considered to be progression-free at 6 months if the patient has disease assessment demonstrating non-progression for at least 6 months after randomization. The PFS rate at 6 months for each treatment arm will be estimated by dividing the number of patients who are progression-free at 6 months by the total number of patients randomized to the respective treatment arm. The corresponding exact 2-sided 95% CIs will be provided by treatment arm. Kaplan-Meier estimates of the PFS rate at 6 months and the corresponding exact 2-sided 95% CIs will also be provided by treatment arm.

9.4.2.3. Time to Tumor Response

TTR is defined, for patients with an OR per the Lugano Disease Assessment Response, Lugano response classification criteria, as the time from randomization to first documentation of objective tumor response (CR or PR).

TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max, Q1, Q3).

9.4.2.4. Duration of Response

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

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

The 6-month DRR for each treatment arm will be estimated by dividing the number of patients who achieve and maintain an OR for at least 6 months by the total number of patients randomized to the respective treatment arm. The corresponding exact 2-sided 95% CIs will be provided by treatment arm.

9.4.2.5. Disease Control

DC is defined as Best Overall Response of CR, PR, or SD. DC rate (DCR) is the proportion of patients with DC.

DCR will be summarized by frequency counts and percentages.

9.4.2.6. Analysis of PD-L1 and MRD

The relationship between different PD-L1 expression levels in tumor cells and cells of the tumor microenvironment (eg, infiltrating lymphocytes) and selected clinical response parameters will be assessed. The relationship between minimal residual disease burden and selected clinical response parameters will be assessed. Detailed methodology for statistical analysis of these endpoints will be documented in the SAP.

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

The Central Laboratory, analytical laboratories (eg, PK, ADA, NAb), and Pfizer clinical assay group (CAG) colleagues will be unblinded. If early analysis of the PK data is necessary (before database lock and release of the randomization codes for the study), a PK unblinding plan will be developed. A PK analyst, who is not associated with the study team, will conduct the analysis to avoid unblinding of the study team. Blinded analysis of PK/PD samples will only be for Phase 3 component of the study.

9.5.1. Analysis of the Pharmacokinetics of Study Drugs

If data permit or if considered appropriate, plasma pharmacokinetic parameters including the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), trough plasma concentrations (C_{trough}) and area under the plasma concentration versus time curve (AUC_{last}, AUC_{τ}) for avelumab, rituximab, utomilumab, azacitidine and bendamustine will be estimated using non compartmental analysis. Area under the plasma concentration versus time curve to infinity (AUC_{inf}), terminal elimination half life ($t_{1/2}$), oral plasma clearance (CL/F)[CL for IV dosing], apparent volume of distribution (V_{ss}/F or V_z/F)[V_{ss} for IV dosing], accumulation ratio (R_{ac}) will be also estimated. The single-dose and steady state PK parameters will be summarized descriptively by treatment arm, cycle and day.

Select PK parameters (ie, C_{max}, C_{trough}, and other parameters, as appropriate) for each analyte in the three avelumab-based combination regimens will be compared to historical data for that analyte as monotherapy to assess any drug-drug interaction potential among the drugs coadministered within each combination regimen.

For all study drugs, concentrations will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by treatment arm, cycle, day and nominal time. Individual patient and median profiles of the concentration time data will be plotted by treatment arm, cycle and day (single dose and steady state) using nominal times. Individual and median profiles will be presented on both linear linear and log linear scales.

The observed trough concentrations for each study drug will be plotted using a box whisker plot by cycle and day in order to assess the attainment of steady state. The observed accumulation ratio will be summarized descriptively.

9.5.2. 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 study drug exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

9.6. Analysis for Avelumab, Rituximab and Utomilumab Immunogenicity

For the immunogenicity data, the percentage of patients with positive ADA and neutralizing antibodies each will be summarized by treatment for each dosing interval for avelumab, rituximab and utomilumab. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. The effect of ADA on avelumab, rituximab and utomilumab concentrations will be evaluated.

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.

9.7. Analysis of Patient-Reported Outcomes

NCCN-FACT FLymSI-18, Brief Fatigue Inventory (BFI), and EQ-5D-5L will be scored according to their respective validation papers and user's guides.

The FlymSI DRS P will be used to determine the Time to Deterioration (TTD) in physical symptoms of disease. TTD is defined as the time from first dose (baseline) to the first time the patient's score shows a 3 point or greater decrease in the FlymSI DRS P (note: lower scores represent lower quality of life and high symptoms burden on the FLymSI-18 scores). If a patient has not deteriorated prior to the FlymSI DRS P assessment, the patient will be censored at the last time assessment time point. Kaplan Meier plots will be used to display deterioration over time and a log-rank test will be used to compare the TTD between the two treatment arms. The median time and 2-sided 95% CI for the median will be provided based on the Brookmeyer Crowley method.[83]

Yost and Eton (2005) established that a3-point or greater change from baseline as the minimally important difference (MID) change from baseline on the FACT scales because a change that large or greater would correlate with change in disease symptoms and status.[84] For the BFI scores, a 3-point or greater change assumed to meet or surpass the threshold of a minimally important change.

Similarly, the BFI will be used to determine the Time to Deterioration (TTD) in terms of fatigue. TTD is defined as the time from first dose (baseline) to the first time the patient's score shows a 3 point or greater increase in the worst fatigue in the past 24 hours item (ie, item 3) (with higher scores representing higher levels of fatigue on the BFI). If a patient has not experienced deterioration in terms of fatigue (ie, higher fatigue) prior to the last assessment with the BFI questionnaire, the patient will be censored at the assessment time point. Kaplan-Meier plots will be used to display deterioration over time and a log-rank test will be used to compare the TTD between the 2 treatment arms. The median time and 2-sided 95% CI for the median will be provided based on the Brookmeyer-Crowley method.[83]

Additionally, symptom subscale improvement in physical symptoms of disease will be defined as an increase of at least 3 points in the FlymSI–DRS-P subscale score of the FlymSI-18. In terms of fatigue, improvement will be defined as a decrease of at least 3 points from baseline on the worst fatigue question of the BFI. A chi-square test will be used to compare treatment arms. To minimize bias due to differential follow-up, the improvement analysis will be limited to scores observed during the first 4 months of treatment. Within-group and between-group comparisons to baseline in order to assess symptom improvement among treatment arms will also be performed. To test the robustness of the MID of 3 points, sensitivity analyses using 2 and 4 points will be explored.

Patient reported disease-/treatment-related symptoms of lymphoma, function/well-being, and general health status will also be assessed. Summary statistics [mean, standard deviation, median, range and 95% CI] of absolute scores will be reported for all of the subscales of the FlymSI-18, the BFI subscales, utility score and self-reported health status score from the EQ 5D 5L. The mean change of absolute scores from baseline (and 95% CI) will also be

assessed. Line charts depicting the means and mean changes of items and subscales over time will be provided for each treatment arm. Additional exploratory analyses may be performed, such as repeated measures mixed effects modeling and analyses of patients who experienced a complete response.

9.10. Analysis of Other Endpoints

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

9.11. Safety Analysis

The Safety Analysis Set will be the primary population for safety evaluation.

9.11.1. Adverse Events

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

systems and MedDRA preferred term will be reported. Adverse events will be graded by worst NCI CTCAE v4.03 severity grade, and will be summarized by cycle and by relatedness to study treatment.

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

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

9.12. Laboratory Abnormalities

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

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

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

9.13. Electrocardiograms

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on treatment ECG data.

ECG measurements (an average of the triplicate measurements, if applicable) 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, QTc and by study arm. Individual QT (all evaluated corrections) intervals will be listed by treatment arm and time. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions.

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 by study arm and time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post baseline

interval across time points. 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 (one or more correction method will be used). Shift tables will also be provided for ECG abnormality at baseline vs. on treatment (yes, no, not done: (n, %)). Patients experiencing clinically relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

9.14. Interim Analysis

Phase 1b

The purpose of the IA in the Phase 1b component of the study is to allow for early stopping of any treatment arm for futility based on ORR. The cutoff for the IA is 13 weeks after 8 patients in each treatment arm have been randomized. If ≤2 responses are observed for 8 patients in a treatment arm, further enrollment in the treatment arm may be stopped.

Table 21 provides the conditional power of the Phase 1b when the futility boundary is crossed at the time of the IA based on the test of hypothesis described in Section 9.1.

Table 21. Conditional Power for the Phase 1b Based on the Interim Analysis Results

Responders/Number of patients	True ORR=50%	True ORR=60%	True ORR=73%
0/8	<0.001	0.001	0.016
1/8	<0.001	0.004	0.064
2/8	0.001	0.016	0.170

Phase 3

The purpose of the IA in the Phase 3 component of this study is to allow for early stopping of the study for efficacy or futility (based on PFS) and to further assess the safety of the selected Phase 1b avelumab-based combination regimen. The IA will be performed after all of the patients have been randomized in the study.

The Phase 3 component of the study is designed to have 1 IA and the final analysis, both based on the primary PFS endpoint. A formal efficacy boundary (O'Brien-Fleming) for rejecting the null hypothesis is constructed by using the spending function methodology of Lan-DeMets. To protect the integrity of the study and to preserve the Type 1 error rate, a fraction of alpha (0.006) for efficacy will be spent at the IA and accounted for in the overall Type 1 error rate if the IA is performed exactly at the planned number of PFS events. The nominal significance levels for the interim and final efficacy analyses of PFS will be determined by using the Lan-DeMets procedure with an O'Brien-Fleming stopping

boundary. The overall significance level for the efficacy analysis of PFS will be preserved at 0.025 (1-sided test).

The IA will be performed following approximately 109 PFS events (67% of the 164 PFS events planned at the end of the study). If the value of the test statistic exceeds the efficacy boundary ($z < -2.514$, $p < 0.006$), then the superiority of the selected Phase 1b regimen compared to Investigator's Choice chemotherapy in prolonging PFS may be demonstrated. If the value of the test statistic exceeds the futility boundary ($z > 0.037$, $p > 0.515$) the study may be stopped for futility. If the results of the IA indicate serious safety concerns, the Sponsor will communicate with the Health Authorities regarding stopping the relevant investigational arms of the clinical trial.

The key secondary OS endpoint will be analyzed using a hierarchical testing procedure, provided the primary endpoint is statistically significant favoring the selected Phase 1b combination regimen. Up to 3 analyses are planned for OS: at the time of the interim PFS analysis, at the time of the final analysis for PFS, and at 100% (final OS analysis) of the 174 OS events required for each comparison. An α-spending function according to Lan-DeMets (O'Brien-Fleming) independent of the one used for the primary efficacy analysis will be used to determine the efficacy boundary. The trial allows for the stopping of the study for a superior OS result, provided the primary PFS endpoint has already been shown to be statistically significant favoring the selected Phase 1b combination regimen.

9.15. Data Monitoring Committee

This study will use an IRC in the Phase 1b component of the study and an E-DMC for the Phase 3 component of the study.

The IRC will review the safety data from the Phase 1b according to the IRC charter in order to support the selection of an adequately safe experimental arm for the Phase 3 component of the study.

The E-DMC will be responsible for ongoing monitoring of the efficacy and safety of patients in the Phase 3 component of the study according to the E-DMC charter. The recommendations made by the EDMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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 Investigator site may be patient 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 Investigator site for the Inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The Investigator site and Investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. 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 or the physician patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections 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/assent 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 the 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 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/assent 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 the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guidelines for Good Clinical Practice (ICH 1996), and the Declaration of Helsinki.

12.3. Patient Information and Consent

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

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by numerical code based on a numbering system provided by Pfizer in order to de-identify study patients. The Investigator 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/assent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

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

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

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative, and the patient's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The Investigator will retain the original of each patient's signed consent/assent document.

12.4. 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 regulatory 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 All Other Participating Countries

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

13.2. End of Trial in All Participating Countries

End of trial in all other participating countries is defined as last patient last visit (LPLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product 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, 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 (PCD) for

studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD 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 European Union (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 PCD for studies in adult populations or within 6 months of the PCD 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 the principal Investigator (PI) of the results of the study based on information collected or generated by the PI, 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 it is 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 Investigator's sites, and that any subsequent publications by the PI 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, patient to the other requirements of this section.

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

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

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

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Appendix 1. Abbreviations

Abbreviation	Term
5FU	5-Fluorouracil
ABC	Activated B-cell
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	alanine aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
Anti–CTLA-4	Anti-cytotoxic T-lymphocyte-associated antigen-4
ASCT	Autologous stem cell transplant
AUC	Area Under the Curve
$AUC_0\ \tau$	Area under the plasma concentration time curve from time 0 to τ hours post dose
AST	aspartate aminotransferase
BFI	Brief Fatigue Inventory
BICR	Blinded Independent Central Review
BOR	Best Overall Response
CAR-T	Chimeric Antigen Receptor T-Cell
CBC	Complete blood count
CDS	core data sheet
CG	Cancer germline
CLL	Chronic Lymphocytic Leukemia
C_{max}	Maximum Plasma Concentration
CMML	chronic myelomonocytic leukemia
CNS	Central nervous system
CR	Complete response
CRF	case report form
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	Clinical Study Report
CT	Computerized Tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide/Vincristine/Prednisone
CYP	Cytochrome P450
DC	Disease Control
DCR	Disease Control Rate
DLBCL	Diffuse Large B-cell Lymphoma
DLT	Dose-Limiting Toxicity
DMC	data monitoring committee

Abbreviation	Term
DNA	deoxyribonucleic acid
DNMTi	DNA methyltransferase inhibitor
DR	Duration of Response
DRR	Durable Response Rate
DLBCL-NOS	Diffuse Large B-Cell Lymphoma-not otherwise specified
EBV+	Epstein-Barr Virus positive
EC	ethics committee
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
E-DMC	External Data Monitoring Committee
EDP	Exposure during pregnancy
CCI	[redacted]
ePRO	Electronically captured patient reported outcome
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
ESMO	European Society of Medical Oncology
EudraCT	European Clinical Trials Database
FAB	French-American-British
FACIT	Functional Assessment of Chronic Illness Therapy
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FDG	Fluorodeoxyglucose
FFPE	Formalin-Fixed, Paraffin-Embedded
FL	Follicular Lymphoma
FlymSI-18	Follicular Lymphoma Symptom Index – 18 item questionnaire
FSH	Follicle-stimulating hormone
GCB	Germinal Center B-cell
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factors
GGT	Gamma glutamyl transferase
HBV	Hepatitis B Virus
HCV	hepatitis C Virus
HGBCL	High-Grade B-cell Lymphoma
HHV8	Human herpesvirus 8
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
HRQL	Health-Related Quality of Life
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
IHC	Immunohistochemistry

Abbreviation	Term
ICH	International Conference on Harmonisation
ID	Identification
Ig	Immunoglobulin
IND	Investigational New Drug Application
INR	International Normalized Ratio
IP	Investigational Product
IPI	International Prognostic Index
irAE	immune-Related Adverse Event
IRB	Institutional Review Board
IRC	Internal Review Committee
IRR	Infusion related reaction
IRT	Interactive Response Technology
IUD	Intrauterine device
IV	Intravenous
IVR	Interactive Voice Response
IWG	International Working Group
IWR	Interactive Web Response
KIRs	Killer-cell immunoglobulin-like receptors
LDi	Longest diameter
LFT	Liver Function Test
LPD	Local Product Document
LPLV	Last Patient Last Visit
MAP	Mitogen Activated Protein
MCC	Merkel Cell Carcinoma
MDS	Myelodysplastic Syndrome
MDSCs	Myeloid derived suppressor cells
MID	Minimally important difference
MRD	Minimal residual disease
MRI	Medical resonance imaging
MTD	Maximum Tolerated Dose
N/A	Not applicable
Nab	Neutralizing antibodies
NCCN	National Comprehensive Cancer Network
NCCN-FACT FLymSI-18	FACT/NCCN-Lymphoma Symptom Index 18 item questionnaire
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NOS	Not Otherwise Specified
NSAIDs	Nonsteroidal anti-inflammatory drugs
ORR	Overall Response Rate
OS	Overall Survival
PET	Positron Emission Tomography
PBMC	Peripheral blood mononuclear cells

Abbreviation	Term
PBS	Phosphate-Buffered Saline
PCD	Primary Completion Date
PD	Progression of Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PES	Polyether sulfone
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial Response
PRO	Patient Reported Outcome
CCI [redacted]	[redacted]
PT	Prothrombin Time
Q2W	Every 2 weeks
RAEB	Refractory Anemia with Excess Blasts
RAEB-T	Refractory Anemia with Excess Blasts-T
RCC	Renal cell carcinoma
RNA	Ribonucleic acid
R/R	Relapsed/Refractory
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCCHN	Squamous Cell Carcinoma Head and Neck
SCL	Supply Chain Lead
SIB	Suicidal ideation and behavior
SOC	Standard Of Care
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SRSD	Single Reference Safety Document
TEAE	Treatment Emergent Adverse Event
TILs	Tumor Infiltrating Lymphocytes
TO	Target receptor occupancy
TSE	Treatment Side Effect
TSH	Thyroid Stimulating Hormone
TTD	Time to Deterioration
TNFRSF	Tumor Necrosis Factor Receptor Superfamily
ULN	Upper Limit of Normal
US	United States
USPI	United States Package Insert
VAS	Visual Analogue Scale
WHO	World Health Organization

Appendix 2. Response Criteria for Malignant Lymphoma

From the International Workshop to Standardize Response Criteria for Lymphomas

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	Target nodes/nodal masses must regress to ≤1.5 cm in LDi
	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	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	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	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 3. Eastern Cooperative Oncology Group Performance Status (ECOG PS)

Score	Definition
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work or office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

Appendix 4. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (version 4.03, dated 14 June 2010) has been placed in the Study Reference Binder for this protocol. Alternatively, the NCI CTCAE may be reviewed online at the following NCI website: http://ctep.cancer.gov/reporting/ctc.html.

Appendix 5. International Prognostic Index (IPI)

International Prognostic Index[89]

ALL PATIENTS	INTERNATIONAL INDEX, ALL PATIENTS	
Age >60 years	Low	0 or 1
Serum LDH > normal	Low-intermediate	2
Performance status 2-4	High-intermediate	3
Ann Arbor Stage III or IV	High	4 or 5
Extranodal involvement >1 site		