Official Title of Study:

A Phase 1/2a Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (Relatlimab, BMS-986016) Administered Alone and in Combination with Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Relapsed or Refractory B-Cell Malignancies

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CLINICAL PROTOCOL CA224022

A Phase 1/2a Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (Relatlimab, BMS-986016) Administered Alone and in Combination with Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Relapsed or Refractory B-Cell Malignancies

Short Title:

Safety Study of Anti-LAG-3 in Relapsed or Refractory Hematologic Malignancies

Revised Protocol Number: 09

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 09	17-Nov-2020	Revised protocol 09 focuses on clarifying the response evaluation scale utilized for primary endpoint evaluation of response for Cohort D. This is a result of the ongoing study duration and several criterions being introduced in the clinical setting.
Revised Protocol 08	11-Oct-2019	Revised protocol 08 incorporates Administrative Letters 06 and 07 and changes described in the table of Summary of Key Changes.
Administrative Letter 07	27-Nov-2018	Changes the Medical Monitor contact.
Administrative Letter 06	11-Jun-2018	Removes the PK and immunogenicity assessments scheduled on follow-up visit 1 in Table 5.1-3, Follow-Up Procedural Outline (CA224022), and to align with the PK and ADA sampling schedules for relatlimab and nivolumab in Tables 5.5.1-1 and 5.5.1-2.
Revised Protocol 07	28-Mar-2018	Revised protocol 07 incorporates Administrative Letters 03, 04 and 05 and the following changes: require pre-and on-treatment biopsies for all subjects in Part D, adds Survival Follow-up, clarifies eligibility criteria, and updates safety, clinical pharmacology information, and criteria for dose delay and permanent discontinuation. Also includes grammatical revisions and references.
Administrative Letter 05	05-Jan-2018	Administrative Letter 05 change in Study Director and Medical Monitor.
Administrative Letter 04	03-Feb-2017	Administrative Letter 04 change in Study Director and Medical Monitor.
Administrative Letter 03	09-Dec-2016	Administrative Letter 03 defined the intermediate dose used for Part C dose escalation.
Revised Protocol 06	07-Nov-2016	Incorporates Amendment 06.
Amendment 06	07-Nov-2016	Amendment 06 consists of changes in response to a related adverse event of meningitis. Additional neurological eligibility criteria are included to further exclude patients that have a confirmed history of encephalitis, meningitis, or uncontrolled seizures. Also, a neurological exam was added for subjects who experience a study drug related ≥ Grade 2 neurological adverse event. Safety algorithms in Appendix 4 have been updated. Language regarding re-challenge has been added. Laboratory collections have been updated. Administrative changes were also included.
Revised Protocol 05	25-May-2016	Incorporates Amendment 05.
Amendment 05	25-May-2016	Amendment 05 consists of changes in response to a related event of life-threatening grade 4 myocarditis which occurred in a subject receiving combination BMS-986016 and nivolumab on study CA224020. Additional cardiovascular eligibility criteria are included to further exclude patients that are less likely to tolerate and recover from a potential myocarditis event. Screening procedures have been added in support of these new criteria. In addition, more robust and frequent cardiovascular safety monitoring has been incorporated into

Document	Date of Issue	Summary of Change
		the first 8 weeks of study therapy, which is the time period during which immune-related myocarditis is most likely to occur. This amendment should therefore be implemented urgently, and it prospectively applies to all currently on going subjects and future subjects enrolled.
Revised Protocol 04	28-Mar-2016	Incorporates Amendment 04.
Amendment 04	28-Mar-2016	The protocol amendment allows for administration of BMS-986016 in combination with nivolumab in Part C (dose escalation) and in Part D (cohort expansion). The DLT period for Part C has been updated as well as the tumor indications in Part C and D. The statistical sections was updated to align with revised study design. Administrative changes and correction of typographical errors were also included.
Revised Protocol 03	06-May-2015	Incorporates Amendment 03, and Administrative Letter 02
Amendment 03	06-May-2015	The protocol amendment allows for the inclusion of an extended biomarker plan during both, escalation and expansion phases. It also introduces an expansion cohort at [redacted] mg (Part B) in four selected tumor types as well as a conditional expansion cohort at [redacted] mg (Part C) in two selected tumor types. It also includes administrative changes and correction of typographical errors.
Revised Protocol 02	30-Jul-2014	Incorporates Amendment 02, and Administrative Letter 01
Amendment 02	30-Jul-2014	The protocol amendment allows enrollment of subjects with multiple myeloma in Part A and Part B. The number of subjects enrolled will be increased by 12 subjects in Part B. Glucose laboratory assessment may be fasting or non-fasting. Additional changes to inclusion and exclusion criteria are described in the amendment.
Revised Protocol 01	06-Dec-2013	Incorporates Amendment 01
Amendment 01	06-Dec-2013	The following changes were made based on FDA review and feedback: (1) remove language regarding possible addition of 4th subject to first cohort of 3 subjects during dose escalation; (2) modify eligibility criteria related to prior therapy, transplantation or life-prolonging treatments, minimum neutrophil count, and duration of time prior to first dose whereby growth factors and transfusions are prohibited; (3) revise exceptions to non-hematologic DLT criteria; (4) revise hematologic DLT criteria to include Grade 4 anemia in all subjects and Grade 3 anemia in subjects with ≤ Grade 1 anemia at baseline; (5) increase DLT evaluation interval from 6 weeks to 8 weeks; and (6) specify that all subjects who receive at least 1 dose of study drug will be evaluable for DLT.
Original Protocol	28-Oct-2013	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 09:

This amendment focuses on clarifying the response evaluation scale utilized for primary endpoint evaluation of response for Cohort D. This is a result of the ongoing study duration and several criteria being introduced in the clinical setting.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	As noted below.	The synopsis has been updated to reflect all changes made in the sections listed below.
Section 1.3.1: Primary Objectives	The co-primary objective was modified to clarify that tumor response will be evaluated according to the revised International Working Group criteria for Malignant Lymphoma.	Several evaluation scales have been introduced to assess response in HL since the start of the study (ie, Lugano, LYRIC), prompting the need to specify the response criteria utilized for the primary objective.
Section 1.3.3: Exploratory Objectives	Clarified that preliminary efficacy will be assessed in Part D NHL and HL subjects. Clarified that [redacted] will be assessed in DLBCL patients in addition to HL patients in Part D. Clarified that [redacted] will be assessed based on IWG (2007) and Lugano (2014) criteria. Added an exploratory objective to evaluate [redacted] in Part D.	Lugano 2014 incorporates additional dimensions (metabolic response) in evaluation of HL patients. Clinically, it is of interest to see response comparisons between IWG 2007 and Lugano 2014.
Section 5.4: Efficacy Assessments	Added that Lugano 2014 response criteria will be used as an exploratory analysis to evaluate NHL or HL participants for metabolic response. Clarified response types for the PET scan assessments.	As noted above.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 09		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.3.2.3: Efficacy	Clarified that all efficacy analyses will be based on the all treated analysis population except otherwise stated. Added the exploratory endpoints of objective response rate and duration of objective response based on the Lugano 2014 response criteria in the NHL and HL subjects in Part D. Clarified the complete response rate is based on IWG criteria for NHL and HL subjects.	As noted above.
Section 8.3.3.3: Other Efficacy Endpoints	Section added to define progression free survival and complete metabolic response rate based on Lugano (2014) criteria.	As noted above.
Section 8.4.2: Efficacy Analysis	Added complete metabolic response, partial metabolic response, and duration of complete metabolic response. Clarified the analyses will be assessed based on IWG and Lugano criteria.	As noted above.

SYNOPSIS

Clinical Protocol CA224022

Protocol Title: A Phase 1/2a Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (Relatlimab, BMS-986016) Administered Alone and in Combination with Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Relapsed or Refractory B-Cell Malignancies

Short Title: Safety Study of Anti-LAG-3 in Relapsed or Refractory Hematologic Malignancies

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Relatlimab (BMS-986016, anti–LAG-3 antibody) is supplied as a sterile [redacted] mg/mL or [redacted] mg/mL formulation to be administered as an intravenous (IV) infusion. Nivolumab (BMS-936558) is available as a sterile [redacted] mg/mL formulation to be administered as an IV infusion.

In Part A (dose escalation monotherapy), relatlimab will be administered at doses of [redacted] mg once every 2 weeks (Q2W), in 8-week cycles, for up to 12 cycles of study therapy.

Part B, cohort expansion, monotherapy, will be carried out at [redacted] mg. The dose selected has not exceeded the maximum tolerated dose [MTD], or maximum administered dose [MAD] (if an MTD is not established) identified in Part A, monotherapy escalation. Study therapy will be administered once every 2 weeks, in 8-week cycles, for up to 12 cycles.

In Part C (dose escalation, combination therapy), relatlimab will be administered starting at [redacted] mg dose in combination with a fixed dose of nivolumab at [redacted] mg once every 2 weeks, in 8-week cycles, for up to 12 cycles of study therapy. The intermediate dose of relatlimab (anti-LAG-3) [redacted] mg and nivolumab (BMS-936558) [redacted] mg was also tested under MTD and shown to be well-tolerated.

Part D is a cohort expansion, combination therapy. The doses selected for Part D will not exceed the MTD (or MAD if no MTD is determined) in Part C, but may incorporate assessment of other data including toxicities and PK and pharmacodynamic data from Parts A, B and C and data from the CA224020 study. Doses to be considered may include doses intermediate to those evaluated in Part C if recommended by the Investigators and the Sponsor. Modeling may be used to help inform the selection of the combination dose level to carry forward in Part D if a dose below the MTD is chosen. Study therapy will be administered once every 2 weeks, in 8-week cycles, for up to 12 cycles. The combination of anti-LAG-3 [redacted] mg and nivolumab [redacted] mg was selected for expansion in Part D after showing the tolerability in Part C.

Study Phase: Phase 1/2a

Research Hypothesis: It is anticipated that anti–LAG-3 antibody (relatlimab), administered as monotherapy or in combination with nivolumab, will demonstrate adequate safety and tolerability, as well as a favorable risk/benefit profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

Objectives:

Primary Objective:

- The primary objective is to characterize the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD) of relatlimab administered alone or in combination with nivolumab to subjects with relapsed or refractory B-cell malignancies.
- The co-primary objective in combination therapy expansion Part D is to investigate the preliminary efficacy of relatlimab in combination with nivolumab in subjects with relapsed or refractory Hodgkin lymphoma (HL), and relapsed or refractory Diffused Large B Cell lymphoma (DLBCL). Tumor response will be evaluated according to the revised International Working Group (IWG) criteria for Malignant Lymphoma (2007 IWG criteria); see Appendix 1.

Secondary Objectives:

The secondary objectives are:

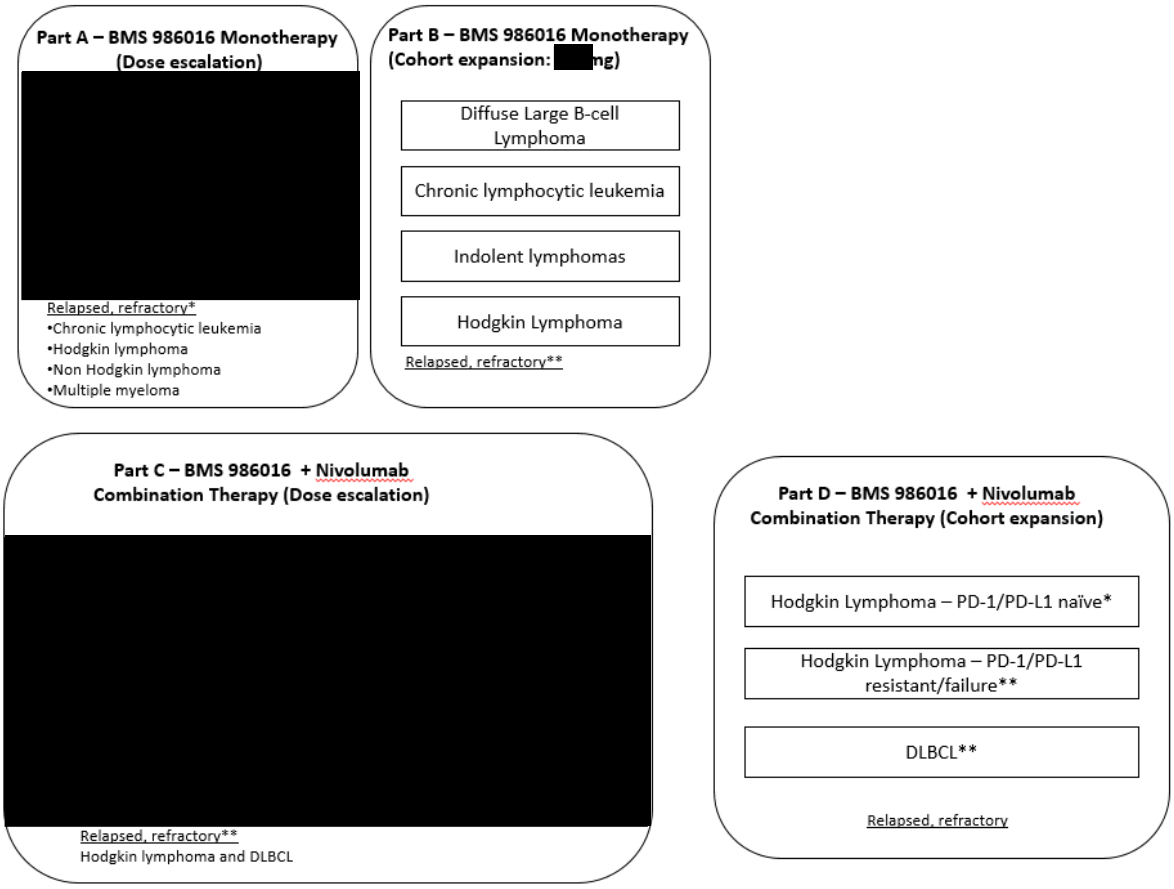
- To characterize the pharmacokinetics (PK) of relatlimab administered as monotherapy or in combination with nivolumab
- To characterize the immunogenicity of relatlimab administered as monotherapy or in combination with nivolumab

Exploratory Objectives:

- [redacted]
- To characterize pharmacokinetics and immunogenicity of nivolumab in combination with relatlimab.
- To evaluate the pharmacodynamic activity of relatlimab in the peripheral blood and tumor tissue as measured by, but not limited to, flow cytometry, immunohistochemistry, soluble factor analysis, and gene expression (eg, microarray technology and/or quantitative reverse transcription polymerase chain reaction [RT-PCR] and/or ribonucleic acid sequencing [RNAseq]).
- To investigate the association between biomarkers in the peripheral blood and tumor tissue, such as [redacted] expression, lymphocyte infiltration, neoantigen status, inflammatory gene signatures, with safety and efficacy following treatment with relatlimab administered as monotherapy and in combination with nivolumab.
- To determine the receptor occupancy of [redacted] in the peripheral blood and bone marrow.
- To explore the preliminary antitumor activity of relatlimab administered as monotherapy in subjects with relapsed or refractory B-cell malignancies.
- To characterize T-cell function in response to relatlimab administered as monotherapy or in combination with nivolumab.
- To explore exposure-response relationships in subjects treated with relatlimab as monotherapy and in combination with nivolumab.
- To assess the overall survival (OS) rates and progression-free survival (PFS) rates at various time points in HL and DLBCL patients in Part D. PFS will be assessed based on IWG (2007) criteria and the Lugano (2014) criteria.
- To evaluate tumor metabolic response per Lugano 2014 criteria using Deauville scoring (Appendix 7) in NHL and HL patients in Part D.

Study Design: This is a Phase 1/2a, open-label study of relatlimab administered as monotherapy or in combination with nivolumab to subjects with relapsed or refractory B-cell malignancies. The study will be conducted in 4 parts. Part A consists of a 3 + 3 + 3 dose escalation design in subjects with relapsed or refractory Chronic Lymphocytic Leukemia (CLL), HL, NHL, and multiple myeloma (MM) with relatlimab administered as monotherapy. Part B consists of cohort expansion in [redacted] disease-restricted populations of [redacted] to [redacted] subjects each with relatlimab administered as monotherapy Part C consists of a 3+3+3 dose escalation design in subjects with advanced HL and DLBCL with relatlimab administered in combination with nivolumab. Part D consists of cohort expansion in three disease restricted populations of [redacted] to [redacted] subjects each with relatlimab administered in combination with nivolumab (Figure 1).

Figure 1: Study Design Schematic



* In Part A, and selected cohort in Part D (ie, Hodgkin Lymphoma PD-1/PD-L1 naive cohort), subjects will be naive to immune cell-modulating antibody regimens (ICMARs), such as but not limited to anti PD-1, anti PD-L1, anti PD-L2, anti CTLA-4, anti-KIR, and/or anti-OX40 antibodies. Prior anti-CD20, alemtuzumab, and/or anti-CD30 antibody therapy are allowed.

** In Part B, Part C, and selected cohorts in Part D (ie, Hodgkin Lymphoma anti-PD-1/PD-L1 resistant/failure cohort and Diffuse Large B-Cell Lymphoma cohort),subjects will be naive to immune cell-modulating antibody regimens (ICMARs), such as, but not limited to anti CTLA-4, anti PD-L2, anti-KIR, and/or anti-OX40 antibodies. Prior anti-PD-1, anti-PD-L1, anti CD137, anti-CD20, alemtuzumab, and/or anti-CD30 antibody therapy are allowed.

Subjects will complete up to 4 periods of the study: Screening (up to 28 days), Treatment (up to a maximum of [redacted]-week cycles of study therapy), Clinical Follow-up (135 days following the last dose of study drug) and **Survival Follow-up** (up to [redacted] years following the first dose of study drug). Women of childbearing potential (WOCBP) will have additional follow-up assessments through Day 165 for home pregnancy tests. An independent period, Re-challenge, may be conducted in selected cases at progression.

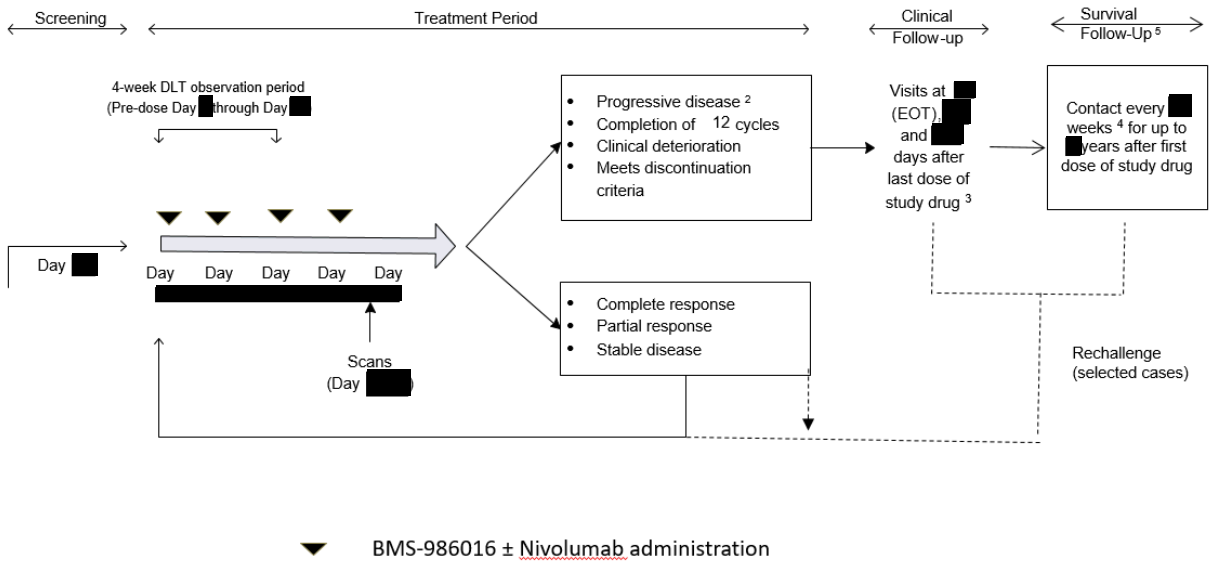
The **Treatment Period** consists of up to twelve 8-week treatment cycles. Each treatment cycle comprises [redacted] doses of relatlimab administered on Days [redacted]. Subjects will be allowed to continue study therapy until the first occurrence of either: (1) meeting criteria for discontinuation as described in Section 4.3.5, (2) completion of the maximum number of twelve 8-week cycles, (3) confirmed progressive disease (PD), or (4) clinical deterioration. Subjects who discontinue treatment will enter a 135-day **Clinical Follow-up** period. After completion of the **Clinical Follow-up period**, HL patients in Parts C and D will enter the **Survival Follow-up period**. During this period, clinic visits or telephone contact every 12 weeks will be performed to assess survival status. For participants who discontinue study treatment prior to disease progression, diagnostic imaging will be obtained every 6 months after the first clinical

follow-up in year 1 and in year 2, and annually thereafter for a total of 5 years maximum (since the first dose of the study drug) until disease progression. **Re-challenge** may be conducted in selected cases at progression.

If subjects progress during the Clinical Follow-Up period or the Survival Follow-Up period, they could further receive therapy with relatlimab alone or in combination with nivolumab (Re-challenge period) as long as the risk:benefit ratio is considered favorable by the Investigator and the Medical Monitor and eligibility criteria is met (Section 3.3). The original dose and schedule and protocol rules would apply accordingly. Thus, subjects could receive therapy for up to 12 additional eight-week cycles. Subjects will not be re-challenged a second time. Collection of archival tissue (baseline) and tumor biopsies (baseline and on-treatment) will be optional for subjects enrolled for re-challenge. PK and biomarker monitoring will be limited (Sections 5.5 and 5.7).

A study schematic is shown in Figure 2.

Figure 2: Study Schematic for Parts A,1 B, C, and D



1 Part A DLT period: 8 weeks.

2 Treatment beyond progression may be considered in selected subjects as described in Protocol Section 4.3.4.

3 WOCBP will have additional follow-up assessments through Day 165 for home pregnancy tests.

4 For participants who discontinue study treatment prior to disease progression, diagnostic imaging will be obtained every 6 months after the first clinical follow-up in year 1 and in year 2, and annually thereafter for a total of 5 years maximum (from the first dose of the study drug) until disease progression.

5 Survival follow up is for HL patients recruited in Parts C and D only.

Dose Escalation (Part A): In Part A, a 3 + 3 + 3 design will be used to assess the safety of relatlimab. The dose levels evaluated during dose escalation are provided in Figure 1. Dose escalation rules are outlined below. [redacted] subjects will initially be treated in each dose cohort; in Dose Cohort 1, the first [redacted] subjects will be designated as sentinel subjects and will begin treatment at least 5 days apart. Subjects in subsequent cohorts will not be required to observe the 5-day interval between treatment start dates.

Dose escalation will be based on the number of DLTs experienced during the DLT evaluation interval as determined by the Medical Monitor and Investigators. The DLT evaluation interval begins on the first day of treatment and continues for 8 weeks, ie, through Day [redacted] of the first cycle.

Dose escalation in Part A (Table 1) will proceed as follows:

- If none of the first [redacted] evaluable subjects in a dose cohort experiences a DLT within the DLT evaluation interval, then the next [redacted] subjects will be treated at the next higher dose cohort.
- If [redacted] of the first [redacted] evaluable subjects in a cohort experiences a DLT within the DLT evaluation interval, then [redacted] additional subjects will be treated in that dose cohort.
  - If no more than [redacted] of the first [redacted] evaluable subjects experiences a DLT during the DLT evaluation interval, then the next [redacted] subjects will be enrolled at the next higher dose cohort.
  - If [redacted] of the first [redacted] evaluable subjects in a cohort experience a DLT, that cohort will be expanded to [redacted] evaluable subjects.
- If [redacted] of the first [redacted] evaluable subjects, [redacted] of the first [redacted] evaluable subjects, or [redacted] of the first [redacted] evaluable subjects in a cohort experience a DLT within the DLT evaluation interval, that dose level will have exceeded the MTD and dose escalation will be terminated.

Table 1: Relatlimab Dose Escalation Schedule for Part A - Relatlimab Monotherapy

Dose Cohort Number	Relatlimab Dose (IV; mg)	Total Subjects
1	[redacted]	n = approximately [redacted]
2		n = approximately [redacted]
3		n = approximately [redacted]
4		n = approximately [redacted]
Total		N = approximately [redacted]

In consultation with Investigators, the Sponsor may investigate dose levels intermediate to those defined in the protocol. Prior to declaring the MTD (or MAD), and in consultation with Investigators, the Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Dose escalation rules (cohort size, DLT evaluation interval, cohort expansion criteria, etc.) will apply to the additional cohorts. A maximum of [redacted] subjects will be enrolled in any additional dose cohorts.

Cohort Expansion (Part B): The purpose of this cohort expansion is to gather additional safety, tolerability, PK, and pharmacodynamic information regarding relatlimab dosed at [redacted] mg. The dose selected for Part B has not exceeded the MTD in Part A (the MTD was not reached at up to [redacted] mg relatlimab Q2W in monotherapy).

In Part B, the four expansion cohorts will be restricted to the tumor types listed in Figure 1 and Table 2. Continuous evaluation of toxicity events will be assessed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds [redacted] across all subjects treated in the Part B cohort expansions, the findings will be discussed with the Medical Monitor and Investigators; further enrollment may be interrupted. Depending on the nature and grade of the toxicity and after assessing the risk:benefit ratio, the dose for all or for select cohorts may be reduced.

Table 2: Tumor Types Eligible For Part B - Cohort Expansion Relatlimab Monotherapy

Tumor Type	Total Subjects
Chronic Lymphocytic Leukemia (CLL)	approximately [redacted]
Diffuse Large B-Cell Lymphoma (DLBCL)	approximately [redacted]
Indolent non-Hodgkin lymphoma	approximately [redacted]
Hodgkin Lymphoma (HL)	approximately [redacted]
Total	approximately [redacted]

All subjects in Part B will be naive to immune cell-modulating antibody regimens (ICMARs), such as, but not limited to anti-CTLA-4, anti PD-L2, anti-KIR, and/or anti-OX40 antibodies except for anti-PD-1, anti-PD-L1, anti-CD137, anti-CD20, alemtuzumab, or anti-CD30 antibody therapy.

Cohort Escalation Combination Therapy (Part C): As in Part A, a 3 + 3 + 3 design will also be used in Part C to assess the safety of relatlimab given in combination with nivolumab as a sequential infusion. A fourth subject may be enrolled at the beginning of a dose escalation cohort following agreement between the Investigator and the Sponsor/Medical Monitor, if subject is able to start the first day of dosing within approximately one week of the third subject in the same dose escalation cohort.

The dosages during dose escalation are provided in Figure 1 and Table 3.

Treatment in Part C will be initiated after the decision is made to escalate to the fourth dose cohort ([redacted] mg anti-LAG-3 in combination with [redacted] mg anti-PD-1) in CA224020 study. At no point will the dose of relatlimab administered in combination with nivolumab (Part C) exceed doses of relatlimab that have been demonstrated previously to be safe on the monotherapy dose escalation arm (Part A). The escalation cohorts in Part C will be restricted to subjects with 1) HL naive to anti-PD-1/PD-L1, 2) HL (naive to anti-PD-1/PD-L1 or whose disease progresses while-on or within 3 months after treatment with anti-PD-1 or anti-PD-L1 antibody 3) DLBCL.

Dose escalation in Part C will proceed as described for Part A with the exception that the DLT period will be reduced from 8 weeks to 4 weeks (see Section 3.1.5). If no MTD is reached through Dose Cohort 3, then additional cohorts of relatlimab given in combination with nivolumab may be considered based on the aggregate safety experience during dose escalation. Enrollment of additional cohorts will be implemented upon consultation and agreement between Investigators and the Sponsor via a protocol amendment.

Prior to declaring the MTD (or MAD), and in consultation with Investigators, the Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Dose escalation rules (cohort size, DLT evaluation interval, cohort expansion criteria, etc.) will apply to these expanded or additional cohorts. A maximum of [redacted] subjects will be enrolled in any additional or expanded dose cohorts.

After completion of the relatlimab (anti-LAG-3) [redacted] mg and nivolumab (BMS-936558) [redacted] mg cohort, the intermediate dose combination of anti-LAG-3 [redacted] mg and nivolumab [redacted] mg was investigated in Part C. The dose combination ([redacted] mg anti-LAG-3/[redacted] mg nivolumab) was well-tolerated in Part C and therefore selected for Part D (expansion).

No within-subject dose escalations will be permitted. If a dose level is found to exceed the MTD, subjects enrolled in that dose level may be reduced to a lower dose following consultation and agreement between Investigators and the Sponsor.

Table 3: Dose Escalation Schedule for Part C - Relatlimab in Combination with Nivolumab

Dose Cohort Number	Total Subjects	Relatlimab Dose (IV; mg)	Nivolumab Dose (IV; mg)
1	n = approximately [redacted]	[redacted]	[redacted]
2	n = approximately [redacted]		
3	n = approximately [redacted]		
Total	N = approximately [redacted]		

Note: Part C will be limited to subjects with HL (naive to anti-PD-1/PD-L1 or whose disease progresses while-on or within 3 months after treatment with anti-PD-1 or anti-PD-L1 antibody) and DLBCL.

Cohort Expansion Combination Therapy (Part D): The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information in subjects treated with sequential infusion of nivolumab followed by administration of relatlimab. The doses selected for Part D will not exceed the MTD (or MAD if no MTD is determined) in Part C, but may incorporate assessment of other data including toxicities and PK, pharmacodynamic data from Parts A, B and C and data from the CA224020 study. Doses to be considered may include doses intermediate to those evaluated in Part C if recommended by the Investigators and the Sponsor. The intermediate dose of relatlimab (anti-LAG-3) [redacted] mg and nivolumab [redacted] mg, tested below the MTD, and was well tolerated and was selected for extension. Modeling may be used to help inform the selection of the combination dose level to carry forward in Part D if a dose below the MTD is chosen. Three expansion cohorts will be restricted to the tumor types listed in Table 4. Continuous evaluation of toxicity events will be assessed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds [redacted] across all subjects treated in the Part D cohort expansions, the findings will be discussed with the Medical Monitor and Investigators; further enrollment may be interrupted. Depending on the nature and grade of the toxicity and after assessing the risk:benefit ratio, the dose for all or for select cohorts may be reduced.

Table 4: Tumor Types Eligible For Part D - Cohort Expansion Relatlimab in Combination with Nivolumab

Tumor Type	Total Subjects
Hodgkin Lymphoma - anti-PD-1 naive	n=approximately [redacted]
Hodgkin Lymphoma - anti-PD-1 progressed	n=approximately [redacted]
Diffuse Large B-Cell Lymphoma	n=approximately [redacted]
Total	n=approximately [redacted]

Re-challenge in Dose Escalation and Cohort Expansion

If subjects progress during the clinical follow-up period or the survival follow-up period, they could further receive therapy with relatlimab alone or in combination with nivolumab (Re-challenge) as long as the risk:benefit ratio is considered favorable by the Investigator and the Medical Monitor and the following eligibility criteria is met: 1) Subject has confirmed disease progression 2) Subject has not experienced relatlimab related adverse events leading to permanent discontinuation. The original dose and schedule of therapy and protocol rules will apply. Thus subjects could receive therapy for up to 6 additional eight-week cycles.

Subjects who are re-challenged and who subsequently have an objective response will not be included in the primary analysis of efficacy. Responses to re-challenge will be evaluated in a separate analysis. Subjects will not be re-challenged a second time.

Dose-Limiting Toxicities:

For the purpose of guiding decisions regarding dose escalation in Part A, (DLT) will be determined based on the incidence, intensity, and duration of AEs that are related to study drug and that occur within 8 weeks of initiation of study drug (ie, the DLT evaluation interval which begins on the first day of treatment and ends on Day 56 of the first cycle).

For the purpose of guiding decision in combination dose escalation in Part C, (DLT) will be determined based on the incidence, intensity, and duration of AEs that are related to study drug and that occur within 4 weeks of initiation of study drug (ie, the DLT evaluation interval which begins on the first day of treatment and ends on Day 29 of the first cycle).

Adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). For the purpose of subject management, any AE that meets DLT criteria, regardless of the cycle in which it occurs, will lead to dose interruption.

Dose escalation will be based on the number of DLTs experienced during the DLT evaluation interval as determined by the Medical Monitor and Investigators.

No intra subject dose escalation is allowed. In Part A, subjects who receive at least 1 dose of study drug during the 8-week evaluation interval will be considered evaluable for DLT determination. In Part C, subjects who receive at least 2 doses of study drug during the 4-week evaluation interval will be considered evaluable for DLT determination. Subjects who withdraw from the study during the DLT evaluation interval for reasons other than a DLT and/or for whom safety data are unavailable for the entire DLT evaluation interval may be replaced at the same dose level. In the event that an infusion cannot be administered at a scheduled visit during the DLT evaluation interval, it must be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the originally scheduled visit should be performed and subjects will be considered evaluable for DLT determination. If the delay is more than 7 days, the dose will be considered missed and will not be replaced. Subjects with a delay of more than 7 days will not be considered evaluable for DLT determination. Unevaluable subjects may be replaced at the same dose level.

Duration of Study: Subjects will be allowed to continue on therapy for up to twelve 8-week cycles or confirmed PD or until meeting criteria for discontinuation as described in Section 3.5. Treatment beyond progression may be considered in select subjects as described in Section 4.3.4. Subjects may be on study for a total of up to approximately 5 years, including a 28-day screening period, up to twelve 8-week cycles of treatment, a 135-day clinical follow-up period, and up to 5 years of follow-up for survival (beginning from the first dose of study drug). The study will end once survival follow-up has concluded. For WOCBP, additional home pregnancy tests through Day [redacted]. The total duration of the study is expected to be approximately 9-10 years from the time of the first visit of the first subject to the required survival follow-up of the last subject enrolled. If subjects progress during the clinical follow-up prior or the survival follow-up period, could further receive therapy with relatlimab alone or in combination with nivolumab (Re-challenge) as long as they meet eligibility criteria and the risk:benefit ratio is considered favorable by the Investigator and the Medical Monitor. The original dose and schedule and protocol rules would apply accordingly. Subjects will not be re-challenged a second time.

Number of Subjects: Approximately [redacted] subjects may be dosed.

Study Population: Male and female subjects with histologic or cytologic confirmation of CLL, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma who have relapsed following prior treatment or been refractory to prior treatment and who meet all entry criteria will be eligible to participate

***Dose Escalation (Part A)*:** Adult subjects with relapsed or refractory non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), chronic lymphocytic leukemia (CLL), or multiple myelomas are eligible.

Cohort Expansion (Part B): Four disease-restricted groups will be permitted during cohort expansion per Table 2.

Cohort Escalation Combination Therapy (Part C): Adult subjects with relapsed or refractory Hodgkin lymphoma, and Diffuse Large B-Cell Lymphoma.

Cohort Expansion Combination Therapy (Part D): Three disease-restricted groups will be permitted per Table 4.

Parts A, B, C, and D: Neutrophil count must be > 750/μL and platelet count > 50,000/μL. Subjects with primary cutaneous lymphoma, lymphoproliferative diseases associated with primary immune deficiencies, and lymphomas associated with human immunodeficiency virus (HIV) infection are excluded. Subjects with solitary bone or solitary extramedullary plasmacytoma as the only evidence or plasma cell dyscrasia, subject with Monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma or Waldenstrom's macroglobulinemia or active plasma cell leukemia are excluded. Subjects with autoimmune disorders are also excluded.

Women must not be nursing or pregnant. WOCBP must have a negative pregnancy test within 24 hours prior to receiving their first dose of study medication. WOCBP must agree to follow instructions for method(s) of contraception based on the information in Appendix 3 for a total of 24 weeks after their last dose of investigational drug (a period of 30 days plus the time required for the investigational drug to undergo 5 half-lives [ie, 165 days total or 24 weeks]).

Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception based on the information in Appendix 3 for a total of 33 weeks after their last dose of investigational drug (a period of 90 days plus the time required for the investigational drug to undergo 5 half-lives [ie, 225 days total or 33 weeks]).

Study Assessments:

- Safety outcome measures: Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, electrocardiograms (ECGs), physical examinations, pulse oximetry, and clinical laboratory tests. AEs will be assessed continuously during the study and for 135 days after the last treatment. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and reviewed for potential significance and importance. AEs and laboratory tests will be graded using the NCI CTCAE v4.0.
- Efficacy measures: Tumor responses will be determined for subjects with adequate data as defined by the following efficacy criteria.
  - NHL and HL subjects: Revised Response Criteria for Malignant Lymphoma (Appendix 1)
  - NHL or HL subjects who had FDG-PET scans performed in the pre-treatment period and during this study: retrospective assessment using Lugano 2014 Response Criteria (Appendix 7)
  - CLL subjects: Guidelines for the Diagnosis and Treatment of Chronic Lymphocytic Leukemia (Appendix 2)
  - MM subjects: Response Criteria Modified from IMWG for Multiple Myeloma (Appendix 6)
- Pharmacokinetic measures: Serial serum samples will be collected from all subjects at specified time points to evaluate concentrations of relatlimab and/or nivolumab. PK parameters such as Cmax, Ctrough, Tmax, AUC(TAU), CLT, and AI will be derived from serum concentration versus time data.
- Immunogenicity measures: Serum samples will be collected from all subjects at specified time points to evaluate development of anti-drug antibodies (ADA) to relatlimab and/or nivolumab.
- Exploratory Biomarker measures: The sample collection and biomarker assessment strategy is designed to address mechanisms of action, pharmacodynamic changes associated with relatlimab administered as monotherapy or in combination with nivolumab, and potential identification of predictive safety and efficacy biomarkers associated with relatlimab, and to evaluate potential mechanisms of resistance to relatlimab. To address these key questions, peripheral blood, serum, and biopsy samples will be collected prior to and during study drug treatment in Parts A, B, C, and D, of this study.

Statistical Considerations:

Sample Size:

Dose escalation (Part A and C): The sample size at each dose depends on observed toxicity and cannot be precisely determined. Part A will have [redacted] to [redacted] subjects in each cohort.

Cohort expansion (Part B): Approximately [redacted] subjects at [redacted] mg dose of relatlimab together with [redacted] subjects from Part A [redacted] mg dose level (a total of [redacted] subjects) will provide better understanding of the safety profile at

[redacted] mg dose level. If [redacted] of [redacted] subjects or [redacted] of [redacted] subjects (ie, [redacted]) experience a toxicity there is at least [redacted] confidence that the true toxicity rate is not greater than [redacted] (based on Clopper-Pearson exact binomial 1-sided [redacted] confidence interval). In addition, administration of relatlimab at the dose of [redacted] mg to [redacted] or [redacted] subjects provides [redacted] probability of observing at least one occurrence of any adverse event that would occur with [redacted] or [redacted] incidence, respectively, in the population from which the sample was drawn.

Cohort Expansion for Combination Therapy (Part D): The objective of this expansion in combination with nivolumab is, in addition to demonstrating adequate safety and tolerability, to evaluate a favorable risk/benefit assessed by signal seeking for anti-PD-1/PD-L1 progressed nivolumab HL, improvement in complete response rate (CRR) for anti-PD 1/PD-L1 naive HL relative to PD-1 monotherapies, and improvement in objective response rate (ORR) for DLBCL relative to existing available therapies.

A 2-stage design (Fleming's), which allows to stop early for futility as well as for efficacy, will be used as a guidance for each disease cohort with reasonable false positive rate (eg, FPR [redacted]) and false negative rate (eg, FNR [redacted]) based on assumptions of true (target) and historic response rate for each cohort. Each disease cohort will be handled independently and there will be no multiplicity adjustment. The assumed historic and target response rates may change over time and may need to be adjusted by the time response data from this study are available. Enrollment may continue into stage 2 while the planned number of subjects for stage 1 are followed for efficacy evaluable tumor assessments. There will be no stopping of a disease cohort for efficacy.

For anti-PD-1/PD-L1 progressed HL, the assumed target response rate will be [redacted]% vs [redacted]% of inefficacious rate; as there is no standard of care available in this patient population. For anti-PD-1/PD-L1 naive HL, the assumed target CRR will be [redacted]% vs [redacted]% observed with anti-PD 1 monotherapy. For DLBCL, the assumed target ORR will be [redacted] vs [redacted]%, which was obtained from Study CA209039 by averaging the observed rates of monotherapy [redacted] and a combination treatment with ipilimumab [redacted]. The sample size and operational characteristics of using Fleming's 2-stage design are provided, as an example, in Table 5, although not used for statistical hypothesis testing.

Guided by Table 5, approximately [redacted] subjects, for example, will be treated in Stage 1 for an initial evaluation of efficacy. This will inform potential early decisions and guide planning/operations, or early termination after taking into consideration of additional data such as time to and/or duration of response, and safety. For example, assuming the true response rate is [redacted] for anti-PD-1/PD-L1 progressed HL cohort when treated with relatlimab in combination with nivolumab, if there are [redacted] or more responses in [redacted] subjects, the cohort may be stopped for efficacy and consider larger scale comparative trials. The probability of early stopping for efficacy is approximately [redacted] if in fact the treatment is efficacious. If there is no response in [redacted] treated subjects, the cohort may be stopped for futility. The probability of early stopping for futility is approximately [redacted] if in fact the treatment is inefficacious, eg, [redacted]. If there is just [redacted] response, an additional [redacted] subjects may be treated to collect more data. This design yields a FPR of [redacted] when the true response rate is [redacted] and FNR of [redacted] when the true response rate is [redacted] rather than [redacted]. For anti-PD-1/PD-L1 naive HL and DLBCL cohorts assuming the true response rate is [redacted] when treated with relatlimab in combination with nivolumab, if there are [redacted] or more responses in [redacted] subjects, the cohort may be stopped for efficacy. The probability of early stopping for efficacy is approximately [redacted] if in fact the treatment is efficacious. If there are [redacted] or fewer responses in [redacted] treated subjects, the cohort may be stopped for futility. The probability of early stopping for futility is approximately [redacted] if in fact there is no improvement with the combination treatment. If there are [redacted] or [redacted] responses in [redacted] treated subjects, additional [redacted] subjects may be treated to collect more data. This design yields a FPR of [redacted] when the true response rate is [redacted] and FNR of [redacted] when the true response rate is [redacted].

Table 5: Example of a Two-stage Design Characteristics

Cohort[a]	Historic/Target Rate (%)	Stage	Cumulative Sample Size	Conclude Futility If R[b]	Conclude Efficacy If R	PET[c] for futility (%)	PET for efficacy (%)	FPR/FNR[d] (%)
HL anti-PD-1/PD-L1 progressed	[redacted]	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		2						[redacted]
HL anti-PD-1/PD-L1 naive and DLBCL	[redacted]	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		2						[redacted]

[a] DLBCL: diffuse large B cell lymphoma.

[b] R is the cumulative number of responses at the end of stage.

[c] Probability of early termination.

[d] False positive rate/false negative rate.

Endpoints

Primary Endpoints

The primary endpoint of this Phase 1 study is safety as measured at the study level by the rate of AEs, SAEs, AEs leading to discontinuation, deaths, and laboratory abnormalities, assessed during treatment and for up to 135 days after the last treatment. All subjects who receive at least one dose of relatlimab alone or in combination with nivolumab will be analyzed for safety. Co-primary endpoint in Part D is objective response rate (ORR) and duration of response (DOR).

Secondary Endpoints

Pharmacokinetics Select PK parameters, such as Cmax, Ctrough, Tmax, AUC(TAU), CLT, and AI, will be assessed from concentration-time data at select time points throughout treatment with relatlimab administered alone or in combination with nivolumab

Immunogenicity The proportion of subjects who are ADA-positive at baseline, the proportion of subjects who become ADA-positive on study, and the proportion of subjects who remain ADA-negative to relatlimab will be measured during treatment and for up to 135 days after their last treatment in post-treatment follow-up.

Efficacy: All efficacy analyses will be based on the all treated analysis population except otherwise stated. Co-primary, secondary and exploratory efficacy endpoints for Part D subjects are as follows:

Objective Response Rate (ORR)

ORR based on investigator assessment, according to the applicable criteria based on tumor type, will be a co-primary endpoint in Part D. For the NHL and HL subjects, the ORR will be based on the IWG (2007) response criteria. In addition to the primary ORR endpoint, an exploratory endpoint of ORR based on the Lugano (2014) response criteria in the NHL and HL subjects in Part D will be assessed. For the Lugano criteria, response is defined as complete metabolic response (CMR) and partial metabolic response (PMR).

Duration of Objective Response (DOR)

DOR is defined as the time between the date of first documented response (CR or PR) to the date of the first objectively documented progression as per criteria relevant to each disease type in Part D (Appendices 1, 2, and 6)], or death due to any cause, whichever occurs first. For subjects who neither progress nor die, DOR will be censored on the date of their last tumor assessment. Subjects who start subsequent therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy. This endpoint will only be evaluated in subjects with objective response of CR or PR. DOR will be evaluated based on investigator assessments. DOR is co primary endpoint in Part D. DOR based on the Lugano (2014) response criteria, response defined as CMR or PMR, will be assessed for the NHL/HL subjects in Part D as an exploratory endpoint.

Complete Response (CR) Rate and Duration

The CR rate is defined as the number of subjects with a best overall response (BOR) of CR according to the applicable criteria based on tumor type, based on IWG criteria for NHL and HL subjects, divided by the number of treated subjects. The duration of CR (DoCR) will only be evaluated in subjects with BOR of CR and is defined as the time from first documentation of CR (the date of first negative FDG-PET scan) to the date of initial objectively documented progression as determined using the applicable criteria based on tumor type or death due to any cause, whichever occurs first. Censoring will be applied as per DOR definition. CR rate and DoCR will be evaluated based on investigator assessments. CR rate is an exploratory endpoint in this study.

Progression Free Survival (PFS) Rate

PFS is defined as the time from first dose to the date of first objectively documented progression, per applicable criteria based on tumor type or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor

assessments and did not die will be censored on the date of first dose. Subjects who started any subsequent anti-cancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy. The PFS rate at time T is defined as the probability that a subject has not progressed and is alive at time T following first dose. PFSR will be assessed at Weeks 16, 24, 32, 40, and 100, and evaluated based on investigator assessments. PFS will be an exploratory endpoint in this study.

Overall Survival (OS) Rate

OS is defined as the time between the date of first dose and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive. The overall survival rate at time T is defined as the probability that a subject is alive at time T following first dose OS will be assessed at various time points in HL patients in Part D.

Exploratory Endpoints:

Biomarkers Biomarkers endpoints from peripheral blood may include measures such as levels of soluble factors, as well as activation and proliferation of subsets of immune cells including but not limited to subset of T cells characterized by immunophenotyping, at each scheduled time point. Biomarker endpoints from tumor biopsies may include, but will not be limited to, expression of immune activation genes, the architecture of immune cells in the tumor and expression of LAG3, major histocompatibility complex (MHC) class II, programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1). Measures of receptor occupancy as characterized in peripheral blood, bone marrow, and lymph node (if available) may also be provided.

Receptor Occupancy Measures of receptor occupancy as characterized in peripheral blood, bone marrow, and lymph node (if available) will be provided.

Other Efficacy Endpoints

PFS based on Lugano (2014) Criteria PFS for a subject is defined as the time from the first dosing date to the date of first progressive metabolic disease or death due to any cause (death occurring after retreatment will not be considered), whichever occurs first. Subjects who died without a reported prior progression will be considered to have progressed on the date of their death. The censoring rules applied to the PFS endpoint based on the IWG criteria will also be used for this endpoint.

Complete Metabolic Response Rate based on Lugano 2014 Criteria The CMR rate is defined as the number of subjects with a BOR of CMR based on the Lugano (2014) criteria divided by the number of treated subjects. The duration of CMR (DoCMR) will only be evaluated in subjects with BOR of CMR and is defined as the time from first documentation of CMR (the date of first negative FDG-PET scan) to the date of initial objectively documented progressive metabolic disease based on the Lugano (2014) criteria or death due to any cause, whichever occurs first. Censoring will be applied using the DOR definition. CMR rate and DoCMR will be evaluated based on investigator assessments.

Analyses:

Unless otherwise specified, safety data from Parts A-D will be summarized both (1) overall by dose level and across all dose levels and (2) by dose level and across all dose levels within each tumor type. Efficacy data will be summarized by dose level within each tumor type and patient population.

Efficacy Individual ORR, CRR, DOR, CMR, PMR, and PFS (based on IWG and Lugano criteria) will be determined. BOR outcomes will be summarized using frequency tables together with 2-sided 95% confidence intervals. Time to event distribution (eg, PFS, DOR, and DoCMR) will be estimated using Kaplan-Meier (K-M) method. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology (using log-log transformation for constructing the confidence intervals). Rates at fixed time points (e.g. PFSR 24 weeks) will be derived from the K-M estimate and corresponding confidence interval will be derived based on Greenwood formula. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method. OS data will be analyzed similarly to PFS data analysis.

Safety: All subjects who receive study drug therapy will be evaluated for safety endpoints. All recorded AEs will be coded according to the most current version of MedDRA and be graded using the NCI CTCAE version 4.0. AEs will be listed and subjects with AEs will be summarized based on the event with worst CTC grade by system organ class (SOC) and preferred term (PT), counting once at the PT term level and once at the SOC level, for each dose, dosing regimen, and overall. Vital signs and clinical laboratory test results will be listed and summarized by treatment. In addition, the worst grade of a laboratory measure observed on-study by the baseline grade (per CTCAE v 4) will also be generated for selected laboratory tests. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator and abnormalities, if present, will be listed.

Pharmacokinetics: PK parameters for relatlimab as monotherapy and in combination with nivolumab will be calculated using noncompartmental analyses. Summary statistics will be tabulated for the PK parameters of relatlimab by treatment and study day/week. To describe the dependency on dose of relatlimab, scatter plots of Cmax and AUC (TAU) versus dose may be provided for each day measured. Dose proportionality of BMS 986016 will also be assessed based on a power model. Summary statistics of nivolumab exposure at trough and end of infusion will be tabulated separately.

Immunogenicity: A listing will be provided for all available immunogenicity data. The number and percent of subjects who meet specified endpoint definitions in the statistical analysis plan (SAP) will be summarized for each drug. To examine the potential relationship between immunogenicity and safety, a table summarizing the frequency and type of AEs of special interest may be explored by immunogenicity status. In addition, potential relationships between immunogenicity and efficacy, pharmacodynamic markers, and/or PK may also be explored.

Exploratory Biomarkers: The pharmacodynamic effect on TILs, MILs, and other key tumor markers in subjects who undergo biopsy will be summarized using summary statistics and plots. In addition, the correlation of [redacted] or [redacted] changes and tumor marker expression with measures of peripheral blood markers may be explored graphically, and using appropriate modeling approaches based on data availability. Associations of biomarker measures from peripheral blood or tumor biopsy with clinical outcomes may also be explored graphically and further assessed as needed by methods such as, but not limited to, logistic regression and characterized by appropriate statistics.

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1 INTRODUCTION AND STUDY RATIONALE

The use of immunotherapy in the treatment of cancer is based on the premise that tumors evade the endogenous immune response by being recognized as self, and not non-self. Tumors develop immune resistance using different mechanisms; the goal of immunotherapy is to counteract these resistance mechanisms, enabling the endogenous immune system to reject tumors. The recent success of immune-modulating agents blocking checkpoint inhibitor molecules (eg, programmed cell death 1 [PD-1], programmed cell death protein ligand 1 [PD-L1], and cytotoxic T lymphocyte–associated antigen 4 [CTLA-4]) in patients with refractory solid tumors has provided proof-of-concept of the efficacy of immune system activation as a therapeutic modality. Specifically, patients with metastatic melanoma had an increase in overall survival when treated with the anti–CTLA-4 antibody, ipilimumab.[1] Moreover, the same patient population treated with the combination of ipilimumab and an anti–PD-1 antibody (nivolumab, BMS-936558) achieved an unprecedented 53% response rate and prolonged responses.[2] Recent preclinical data support the clinical testing of yet another checkpoint inhibitor molecule, lymphocyte activation gene 3 (LAG-3), as a relevant therapeutic target in select hematological malignancies. Current concepts suggest that therapy with immune-modulating agents may achieve robust and prolonged responses and deserves to be further explored.

1.1 Study Rationale

1.1.1 Relapsed Refractory Hematological Malignancies as Unmet Medical Needs

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of lymphoproliferative malignancies with distinct clinical outcomes and responses to treatment. There are an estimated 69,740 new cases to be diagnosed in the United States in 2013.[3] The NHLs can be divided into 2 prognostic groups: the indolent lymphomas (eg, follicular) and the aggressive lymphomas (eg, diffuse large B-cell [DLBCL], mantle cell, Burkitt). Aggressive lymphomas have an overall survival of approximately 60% at 5 years. Despite the fact that half of the aggressive cases are cured, the vast majority of relapses occur in the first 2 years after therapy. The concerning issue is that not all patients tolerate standard treatment with high-dose therapy and stem cell rescue at relapse.[4]

Chronic lymphocytic leukemia (CLL) is the most commonly diagnosed leukemia among adults in the United States, with approximately 16,000 new cases estimated in the United States for 2013.[3] The median age at diagnosis is 72 years, with approximately 70% of patients diagnosed at older than 65 years (and 40% diagnosed at age ≥ 75 years).[5] Thus, CLL mainly affects elderly patients who cannot tolerate current myelosuppressive regimens used in younger and fitter patients.[6]

Hodgkin's lymphoma (HL) is yet another malignancy of lymphoid tissue with an estimated 9,290 new cases in the United States in 2013.[3] HLs can be divided into 2 pathology groups: classical HL (CHL) and lymphocyte-predominant HL (LPHL). In Western countries, CHL accounts for 95% of HL cases. CHL is pathologically characterized by the presence of Hodgkin-Reed-Sternberg (HRS) cells in an inflammatory background. Combined chemotherapy

and radiotherapy result in durable response rates but at the expense of significant morbidity (eg, secondary malignancies, cardiac disease, and infertility). Unfortunately, around 30% of patients will become refractory to initial therapy or will relapse. The therapeutic options for refractory or relapsed patients are very limited and also carry a high morbidity rate.[4]

Multiple myeloma (MM) is an incurable malignancy arising from postgerminal mature B cells, characterized by an excess of monotypic plasma cells in the bone marrow, resulting in elevated levels of monoclonal immunoglobulins in the serum and/or urine. In the United States, the estimated annual diagnosed incidence is 16,000, with approximately 50,000 prevalent cases. Multiple myeloma accounts for 10% of all hematologic malignancies and 1% of all malignancies. Advances in therapy have improved outcomes but the disease remains essentially incurable and is associated with a high morbidity and mortality.

To address these unmet medical needs, compounds that have novel mechanisms of action with relevant single-agent activity and good safety profiles need to be evaluated in clinical studies with the goal of achieving a better therapeutic index when used in combination regimens.

1.1.2 Rationale for Nivolumab Therapy

Programmed cell death 1 (PD-1) is a cell surface signaling receptor that plays a critical role in the regulation of T cell activation and tolerance.[7] It is a type I transmembrane protein and together with BTLA, CTLA-4, ICOS, and CD28, make up the CD28 family of T cell co stimulatory receptors. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[8] It is also expressed on natural killer (NK) cells.[9] Binding of PD-1 by its ligands PD L1 and PD-L2, results in phosphorylation of the tyrosine residue in the proximal intracellular immune receptor tyrosine inhibitory domain, followed by recruitment of the phosphatase SHP-2, eventually resulting in down-regulation of T cell activation. One important role of PD-1 is to limit the activity of T cells in peripheral tissues at the time of an inflammatory response to infection, thus limiting the development of autoimmunity.[10] Evidence of this negative regulatory role comes from the finding that PD-1deficient mice develop lupus-like autoimmune diseases including arthritis and nephritis, along with cardiomyopathy.[11,12] In the tumor setting, the consequence is the development of immune resistance within the tumor microenvironment.

PD-1 is highly expressed on tumor-infiltrating lymphocytes, and its ligands are upregulated on the cell surface of many different tumors.[13] Multiple murine cancer models have demonstrated that binding of ligand to PD-1 results in immune evasion. In addition, blockade of this interaction results in antitumor activity. These findings provided the rationale for testing PD 1 pathway blockade in clinical trials.

Nivolumab is a fully human monoclonal antibody that binds to PD-1 with nanomolar affinity and a high degree of specificity, thus precluding binding of PD-1 to its ligands PD-L1 and PD-L2.[14] Nivolumab does not bind other related family members, such as BTLA, CTLA-4, ICOS, or CD28.

Nivolumab has demonstrated clinical activity as monotherapy in subjects with a variety of hematological advanced malignancies including diffuse large B-cell lymphoma, follicular

lymphoma, and Hodgkin's lymphoma. Treatment with Nivolumab is indicated for patients with unresectable or metastatic melanoma as both a monotherapy and in combination with ipilimumab. Nivolumab is also approved for non-small cell lung cancer following failure on or after platinum based therapy, as well as for advanced renal cell carcinoma following treatment with an anti-angiogenic therapy (Section 1.7.3.2).

1.1.3 LAG-3 and T Cell Exhaustion

LAG-3 (CD223) is a type I transmembrane protein that is expressed on the cell surface of activated $CD4^+$ and $CD8^+$ T cells and subsets of natural killer (NK) and dendritic cells.[15,16] LAG-3 is closely related to CD4, which is a co-receptor for T helper cell activation. Both molecules have 4 extracellular Ig-like domains and require binding to their ligand, major histocompatibility complex (MHC) class II, for their functional activity. In contrast to CD4, LAG-3 is only expressed on the cell surface of activated T cells and its cleavage from the cell surface terminates LAG-3 signaling. LAG-3 can also be found as a soluble protein but it does not bind to MHC class II and its function is unknown.

It has been reported that LAG-3 plays an important role in promoting regulatory T cell (Treg) activity and in negatively regulating T cell activation and proliferation.[17] Both natural and induced Treg express increased LAG-3, which is required for their maximal suppressive function.[18,19] Furthermore, ectopic expression of LAG-3 on $CD4^+$ effector T cells reduced their proliferative capacity and conferred on them regulatory potential against third party T cells.[19] Recent studies have also shown that high LAG-3 expression on exhausted lymphocytic choriomeningitis virus (LCMV)-specific $CD8^+$ T cells contributes to their unresponsive state and limits $CD8^+$ T-cell antitumor responses.[20,21] In fact, LAG-3 maintained tolerance to self and tumor antigens via direct effects on $CD8^+$ T cells in 2 murine models.[21]

Immune tolerance observed in the setting of tumor development and tumor recurrence, however, seems to be mediated by the co-expression of various T-cell negative regulatory receptors, not solely from LAG-3. Data from chronic viral infection models,[20,21,22] knock-out mice,[23,24,25] tumor recurrence models,[26] and, to a more limited extent, human cancer patients,[26,27,28] support a model wherein T cells that are continuously exposed to antigen become progressively inactivated through a process termed "exhaustion." Exhausted T cells are characterized by the expression of T-cell negative regulatory receptors, predominantly CTLA-4, PD-1, and LAG-3, whose action is to limit the cell's ability to proliferate, produce cytokines, and kill target T cells and/or to increase Treg activity. However, the timing and sequence of expression of these molecules in the development and recurrence of each tumor type have not been fully characterized.

1.1.4 LAG-3 Expression in Hematological Malignancies

The expression of the checkpoint inhibitors PD-1 and PD-L1 in NHLs,[29,30,31,32] CLL,[33,34] HL,[35,36] and MM[37,38] has been associated with T cell exhaustion. Interestingly, the expression of these molecules may be driven by mutations leading to constitutive activity of their enhancers/promoters and/or by the infection of host T cells by Epstein Barr virus (EBV), among other factors.[39]

Emerging data indicates that LAG-3 expression on tumor-infiltrating lymphocytes (TILs) and peripheral blood could also be mediating T cell exhaustion in hematological malignancies.

In primary CHL, for example, a small number of HRS cells are surrounded by a profuse inflammatory infiltrate. Yet, HRS cells fail to evoke an effective T cell response despite the expression of class II MHC on tumor cells. This effect, known as the "paradox effect,"[40] could very well be mediated by T cell exhaustion. In this regard, Gandhi et al. have shown strong expression of LAG-3 on TILs in proximity to HRS cells, particularly in cases with EBV tissue positivity. In these HL subjects, circulating CD4+LAG-3hi cells were only elevated at diagnosis or at clinical relapse, but not during remission.[28] Although FOXP3 positivity was neither linked to LAG-3 nor EBV tissue status, both Treg and LAG-3+ CD4+ T cells were shown to be involved in tumor immune evasion because the expression of FoxP3 and LAG-3, respectively, coincided with the impairment of tumor-specific T cell responses. These results, in addition to the known expression of PD-L1 and PD-L2 on tumor cells and PD-1 on infiltrating lymphocytes and peripheral T cells in HL,[35] strongly suggest an ongoing "exhausted T cell phenotype" in HL subjects. In fact, an increased PD-1 expression on TILs has been determined as a stage-independent negative prognostic factor of overall survival as opposed to the number of FOXP3+ Tregs.[41] The contribution of LAG-3 in this regard remains to be determined.

Little is known about the expression and functions of LAG-3 in NHLs. LAG-3 expression has been documented in a subtype of DLBCL defined by gene expression profiling as "host response tumor". These tumors have prominent T cell/dendritic cell infiltrates resembling those of smaller provisional (WHO) subtype of DLBCL, T cell/histiocyte-rich B-cell lymphoma (T/HRBCL).[42] Since HR-DLBCL patients did not have the best outcomes following empiric chemotherapy in this study, the authors inferred that their immune responses were ineffective due to the expression of inhibitory receptors on CD8+ T cells[43] or that tumors were inherently refractory to CHOP-based treatment. Interestingly, some aggressive B-cell and EBV-associated lymphomas also display ineffective T cell immune responses and express PD-L1 on tumor cells and infiltrating macrophages.[39] Furthermore, the histology of EBV-positive DLBCL also resembles the changes found in HL, including HRS-like large cells admixed with abundant reactive small lymphocytes.[44] The link between these findings and LAG-3 expression and function is yet to be established.

It is also possible that LAG-3 expression may be a marker of uncontrolled clonal expansion in select leukemias. When B-cell CLL is associated with the expression of unmutated immunoglobulin heavy variable (IGHV) genes, it becomes a more aggressive form of CLL. By using gene co-expression network analysis, Zhang et al. found a gene set (ie, LAG-3, LPL, ZAP70) that is assigned to unmutated IGHV in CLL cells.[45] Furthermore, Kotaskova et al. documented that high expression of LAG-3 on CLL cells correlates with unmutated IGHV status and reduced treatment-free survival.[46] In addition, Dickinson et al. described a specific association of 11q22.3 deletion with bulky lymphadenopathy and expression of ZAP-70 and LAG-3 in CLL.[47] In summary, these data suggest an association of LAG-3 expression with T cell exhaustion leading to bulky disease and poor prognosis. In contrast, the association between PD-1 expression and

clinical outcome is not clear. In one series, for example, only 5% of 66 CLL/SLL cases showed unequivocal PD-1 positivity of leukemic cells by IHC.[30] The effects of both LAG-3 and PD-1 expression and interaction on TILs, marrow-infiltrating lymphocytes (MILs), and peripheral blood from CLL patients remain to be elucidated.

Multiple myeloma (MM) is a malignant proliferation of plasma cells that produces monoclonal immunoglobulins, usually IgG or IgA (60% and 20% of cases, respectively). MM is associated with T cell abnormalities including quantitative and functional defects of CD4+ T cells.[48] In relation to the latter, T cells from MM subjects have been shown to overexpress PD-1while their malignant plasma cells express PD-L1.[37] So, it is expected that other checkpoint inhibitor molecules, such as LAG-3, may be overexpressed in peripheral T cells and/or in marrow infiltrating-T-cells (ie, MILs) too. Furthermore, six tag SNPs in CD4 & LAG-3 genes (out of 97 immune-genes tested in peripheral blood) have been significantly associated with MM risk[48]. So, it is hypothesized that genetic variations in the CD4/LAG-3 gene regions may be related to dysfunctional T-cell responses resulting in a loss of control over B-cell proliferation.

Epstein-Barr virus infection is yet another factor to consider in the potential induction of T cell exhaustion in hematological malignancies. It is known that EBV-associated CLL, Richter's syndrome, and lymphoma cases are usually more aggressive than their EBV(-) counterparts.[44,49,50,51,52] Interestingly, the expression of checkpoint inhibitors like PD-L1 has also been documented in EBV-associated malignancies.[39,36] Thus, the chronic viral infection may be inducing the co-expression of other regulatory inhibitors as documented in chronic viral infection models. In the LCMV mouse model, for example, the co-expression of PD-1, LAG-3, and other inhibitory receptors correlated with greater T cell exhaustion and more severe infection. Blockade of PD-1 and/or LAG-3 with specific, targeted antibodies was able to improve T cell responses and reduce viral load infection.[20]

Altogether, these data suggest that T cell exhaustion induced by the aberrant expression of checkpoint inhibitor molecules (including LAG-3) and epigenetic factors (eg, EBV infection) may have an effect on the pathogenesis and outcomes of subjects with hematological malignancies.

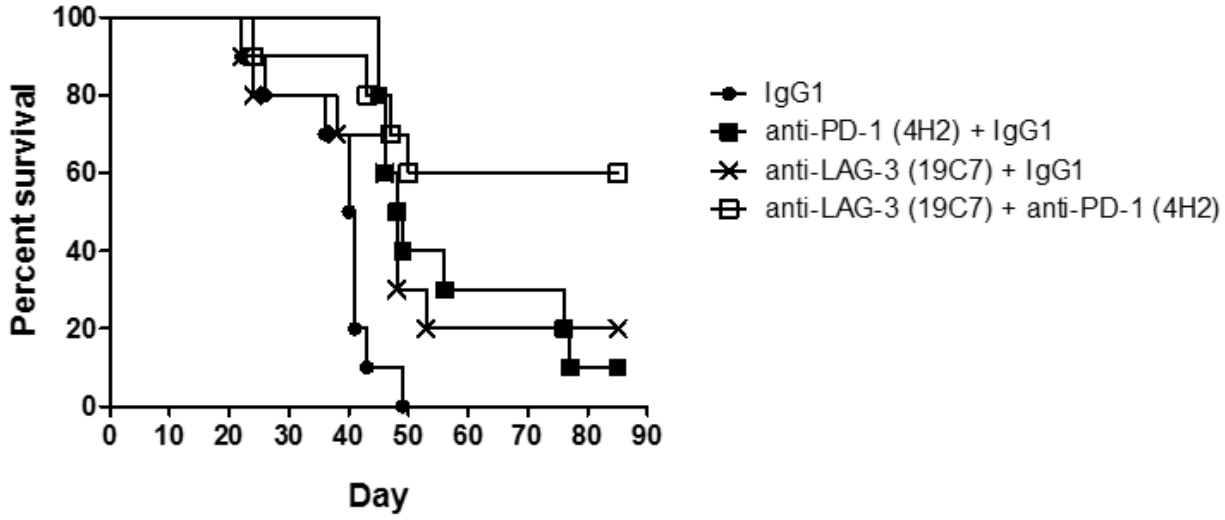
1.1.5 Rationale for Anti-LAG-3 Antibody (Relatlimab, BMS-986016) Therapy

Relatlimab (BMS-986016) is a fully human antibody specific for human LAG-3 that was isolated from immunized transgenic mice expressing human immunoglobulin genes. It is expressed as an IgG4 isotype antibody that includes a stabilizing hinge mutation (S228P) for attenuated Fc receptor binding in order to reduce or eliminate the possibility of antibody- or complement-mediated target T cell killing. Relatlimab binds to a defined epitope on LAG-3 with high affinity (Kd, 0.25-0.5 nM) and specificity and potently blocks the interaction of LAG-3 with its ligand, MHC class II (IC50, 0.7 nM). The antibody exhibits potent in vitro functional activity in reversing LAG-3–mediated inhibition of an antigen-specific murine T-cell hybridoma overexpressing human LAG-3 (IC50, 1 nM). In addition, relatlimab enhances activation of human T cells in superantigen stimulation assays when added alone or in combination with nivolumab (anti–PD-1 antibody).

1.1.6 Preclinical Studies Utilizing Murine Anti-PD-1 and Anti-LAG-3 Antibodies

The importance of LAG-3 as an immunotherapy target was initially validated in the A20 murine in vivo model using a surrogate antibody specific for mouse LAG-3[53] and anti-PD-1. One study evaluated tumor growth inhibition in a syngeneic tumor model (ie, A20 B-lymphocyte sarcoma). Mice were injected intravenously with the syngeneic A20 cell line and subsequently randomized to treatment with either control IgG, anti-LAG-3 (19C7), anti PD-1 (4H2), or the combination of anti-LAG-3/anti-PD-1. Survival was assessed as an endpoint of the study and the treatment regimen was considered active if it produced a statistically significant survival extension relative to animals treated with control IgG. The median survival of mice treated with control IgG was 40.5 days and all animals were dead by Day 49. Anti-Lag-3 administration resulted in a statistically significant survival extension, with a median survival of mice in this group of 48 days and 20% of mice alive beyond Day 85. Administration of anti-PD-1 increased the median survival to 48.5 days, with 10% of the mice alive at day 85. Anti-Lag-3 antibody administered in combination with anti-PD-1 antibody provided enhanced anti-tumor activity above the activity of either agent alone with a 60% of the mice alive beyond Day 85 (see Figure 1.1.6-1).

Figure 1.1.6-1: Antitumor Activity of Anti-PD-1 and LAG-3 Antibody in the A20 Model



Source: Adapted from Figure 1 of the Scientific Report of Study No. BDX-1408-263.[53]

1.1.7 Rationale for Combination of Anti-LAG-3 Antibody (Relatlimab) and Nivolumab

T-cell exhaustion induced by the expression of one or more checkpoint molecules on immune-modulating cells (or tumor cells) has been documented in different hematological malignancies during active disease. Some of these malignancies have underlying chronic viral

infections which may also contribute to maintain T cell exhaustion. EBV infection, for example, has been correlated with expression of checkpoint molecules in Hodgkin lymphoma and DLBCL.

Combined inhibition of T cell checkpoint molecules, such as CTLA-4, PD-1, and LAG-3, in preclinical models provides synergistic improvement in T cell activity, control of virus replication, and tumor inhibition in animal models. Thus, the combination of relatlimab and nivolumab (an anti–PD-1 antibody) in hematological malignancies is expected to: 1) increase the number, type, and duration of responses in tumors known to respond to T cell checkpoint inhibitors; 2) rescue an adaptive response where patients are refractory to T cell checkpoint inhibitors and have progressed clinically; and/or 3) enhance the antitumor immunity in malignancies associated with chronic viral infections (eg, HPV, EBV, HCV, HBV, etc).

1.1.8 Rationale for Dose Selection

Study CA224022 currently consists of 4 parts, A to D. Part A consists of a 3 + 3 + 3 dose escalation design with relatlimab administered as monotherapy in subjects with advanced hematological malignancies while Part B consists of expansion cohorts of approximately [redacted] to [redacted] subjects each in disease-restricted populations, with relatlimab administered as monotherapy at [redacted] mg flat dose. Amendment 3 to Study CA224022, introduces: 1) Part C, 3+3+3 dose escalation design with relatlimab administered in combination with nivolumab in disease-restricted populations 2) Part D dose expansion cohorts of approximately [redacted] to [redacted] subjects each to assess relatlimab and nivolumab effects in selected tumor types.

1.1.8.1 Rationale for Flat Dosing

Therapeutic monoclonal antibodies doses have been routinely calculated on a body size basis with a perception that this approach may reduce intersubject variability in drug exposure compared with a flat dose approach. However, recent analyses of marketed and experimental monoclonal antibodies have demonstrated that body weight-based dosing did not always offer advantages over flat dosing in reducing exposure variability.[54,55] Since the magnitude of the impact of body weight on the human PK of relatlimab is not yet determined and it is unknown if body size-based dosing would increase or decrease intersubject variability, this study will utilize a flat dose escalation and expansion since it is the simpler of the 2 approaches and may result in fewer dosing errors.

Flat doses for this study have been normalized for an average 80-kg adult cancer patient. A dataset from a recent internal preliminary population pharmacokinetics (PPK) analysis for another immuno-oncology monoclonal antibody contained 325 subjects with a median weight of 81 kg. This value aligns well with a study by Bai et al, which found a median weight of 78 kg in 2,519 adult patients with rheumatoid arthritis, breast cancer, colorectal cancer, non-small cell lung cancer, ovarian cancer, and non-Hodgkin's lymphoma.[55]

Additionally, relatlimab flat dose of [redacted] to [redacted] mg as monotherapy and up to [redacted] mg in combination with nivolumab (both given every 2 weeks [Q2W]) has been studied in across the 40 to 120 kg weight range in adults. Relatlimab flat dose [redacted] mg administered Q2W in combination with nivolumab is currently under evaluation in this trial.

1.1.8.2 Rationale for [redacted]-minute Nivolumab Infusion

Long infusion times place a burden on subjects and treatment centers. Establishing that nivolumab can be safely administered using shorter infusion times of [redacted] minutes duration in subjects will diminish the burden provided no change in safety profile. Previous clinical studies show that nivolumab has been administered safely over [redacted] minutes at doses ranging up to [redacted] mg/kg over long treatment duration. In Study CA209010, (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions ([redacted] at [redacted] mg/kg, [redacted] at [redacted] mg/kg and [redacted] at [redacted] mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of [redacted] minutes for [redacted] mg and [redacted] flat doses of nivolumab (~ 60% of the dose provided at [redacted] mg/kg) are not expected to present safety concerns compared to the prior experience at [redacted] mg/kg nivolumab dose infused over a [redacted] minute duration.

1.1.8.3 Part A — Relatlimab Dose

The dose selected for this study is based on all available nonclinical data. There was no observed abnormal phenotype in the LAG-3 knockout mice and no pathological changes associated with relatlimab monotherapy administered to mice ([redacted] µg twice weekly x 4 weeks, approximately [redacted] mg/kg). In vitro studies suggest that relatlimab does not induce cytokine release. No adverse effects were observed in the repeat-dose Good Laboratory Practice (GLP) cynomolgus monkey toxicity study at the highest administered dose, [redacted] mg/kg/week, which was considered the no-observed-adverse-effect level (NOAEL) and highest non-severely toxic dose (HNSTD). Simple allometry was used to project human PK parameters and to calculate the human equivalent dose (HED) for this NOAEL. With an added 10-fold safety factor, the maximum recommended starting dose (MRSD) based on the cynomolgus toxicology study is [redacted] mg/kg (intravenous [IV] infusion, Q2W) in humans. However, relatlimab showed different binding affinity between cynomolgus and human LAG-3 in *in vitro* studies and this must be taken into account for the selection of the starting dose. Studies in a LAG-3–transfected Chinese hamster ovary (CHO) model indicated the binding affinity of relatlimab for cynomolgus LAG-3 is approximately [redacted]-fold weaker than that for human LAG-3. Additional data generated from activated human and cynomolgus T cells have indicated that the affinity difference could be as high as [redacted]-fold; the HED with an affinity correction targeted to achieve [redacted] (the most conservative safety factor) of the AUC at the NOAEL in monkey is [redacted] mg/kg. This approach of linear adjustment for the highest observed affinity difference is considered conservative, as it is based on an NOAEL, and does not take into account potential nonlinearity in drug exposure at the resulting low dose levels. This approach assumed linear PK for extrapolation to low dose levels (ie, [redacted] mg/kg). However, the 2 mouse tumor efficacy studies of mouse anti-LAG-3 surrogate antibody (19C7) showed more than dose proportional exposure increases between [redacted] and [redacted] mg/kg in monotherapy and between [redacted] and [redacted] mg/kg when 19C7 was co-administered with anti-PD-1, whereas the exposure of 19C7 was dose-proportional at doses higher than [redacted] mg/kg. This nonlinear PK, presumably due to the target-mediated binding and/or disposition (TMDD), could be possible for relatlimab at lower doses in cancer patients. This would result in lower exposures than projected in the lowest dose cohorts.

An antitumor study with the 19C7 anti-LAG-3 antibody (a surrogate antibody with similar binding affinity for murine LAG-3 as relatlimab to human LAG-3) in a Sa1N model (the most sensitive mouse model tested) showed dose-dependent efficacy. Modeling and simulations based on these data project that a human dose of [redacted] mg/kg has the potential to produce tumor growth inhibition (TGI) of [redacted] to [redacted] and a [redacted] mg/kg dose has the potential to result in [redacted] to [redacted] TGI, depending on different tumor growth kinetics and tumor killing potency translation from mouse tumor model to the clinic. A [redacted] TGI in preclinical models at clinically relevant exposures has generally been shown to correlate with clinical efficacy.[56]

To balance the potential for pharmacologic activity and reasonable safety in this cancer patient population, a dose of [redacted] mg ([redacted] mg/kg) was selected as the starting dose for Part A. This dose is less than [redacted] of the human equivalent of the NOAEL ([redacted] mg; [redacted] mg/kg) and is below the HED after a linear adjustment of the NOAEL target exposure for the highest affinity difference estimate of [redacted]-fold ([redacted] mg; [redacted] mg/kg). No additional safety factor was added to the affinity-adjusted calculation because a linear adjustment is expected to be a conservative approach. Based on the model from the mouse efficacy data, this dose has the potential to have antitumor activity in humans. The calculated safety multiple for the [redacted]-mg ([redacted] mg/kg) dose is [redacted]-fold based on the NOAEL of [redacted] mg/kg/week in the repeat-dose monkey study without accounting for affinity differences. In addition, a staggered dosing (sentinel subject) approach will be used in the first dose cohort as described in Section 3.1.2. The top dose of [redacted] mg ([redacted] mg/kg) is projected to have the potential for [redacted] to [redacted] TGI from the most sensitive model in mouse.

1.1.8.4 Part B — Relatlimab Dose

The [redacted] mg dose selected for this expansion phase is based on recent safety, PK and PD data obtained from subjects treated with relatlimab monotherapy in the CA224020 and CA224022 studies in solid tumors and hematological malignancies, respectively.

The treatment with relatlimab at doses between [redacted] and [redacted] mg has been well tolerated and the MTD has not yet been reached (see safety section in Section 1.4.1.4). The trough concentration at [redacted] hours after first dose of [redacted] mg relatlimab was ~ [redacted] µg/mL, which is a concentration that induces [redacted] in the presence of [redacted] in vitro[57]. Furthermore, available data from subjects treated with [redacted] and [redacted] mg relatlimab showed receptor occupancy of [redacted] and [redacted], respectively. Finally, tumor growth inhibition in the mouse [redacted] tumor model was [redacted]% and [redacted] at days [redacted], respectively, when animals were treated with a dose of an anti-LAG-3 antibody equivalent to the [redacted] mg tested in humans (ie, [redacted] mg/kg). So, it is anticipated that a dose of [redacted] mg in expansion cohorts will be a well-tolerated dose achieving adequate receptor occupancy and active plasma concentrations.

1.1.8.5 Part C - Dose Escalation - Combination of Relatlimab and Nivolumab

In Part C, dose escalation combination, three dose escalation cohorts will be evaluated, starting with nivolumab administered at a dose of [redacted] mg followed by infusion of relatlimab at the dose of [redacted] mg.

The starting doses for Part C were selected based on all nonclinical data available from studies of the combination and relatlimab monotherapy and on emerging clinical safety and pharmacokinetic data from Study CA224020 where relatlimab was administered in combination with nivolumab in subjects with advanced solid tumors.

In the repeated dose GLP toxicology study, a dose of [redacted] mg/kg/week of relatlimab + [redacted] mg/kg/week nivolumab was considered the severely toxic dose in [redacted] of the animals (STD[redacted]; refer to Section 1.4.1.2).

The preliminary PK of relatlimab is approximately dose proportional at dose range of [redacted] to [redacted] mg. The PK of relatlimab and nivolumab do not appear to alter when given in combination (refer to Section 1.4.1.4).

The combination of relatlimab and nivolumab is currently tested in patients with advanced solid tumors in the clinical Study CA224020. Preliminary data analysis was performed on [redacted] patients treated in combination therapy, on CA224020 as of [redacted]. [redacted] patients received [redacted] mg relatlimab and [redacted] mg nivolumab, [redacted] patients were treated with [redacted] mg relatlimab and [redacted] mg nivolumab and [redacted] patients received [redacted] mg relatlimab and [redacted] mg nivolumab.

In cohort #1, [redacted] subjects with advanced solid tumors were treated with [redacted] mg relatlimab and [redacted] mg nivolumab. One patient with [redacted] cancer experienced an AE of Grade 3 mucosal inflammation [redacted] days after the first administration of the treatment, which was considered a DLT. As a result, the cohort was expanded to [redacted] subjects, and [redacted] additional subjects were enrolled. However, [redacted] additional subject with [redacted] cancer discontinued study drug due to disease progression prior to completion of the DLT period, and it was necessary to replace her with an additional subject ([redacted] subjects total). [redacted] out of [redacted] evaluable patients treated with [redacted] mg relatlimab and [redacted] mg nivolumab were able to complete the DLT period without any relevant AE.

Nine patients were treated in cohort #2 ([redacted] mg relatlimab/[redacted] mg nivolumab). Study drug was discontinued in one subject with [redacted] cancer due to a DLT of Grade 4 ventricular fibrillation. The cohort was subsequently expanded to [redacted] subjects. However, study drug was discontinued in [redacted] subjects (one with [redacted] cancer and the other with [redacted] tumor) due to disease progression prior to completion of the DLT period. [redacted] out of [redacted] evaluable patients treated with [redacted] mg relatlimab/[redacted] mg nivolumab were able to complete the DLT period without any relevant AE.

Preliminary analysis from the [redacted] subjects dosed with the combination of [redacted] mg relatlimab and [redacted] mg nivolumab in cohort #3 is summarized. One subject with thyroid cancer developed an asymptomatic Grade 4 lipase elevation that was a protocol defined DLT (day + 29 post first dose) requiring the patient to discontinue treatment. The lipase level decreased to normal within [redacted] hours and the patient remained asymptomatic. The cohort was thus expanded to [redacted] subjects. Study drug was discontinued in [redacted] subjects ([redacted] with [redacted] cancer and the other with [redacted] cancer) due to disease progression prior to completion of the DLT period, so these subjects were replaced. [redacted] subjects have completed the DLT period and continued on treatment. No subject in this cohort has experienced a clinically significant Grade 3 or higher drug related adverse event. Given that only [redacted] out of [redacted] DLT evaluable subjects experienced a protocol defined DLT the dose

of [redacted] mg relatlimab combined with [redacted] mg nivolumab is deemed safe and escalation to a dose of [redacted] mg relatlimab and [redacted] mg nivolumab is commencing.

As mentioned previously, a dose of [redacted] mg/kg/week of relatlimab + [redacted] mg/kg/week nivolumab was considered the [redacted]. Known human nivolumab PK parameters were used to calculate the HED. The same approach to identifying human equivalent doses as described for monotherapy was used. With an added [redacted]-fold safety factor, the MRSD based on the [redacted] is [redacted] mg/kg in humans. The starting nivolumab dose for subjects in Part B is [redacted] mg ([redacted] mg/kg), which is the flat dose equivalent of the dose selected for the global Phase 3 program ([redacted] mg/kg) which has been well tolerated in monotherapy.[14]

Taken together, pre-clinical and the preliminary safety data suggest that [redacted] mg relatlimab in combination with [redacted] mg nivolumab is safe and well tolerated dose in patients with advanced malignancies. Therefore, the proposed starting dose for Part C is [redacted] mg ([redacted] mg/kg) relatlimab in combination with [redacted] mg nivolumab ([redacted] mg/kg) is not expected to be toxic. At no point will the dose of relatlimab administered in combination with nivolumab (Part C) exceed doses of relatlimab that have been demonstrated previously to be safe on the monotherapy dose escalation/expansion arms (Part A and B).

In Part C, the sequential infusion of both drugs will start with nivolumab administration first followed by infusion of relatlimab.

1.1.8.6 Part D - Dose Expansion - Combination of Relatlimab and Nivolumab

In Part D, cohort expansion, relatlimab and nivolumab will be administered at the combination doses selected for Part C, and may represent the maximum tolerated dose (MTD), maximum administered dose (MAD), or an alternative dose selected from dose escalation Part C. The selected dose may not exceed the MTD/MAD established in Part C. Study therapy will be administered with infusion of nivolumab first followed by relatlimab administration.

1.2 Research Hypothesis

It is anticipated that anti–LAG-3 antibody (relatlimab), administered as monotherapy or in combination with nivolumab, will demonstrate adequate safety and tolerability, as well as a favorable risk/benefit profile, to support further clinical testing. No prospective hypotheses are being formally evaluated.

1.3 Objectives(s)

1.3.1 Primary Objectives

- The primary objective is to characterize the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD) of relatlimab administered alone or in combination with nivolumab to subjects with relapsed or refractory B-cell malignancies.
- The co-primary objective in combination therapy expansion Part D is to investigate the preliminary efficacy of relatlimab in combination with nivolumab in subjects with relapsed or refractory Hodgkin lymphoma (HL), and relapsed or refractory Diffused Large B Cell lymphoma (DLBCL). Tumor response will be evaluated according to the revised International

Working Group (IWG) criteria for Malignant Lymphoma (2007 IWG criteria); see Appendix 1.

1.3.2 Secondary Objectives

The secondary objectives are:

- To characterize the pharmacokinetics (PK) of relatlimab administered as monotherapy or in combination with nivolumab.
- To characterize the immunogenicity of relatlimab administered as monotherapy or in combination with nivolumab.

1.3.3 Exploratory Objectives

Exploratory objectives are:

- [redacted]
- To characterize pharmacokinetics and immunogenicity of nivolumab in combination with relatlimab.
- To evaluate the pharmacodynamic activity of relatlimab in the peripheral blood and tumor tissue as measured by, but not limited to, flow cytometry, immunohistochemistry, soluble factor analysis, and gene expression (eg, microarray technology and/or quantitative reverse transcription polymerase chain reaction [RT-PCR] and/or ribonucleic acid sequencing [RNAseq]).
- To investigate the association between biomarkers in the peripheral blood and tumor tissue, such as [redacted] expression, lymphocyte infiltration, neoantigen status, inflammatory gene signatures, with safety and efficacy following treatment with relatlimab administered as monotherapy and in combination with nivolumab.
- To determine the receptor occupancy of [redacted] in the peripheral blood and bone marrow.
- To explore the preliminary antitumor activity of relatlimab administered as monotherapy in subjects with relapsed or refractory B-cell malignancies.
- To characterize T-cell function in response to relatlimab administered as monotherapy or in combination with nivolumab.
- To explore exposure-response relationships in subjects treated with relatlimab as monotherapy and in combination with nivolumab.
- To assess the overall survival (OS) rates and progression-free survival (PFS) rates at various time points in HL and DLBCL patients in Part D. PFS will be assessed based on IWG (2007) criteria and the Lugano (2014) criteria.
- To evaluate tumor metabolic response per Lugano 2014 criteria using Deauville scoring (Appendix 7) in NHL and HL patients in Part D.

1.4 Product Development Background

Information for nivolumab (BMS-936558, anti-PD-1 antibody) and relatlimab (BMS-986016, anti-LAG-3 antibody) is provided in the sections below; additional details are provided in respective Investigator Brochures (IBs).[14,58]

1.4.1 Relatlimab (BMS-986016, Anti-LAG-3 Antibody)

1.4.1.1 Non-Clinical Pharmacology

The ability of relatlimab to bind recombinant human LAG-3 antigen was determined using Biacore and enzyme-linked immunosorbent assay (ELISA). Binding to human and primate LAG-3+ transfectants and to activated human or primate T cells was measured using flow cytometric and Scatchard analyses. Relatlimab binds to human LAG-3 with high affinity (Kd, [redacted] nM), and inhibits the binding of LAG-3 to cells expressing its ligand, MHC class II (IC50, [redacted] nM). Relatlimab binds to cynomolgus LAG-3 on transfected CHO cells and on activated cynomolgus T cells with a lower affinity (EC50, [redacted] nM) than to activated human T cells. A high concentration of relatlimab, in the absence of secondary co-stimulation, elicits no measurable cytokine response from cultured human peripheral blood cells nor does the drug mediate measurable antibody-dependent or complement-dependent killing of target T cells. Relatlimab promotes the activation of an antigen-specific mouse T-cell hybridoma expressing human LAG-3 in co-culture with an MHC class II-positive antigen-presenting cell. In addition, relatlimab enhances activation of human T cells in superantigen stimulation assays when added alone or in combination with nivolumab (anti–PD-1 antibody). Detailed information can be found in the current version of the relatlimab IB.[58]

1.4.1.2 Toxicity

The nonclinical toxicology package for relatlimab consists of the following studies:

1) Four-Week Intermittent (QW) Intravenous Exploratory Combination Pharmacodynamic and Toxicity Study in Cynomolgus Monkeys with [redacted] Antibody (a precursor of the [redacted] antibody) and Nivolumab.
2) GLP-Compliant Four-Week Intravenous Combination Toxicity Study in Cynomolgus Monkeys with a 6-Week Recovery with Relatlimab and Nivolumab.

The key results were as follows:

- Single-agent relatlimab administered at up to 100 mg/kg/week did not result in adverse changes.
- Combined administration of relatlimab and nivolumab ([redacted]/kg/week, respectively) resulted in morbidity of [redacted] male out of [redacted] monkeys on study Day [redacted] From Days [redacted] to [redacted] this monkey presented with elevated body temperature, shivers, red or clear nasal discharge, fecal changes (unformed, scant or absent feces), decreased feeding behavior, mild dehydration, sneezing, decreased activity, and hunched posture. After [redacted] days of veterinary care and antibiotic treatment, this animal did not show any improvement and was euthanized on Day [redacted] for poor clinical condition. There were no

remarkable gross necropsy findings. Histopathological findings in this monkey included: slight lymphoplasmacytic inflammation of the choroid plexus; minimal to moderate lymphohistocytic inflammation of the vasculature of the brain parenchyma, meninges, spinal cord (cervical and lumbar); and minimal to moderate mixed cell inflammation of the epididymes, seminal vesicles and testes. Clinical pathology changes indicated decreases in red blood cell count, hemoglobin concentration and hematocrit whose cause was unclear, and an increase in fibrinogen correlating with the inflammation observed in the central nervous system (CNS) and male reproductive tract.

- Additional histopathological findings upon combination administration of relatlimab and nivolumab (mg/kg/week, respectively) were limited to minimal to slight non-reversible lymphoplasmacytic inflammation of the choroid plexus in the brain in of remaining monkeys, and minimal lymphohistiocytic inflammation of the vasculature of the brain parenchyma in of remaining monkeys, whose reversibility could not be assessed.
- NOAEL for single-agent relatlimab was considered to be mg/kg/week (mean AUC[0-168h] = µg·h/mL); NOAEL for single-agent nivolumab was considered to be mg/kg/week (mean AUC[0-168h] = µg·h/mL); NOAEL for combination of relatlimab and nivolumab was not determined.
- However, the combination therapy was generally well tolerated and clinical signs of toxicity were observed in only of monkeys (approximately). Therefore, mg/kg/week relatlimab/nivolumab (mean relatlimab AUC[0-168h] = µg·h/mL; mean nivolumab AUC[0-168h] = µg·h/mL) was considered the .
- The doses administered (mg/kg relatlimab and mg/kg nivolumab) are ≥ times higher than the maximum doses proposed for the current study.

3) GLP-Compliant Tissue Cross Reactivity Study in Human and Select Cynomolgus Monkey Tissues with Relatlimab.
   - Positive staining with relatlimab-FITC was observed in the plasma membrane or plasma membrane granules of mononuclear leukocytes of most human tissues, including lymphoid tissues and hematopoetic cells of the bone marrow. In addition, staining with relatlimab-FITC was observed in the cytoplasm of the human pituitary endocrine cell epithelium. Although relatlimab is not expected to have access to the cytoplasmic compartment in vivo and the repeat-dose toxicology studies in monkeys showed no effects on the pituitary gland, these findings may be of clinical significance and will be monitored.
   - In Vitro Cytokine Release and Lymphocyte Activation Assessment with Relatlimab using Human Peripheral Blood Mononuclear Cells.
   - Relatlimab did not induce cytokine release when presented to human PBMCs regardless of concentration, donor, or incubation time. The levels of cytokines observed were either at or near the assay lower limits of quantification with no evidence of dose-dependence or pattern across donors or were generally overlapping with cytokine levels from PBMCs incubated with negative controls ( ).
   - Consistent with the lack of cytokine release, there was no evidence that relatlimab induced activation, as measured by surface expression of and . Expression

levels of these markers on [redacted] cells following stimulation with relatlimab were similar to those observed upon stimulation with negative controls.

– Overall, these data indicate that relatlimab does not possess agonistic potential to induce either [redacted] cellular activation or cytokine release.

Refer to the relatlimab IB,[58] for additional information regarding the nonclinical toxicity of relatlimab.

1.4.1.3 Nonclinical Metabolism and Pharmacokinetics

In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals,[59] no metabolism studies with relatlimab have been conducted in animals. The expected in vivo degradation of monoclonal antibodies (mAbs) is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes.

Relatlimab demonstrated favorable PK properties in cynomolgus monkeys. From both single-dose and repeat-dose IV PK studies, relatlimab decayed bi-exponentially and the exposure was approximately dose-proportional. The systemic clearance (CLTp) ranges from [redacted] to [redacted] mL/h/kg and a terminal half-life (T-HALF) [redacted] to [redacted] hours. The volume of distribution at steady state (Vss) was [redacted] to [redacted] mL/kg, suggesting limited distribution outside the plasma. Anti–relatlimab antibodies were detected in some monkeys but the presence of anti–relatlimab antibodies appeared to have no impact on relatlimab exposure.

1.4.1.4 Clinical Pharmacology

An interim determination of relatlimab multiple dose PK was carried out using all available serum concentration data from Studies CA224020 and CA224022. Noncompartmental analysis was performed using concentration time data after the first dose (Cycle 1) and ninth dose (Cycle 3). In general, the Cmax and AUC(TAU) values over the first dosing interval increased approximately proportional to the increment in the relatlimab dose. Relatlimab accumulation from the first to ninth doses was around [redacted] to [redacted] fold for AUC(TAU) and [redacted] to [redacted] fold for Cmax. Relatlimab effective half-life was estimated to be approximately [redacted] to [redacted] days. The PK of relatlimab and nivolumab was not altered when given in combination.

Relatlimab population PK was best described by a 2-compartment model with parallel linear and non-linear CL. The linear portion represents the FcRn-mediated CL, and non-linear component represents target-mediated CL. The linear CL was [redacted] L/day, and the volume of distribution in the central compartment (VC) was [redacted] L. The Vmax was [redacted] mg/day, and the concentration that achieved [redacted] of Vmax (Km) was [redacted] µg/mL.

Currently available data suggest that relatlimab monotherapy exhibits a low level of immunogenicity, with [redacted] out of [redacted] subjects having at least 1 post-baseline positive ADA samples. There are limited data available in combination cohort to make inference on immunogenicity rate.

1.4.1.5 Clinical Safety-Monotherapy (Part A and Part B) and Combination Therapy (Part C and D) in CA224022

A total of [redacted] subjects have been evaluated in Study CA224022 as of the clinical data cutoff date of [redacted] ([redacted] subjects received relatlimab as monotherapy, and [redacted] subjects received relatlimab in combination with nivolumab). In Part A, monotherapy dose escalation, [redacted] subjects with hematological malignancies were treated with relatlimab at [redacted] mg Q2W ([redacted] subjects), [redacted] mg Q2W ([redacted] subjects), [redacted] mg Q2W ([redacted] subjects), and [redacted] mg Q2W (6 subjects). [redacted] subjects were treated in Part B monotherapy dose expansion with [redacted] mg relatlimab Q2W.[58]

Of the [redacted] subjects treated with relatlimab monotherapy, [redacted] subjects experienced at least 1 AE. The most commonly reported AEs ([redacted] of subjects) were fatigue ([redacted] subjects); back pain ([redacted] subjects); constipation and diarrhea ([redacted] subjects each); nausea ([redacted] subjects); malignant neoplasm progression ([redacted] subjects); abdominal pain, cough, decreased appetite, headache, pain in extremity, upper respiratory tract infection, infusion-related reaction and urinary tract infection (5[redacted] subjects each); and acute kidney injury, anemia, dyspnea, myalgia, night sweats, peripheral edema, oropharyngeal pain, productive cough, rash, and weight decreased ([redacted] subjects each).[58]

Drug-related AEs were reported in [redacted] subjects, with the most commonly reported ([redacted] of subjects) being fatigue ([redacted] subjects); headache and rash ([redacted] subjects each); and infusion-related reaction ([redacted] subjects). Most drug-related AEs were Grade 1 or 2. Grade 3 to 4 drug-related AEs were anemia, amylase increased, lipase increased, and aseptic meningitis ([redacted] each).[58]

The MTD for monotherapy was not reached at the tested doses up to a flat dose of [redacted] mg relatlimab Q2W.[58]

Of the [redacted] subjects treated with relatlimab and nivolumab Q2W (Part C, [redacted] mg relatlimab/[redacted] mg nivolumab Q2W [[redacted] subjects], Part C [redacted] mg relatlimab/[redacted] mg nivolumab Q2W [[redacted] subjects], Part C [redacted] mg relatlimab/[redacted] nivolumab Q2W [[redacted] subject], and Part D, [redacted] mg relatlimab/[redacted] mg nivolumab Q2W [[redacted] subjects]), [redacted] subjects experienced at least 1 event. The most commonly reported AEs ([redacted] of subjects) was fatigue ([redacted] subjects). The reported AEs in at least [redacted] of subjects during combination therapy in Study CA224022 are summarized in the IB.[58]

Drug-related AEs were reported in [redacted] subjects, with the most commonly reported (≥[redacted] of subjects) being fatigue ([redacted] subjects). Grade 3 or 4 drug-related AEs were increased ALT, increased AST, oesophageal spasm, generalized rash, lipase increased, transaminases increased, hypoalbuminaemia, adrenal insufficiency, neutropenia, lymphopenia, thrombocytopenia, autoimmune encephalitis, autoimmune hepatitis, hepatotoxicity, autoimmune disorder, headache and pneumonitis ([redacted] each).[58]

Please refer to relatlimab IB for further details.[58]

1.4.1.6 Serious Adverse Events

At least [redacted] SAE, regardless of causality, has been reported in [redacted] of the [redacted] subjects treated with relatlimab monotherapy in Study CA224022. The most commonly reported SAEs ([redacted] of subjects) were malignant neoplasm progression ([redacted] subjects), acute kidney injury ([redacted] subjects), and dehydration ([redacted] subjects). [redacted] Grade 3 drug-related SAE of aseptic meningitis was reported.[58]

At least [redacted] SAE, regardless of causality, has been reported in [redacted] subjects treated with relatlimab and nivolumab. The reported SAEs occurring in [redacted] or more subjects were malignant neoplasm progression ([redacted] subjects); dyspnoea ([redacted] subjects); and hypoxia, muscular weakness,adrenal insufficiency, neutropenia, and thrombocytopenia ([redacted] subjects each).[58]

Drug-related SAEs were reported in [redacted] of the [redacted] subjects treated with relatlimab and nivolumab. These included Grade 3 to 4 events of esophageal spasm, neutropenia, pneumonitis, thrombocytopenia, adrenal insufficiency, autoimmune hepatitis, autoimmune encephalitis and transaminases increased ([redacted] each).[58]

One of the drug-related SAEs (pancreatitis) led to discontinuation during the Part C dose escalation [redacted] Q2W. The remaining drug-related SAEs were Grade 3 adrenal insufficiency and Grade 3 autoimmune hepatitis ([redacted] Q2W) in Part D dose expansion phase.[58]

1.4.1.7 Infusion Reactions

In Study CA224022, [redacted] subjects were reported with infusion-related reactions during relatlimab monotherapy. [redacted] Grade 1 or Grade 2 infusion-related reactions were reported following administration of relatlimab. [redacted] subject experienced an infusion reaction after administration of rituximab, [redacted] days after the last infusion of relatlimab. Another subject experienced an infusion reaction after administration of daratumumab, [redacted] days after the last infusion of relatlimab.[58]

[redacted] infusion-related reactions, all Grade 3 or less were reported during combination therapy and were considered related to study drug.[58]

1.4.1.8 Adverse Events Leading to Discontinuation

In Study CA224022, there were no AEs leading to study drug discontinuation during relatlimab monotherapy.[58]

As of [redacted], [redacted] AEs leading to discontinuation were reported during combination therapy. [redacted] AEs were considered by the investigator to be related to study drug. These were Grade 3 autoimmune hepatitis, Grade 3 adrenal insufficiency, Grade 2 immune-mediated enterocolitis and a Grade 2 pancreatitis.[58]

1.4.1.9 Deaths

[redacted] of [redacted] subjects treated with relatlimab monotherapy died. [redacted] death was reported within [redacted] days of last dose of study drug. All deaths in subjects treated with relatlimab

monotherapy in Study CA224022 were considered to be due to disease progression and were considered by the investigators to be not related to the study drug.[58]

Of the [redacted] subjects treated with relatlimab and nivolumab in combination therapy, [redacted] subjects died ([redacted] deaths were reported within [redacted] days of last dose of study drug). All deaths were considered to be due to disease progression and were not considered by the investigator to be related to study drug.[58]

1.5 Clinical Safety - Monotherapy (Part A and A1) and Relatlimab in Combination with Nivolumab Therapy (Parts B, C, and D) in Solid Tumor Study CA224020

1.5.1 Adverse Events

As of the clinical data cutoff date of [redacted], [redacted] subjects have been treated in Study CA224020 ([redacted] in monotherapy and [redacted] in combination therapy). A total of [redacted] subjects in Part C and [redacted] subjects in Part D (which included [redacted] subjects in the fixed dose combination [FDC; relatlimab plus nivolumab at a [redacted] ratio] cohort) have been treated with the combination of relatlimab and nivolumab.[58]

Relatlimab monotherapy has had an acceptable safety profile at all tested doses in Parts A and A1 ([redacted] and [redacted] mg, flat dose). Of the [redacted] subjects treated with relatlimab monotherapy, [redacted] subjects experienced at least [redacted] event. The most commonly reported AEs (≥[redacted] of subjects) were malignant neoplasm progression [redacted]; fatigue [redacted]; decreased appetite and nausea ([redacted] each); back pain [redacted]; dizziness and pyrexia ([redacted] each); and anemia, cough, and vomiting ([redacted] each).[58]

Drug-related AEs were reported in [redacted] subjects, with the most commonly reported (≥[redacted] of subjects) being fatigue [redacted]; decreased appetite [redacted]; and arthralgia, cough, dry mouth, headache, lipase increased, maculo-papular rash, myalgia, nausea, pneumonitis, pruritus, and rash ([redacted] each). Most drug-related AEs were Grade 1 or 2. Grade 3 drug-related AEs were lipase increased [redacted], maculo-papular rash, pneumonitis, and drug hypersensitivity ([redacted] each).[58]

The MTD for monotherapy was not reached at the tested doses up to a flat dose of [redacted] mg relatlimab Q2W.[58]

The all-combination group of study CA224020 includes [redacted] subjects treated with relatlimab and nivolumab. The all-combination group includes Parts B + C + D: Part B ([redacted] subjects), Part C ([redacted] subjects) and Part D ([redacted] subjects, including [redacted] in the FDC cohort). Based on an analysis of adverse events in the all-combination group, [redacted] subjects experienced at least [redacted] event. The most frequently reported AEs (≥[redacted]) were malignant neoplasm progression ([redacted]), fatigue ([redacted]), nausea ([redacted]), diarrhea ([redacted]), anaemia ([redacted]), decreased appetite ([redacted]), asthenia ([redacted]), constipation ([redacted]), pyrexia ([redacted]), arthralgia ([redacted]), pruritus ([redacted]), vomiting ([redacted]), cough ([redacted]), dysponea ([redacted]), back pain ([redacted]) and abdominal pain ([redacted]).[58]

Drug-related AEs were reported in [redacted] subjects, with the most commonly reported (≥[redacted] of subjects) being fatigue ([redacted]), pruritus ([redacted]), diarrhea ([redacted]), asthenia ([redacted]), rash ([redacted]),

nausea ([redacted]), arthralgia ([redacted]), and hypothyroidism ([redacted]). Grade 3 drug-related AEs were reported in [redacted] subjects, Grade 4 in [redacted] subjects, and Grade 5 in [redacted]. Grade 3 to 4 drug-related AEs were reported in at least [redacted] subjects included increased lipase ([redacted]), colitis, increased amylase [redacted] each), increased ALT ([redacted]), pneumonitis ([redacted]), diarrhoea ([redacted]), increased AST ([redacted]), autoimmune hepatitis ([redacted]), myocarditis, type 1 diabetes mellitus, gastritis, maculo-papular rash, hypophysitis, hepatitis, anaemia, asthenia, fatigue and mucosal inflammation ([redacted] each).[58]

Part D included all advanced melanoma subjects but different subgroups with different doses and schedules of administration. A separate analysis of the adverse events in Part D is reported in the relatlimab IB.[58]

1.5.2 Serious Adverse Events

At least 1 SAE, regardless of causality, has been reported in [redacted] subjects treated with relatlimab monotherapy. The most commonly reported SAEs (≥ [redacted] of subjects) were malignant neoplasm progression [redacted] and diarrhea, pneumonitis, and spinal cord compression ([redacted] subjects each). There were [redacted] reported drug-related SAEs in monotherapy: pneumonitis, (Grade 2, Grade 3) and Grade 3 allergic reaction; all of which were reported in monotherapy dose cohort of [redacted] mg relatlimab Q2W. All events resolved.[58]

At least 1 SAE, regardless of causality, has been reported in [redacted] of the [redacted] subjects treated with relatlimab and nivolumab in Parts B, C, and D. The most frequently-reported SAE was malignant neoplasm progression [redacted]. All other SAEs occurred at a frequency of ≤ [redacted].[58]

Drug-related SAEs were reported in [redacted] subjects treated with relatlimab and nivolumab in Parts B, C, and D. Grade 3 to 4 drug-related SAEs occurring in [redacted] or more subjects included pneumonitis, colitis, myocarditis, aspartate aminotransferase increase, autoimmune hepatitis, diarrhoea, gastritis, hypophysitis, lipase increased, and type 1 diabetes mellitus. All SAEs, (all at a dose level of [redacted] mg relatlimab/[redacted] mg nivolumab Q2W), were reversible and manageable by withholding study drug administration providing standard medical care, and/or following immune-related AE algorithms.[58]

1.5.3 Infusion Reactions

In Part A, 1 Grade 2 infusion-related reaction has been reported in a subject with [redacted] cancer treated at [redacted] mg relatlimab Q2W. There was also 1 Grade 3 allergic reaction following administration of [redacted] mg relatlimab Q2W.All events were manageable per updated protocol guidelines without need for subsequent treatment discontinuation.[58]

In combination therapy (Parts B, C, and D), [redacted] Grade 1 and [redacted] Grade 2 infusion-related reactions were reported. There were [redacted] Grade 3 or higher infusion reactions reported. The overall frequency [redacted] observed in Study CA224020 is similar to nivolumab monotherapy. In patients receiving nivolumab as a [redacted]-minute intravenous infusion, infusion-related reactions occurred in [redacted] of patients. All events were manageable per updated protocol guidelines, and only

[redacted] subjects required discontinuation, in each case due to recurrent Grade 2 infusion related reactions.[58]

1.5.4 Adverse Events Leading to Discontinuation

At least [redacted] AE leading to discontinuation has been reported in [redacted] subjects [redacted] treated with [redacted] (Parts A and A1). The AEs leading to discontinuation were Grade 5 malignant neoplasm progression (not drug related), Grade 3 allergic reaction (drug related), pneumonitis and wheezing (drug related), and Grade 1 abdominal pain and ascites (not drug related). At least 1 drug-related AE leading to discontinuation has been reported in [redacted] subjects [redacted]. The other drug-related AEs leading to discontinuation were due to allergic reaction.[58]

At least [redacted] AE leading to discontinuation has been reported in [redacted] subjects treated with [redacted] therapy. At least [redacted] drug-related AE leading to discontinuation has been reported in [redacted] subjects. The drug-related AEs leading to discontinuation included colitis ([redacted] subjects); myocarditis and diarrhoea ([redacted] subjects each); and gastritis, immune-mediated hepatitis, AST increased, and pneumonitis ([redacted] subjects each) and pancreatitis, mucosal inflammation, systemic inflammatory response syndrome, autoimmune hepatitis, ALT increased, lipase increased, rash maculo-papular, meningitis aseptic, infusion-related reaction ([redacted] subjects each).[58]

1.5.5 Deaths

Out of [redacted] subjects treated with relatlimab monotherapy in study CA224020, [redacted] subjects died. [redacted] death was reported within [redacted] days of last dose. Five deaths were reported after [redacted] days of last dose. Of the [redacted] subjects that died within [redacted] days of last dose, [redacted] deaths were because of disease progression, while for [redacted] subject the cause of death was unknown. All deaths were considered by the investigator to be not related to study drug. In the database, [redacted] malignant neoplasm progression events with an outcome of death had a CTC Grade 3 or 4.[58]

Out of [redacted] subjects treated with relatlimab and nivolumab in combination therapy, [redacted] subjects had died. Of these deaths, [redacted] occurred within [redacted] days of last dose. Causes of death were reported as disease progression in [redacted] subjects, study drug toxicity (Grade 5 dyspnea, Grade 4 myocarditis, and Grade 3 pneumonitis) in [redacted] subjects, unknown in [redacted] subject, and classified as "Other" in [redacted] subjects.[58]

1.6 Clinical Efficacy - Studies CA224020 and CA224022

As of the cutoff date of [redacted] for Study CA224020, in subjects treated with relatlimab [redacted], partial, transient response was seen in 1 subject with [redacted]. As of the cutoff date of [redacted] for Study CA224022, in subjects treated with relatlimab monotherapy, partial response was seen in 1 subject with [redacted]; complete response was seen in 1 subject with [redacted]; and stable disease was observed in [redacted] subjects with [redacted] and [redacted] subject with [redacted].[58]

Relatlimab in combination with nivolumab has shown the capacity to induce responses in previously heavily treated advanced solid tumors, with the added ability to trigger responses in tumors that have demonstrated resistance to nivolumab therapy. As of the cutoff date of [redacted] for Part B of Study CA224020, in subjects treated with relatlimab and nivolumab combination therapy, partial responses were seen in subjects with [redacted]. In subjects treated with relatlimab and nivolumab combination therapy in Part C of Study CA224020, the overall objective response rate (ORR) was [redacted], response evaluable) with a disease control rate of [redacted]. As of the cutoff date of [redacted] for Study CA224022 in subjects treated with relatlimab and nivolumab combination therapy, partial responses have been seen in subjects with [redacted] with stable disease observed in [redacted] subject for [redacted] months (and treatment was continuing).[58]

1.7 Nivolumab (BMS-936558, Anti-PD-1 Antibody)

1.7.1 Nonclinical Pharmacology

Nivolumab is a fully human, IgG4 (kappa) isotype monoclonal antibody that binds to PD-1 with nanomolar affinity (Kd, [redacted] nM) and a high degree of specificity, thus precluding binding to its [redacted]. Nivolumab does not bind to other related family members, such as [redacted]. Nonclinical testing of nivolumab demonstrated that binding to [redacted] results in enhanced [redacted] and release of [redacted] in vitro. Additional details are provided in the current version of the nivolumab IB.[14]

1.7.2 Toxicity

Toxicology studies in cynomolgus monkeys revealed that nivolumab was well tolerated at doses up to [redacted] mg/kg given twice weekly for [redacted] doses. Drug-related findings were limited to a reversible decrease in triiodothyronine (T3) by [redacted], without concomitant abnormalities in other markers of thyroid function. Additional details are provided in the current version of the nivolumab IB.[14]

Preliminary new nonclinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported.[60] The findings of increased late-stage pregnancy loss and early infant deaths/euthanasia in nivolumab-exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy.

1.7.3 Nonclinical Metabolism and Pharmacokinetics

Please see the nivolumab IB for current data.[14]

1.7.3.1 Clinical Pharmacology

Clinical Pharmacology Single dose pharmacokinetics (PK) of nivolumab was evaluated in subjects with multiple tumor types in CA209001, whereas multiple dose PK is being evaluated in subjects in CA209003. In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from [redacted] subjects from CA209001, CA209002, and CA209003.

Single dose PK of nivolumab was evaluated in [redacted] subjects with multiple tumor types in Study CA209001 in the dose range of [redacted] mg/kg. The median Tmax across single doses ranged from [redacted] hours with individual values ranging from [redacted] hours. Geometric mean Cmax and AUC(INF) of nivolumab administered at dosages of [redacted] mg/kg, [redacted] mg/kg, [redacted] mg/kg, and [redacted] mg/kg demonstrated approximate dose proportionality. Geometric mean clearance (CL), after a single intravenous (IV) dose, ranged from [redacted] to [redacted] mL/h/kg, while mean volume of distribution during the terminal phase (Vz) varied between [redacted] to [redacted] mL/kg across doses. There was moderate variability in PK parameters among subjects, with coefficient of variation (CV) of [redacted] in Cmax, [redacted] in AUC(INF), [redacted] in clearance, and [redacted] in Vz. The mean terminal elimination half-life of nivolumab is [redacted] days, which is consistent with half-life of endogenous IgG4, indicating that the elimination mechanism or nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied. Additional details are provided in the nivolumab IB.[14]

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from [redacted] subjects from CA209001, CA209002 and CA209003. Clearance (CL) of nivolumab is independent of dose in the dose range ([redacted] mg/kg) and tumor types studied. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weights, and hence is appropriate for future clinical trials of nivolumab.

1.7.3.2 Clinical Safety and Activity

Nivolumab has been studied in approximately [redacted] subjects and is widely approved in multiple indications. Extensive details on the safety profile of nivolumab are available in the IB,[14] and will not be repeated herein.

Overall, the safety profile of nivolumab monotherapy as well as combination therapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to [redacted] mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-related adverse events has been defined, for which management algorithms have been developed; these are provided in Appendix 4. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms. For additional material, see the nivolumab IB.[14]

The safety of nivolumab in combination with other therapeutics is being explored in several ongoing clinical trials. The most advanced combination under development is nivolumab and ipilimumab in subjects with [redacted] Thus far, the combination of both agents results in a safety profile with similar types of AEs as either agent alone, but in some cases, with a greater frequency and a higher rate of Grade 3 and 4 AEs than either ipilimumab or nivolumab alone. The safety profile of nivolumab + ipilimumab combination therapy was consistent with the mechanisms of action of nivolumab and ipilimumab. A dose of [redacted] mg/kg n[redacted] mg/kg ipilimumab exceeded the MTD, and both [redacted] mg/kg [redacted] mg/kg ipilimumab and [redacted] mg/kg [redacted] mg/kg ipilimumab were identified as the MTD. For nivolumab monotherapy and combination therapy,

most high grade events were manageable with use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management guidelines provided in this protocol (Section 3.4.4)

Nivolumab has demonstrated clinical activity as monotherapy in subjects with a variety of malignancies including [redacted].

Nivolumab is currently indicated for the treatment of patients with unresectable or metastatic melanoma as both monotherapy and in combination with ipilimumab. Nivolumab is also approved for non-small cell lung cancer following failure on or after platinum based therapy, as well as for advanced renal cell carcinoma following treatment with an anti-angiogenic therapy

Nivolumab has demonstrated clinical activity in a completed Phase 1 study in subjects with advanced Hodgkin's lymphomas (n=23). The response rate was 87%, with complete responses documented in 4 patients (17%) and partial response observed in 16 patients (70%). The safety profile was consistent with prior clinical trials. Serious AEs were documented in 12 patients (53%). Drug related grade 3 AEs were reported in 5 patients (22%), and no grade 4 or 5 drug related adverse events have been observed[61].

1.8 Overall Risk/Benefit Assessment

Subjects who have advanced hematological malignancies have poor prognosis and few curative options.

Administration of relatlimab in pre-clinical models, was able to significant improve anti-tumor responses and increase survival in aggressive lymphoma models (see Section 1.1.6). Thus administration of relatlimab is considered a promising strategy to improve anti-tumor activity in patients affected by advanced hematological malignancies.

Nivolumab has demonstrated clinical activity in subjects with advanced HL, NSCLC, RCC, melanoma, and other tumors. Treatment related adverse events (AEs) include those associated with autoimmune activation, such as pneumonitis, thyroiditis, hepatitis, nephrotoxicity, adrenal insufficiency, and less commonly neurotoxicity and myocarditis. Risk/benefit will be discussed in this section based on adverse events observed in both CA224022 and CA224020, a clinical trial evaluating the combination of relatlimab and nivolumab in subjects with solid tumors.

In the nonclinical GLP toxicology study, lymphoplasmacytic infiltration in the choroid plexus (and spinal cord) was reported at the highest doses of anti–PD-1 antibody [redacted] animals) and the anti–LAG-3 + anti–PD-1 antibody combination ([redacted]). Importantly, these findings were not reported with anti-LAG-3 antibody alone (either the [redacted] mg/kg or [redacted] mg/kg [highest] dose). These include nonspecific histopathology changes, without clinical manifestations in all but one of the animals treated with combination therapy, which have been observed in other studies with antibodies and small molecules in monkeys. Three subjects across both clinical trials, have experienced treatment related and immune mediated aseptic meningitis that have responded to

immunosuppressive therapy. Vigilance regarding the communication and evaluation of potential neurologic toxicity remains an ongoing priority.

Therapy with relatlimab and nivolumab is investigational and it is possible that a higher incidence of immune mediated-adverse events may occur with the combination of 2 antibodies targeting T cells. The immune-related Grade 4 myocarditis event, observed in the CA224020 study, prompted closer monitoring of subjects with ECGs and troponins, as well as tighter eligibility criteria regarding baseline ejection fraction and history of cardiovascular disease. Unanticipated side effects events may also occur, like the Grade 4 VF that was also reported in combination therapy, Part B.in the CA224020 study. There were several confounding factors in this case but, in the absence of a clear etiology, the event was considered treatment-related. In the setting of troponin surveillance, three cases of Grade 1 myocarditis have been documented and managed without progression to subsequent cardiac dysfunction. Adverse events and SAEs will continue to be reviewed expeditiously by the Medical Monitor, investigators and the Pharmacovigilance group to monitor safety. Specific SAE narratives including the Grade 4 ventricular fibrillation event and the Grade 4 myocarditis event are included in the relatlimab IB.[58]

The types of treatment-related AEs, as well as the rates of treatment-related AEs, appeared comparable to historical nivolumab monotherapy rates. All treatment-related AEs, except for the Grade 4 myocarditis ([redacted] mg relatlimab[redacted] mg nivolumab Q2W) and the Grade 4 potential drug induced liver injury ([redacted] mg relatlimab/[redacted] mg nivolumab Q2W), were reversible and manageable by withholding study treatment administration, providing standard medical care, and/or following immune-related AE algorithms.

There is risk associated with tumor biopsies, including bleeding, infection, and pain. While there is no direct benefit to subjects who undergo these procedures, there is significant potential that data generated from these samples will guide the further development of these compounds and may be of direct benefit for others with advanced solid tumors. [redacted]

The potential direct benefit to subjects who participate in the CA224022 study is that both single-agent and combined therapy with these investigational agents may result in a greater proportion of subjects with stabilization of disease, objective response, or increased duration of response than those observed with nivolumab monotherapy. It is also possible that combination therapy may reverse LAG-3 mediated T cell exhaustion and achieve responses in 1) DLBCL, which is known to respond poorly to anti-PD-1 or anti-PD-L1 therapy; 2) HL that was refractory to or progressed after anti-PD-1 therapy. In fact, partial and complete responses as defined by the 2007 International Working Group (IWG) Response Criteria for Malignant Lymphoma[62] (Appendix 1) have been observed with relatlimab monotherapy and in combination with nivolumab, both in the anti-PD-1 naive as well as in the anti-PD-1 resistant setting. Thus, the potential for direct benefit in subjects with few if any alternative treatment options warrants continued evaluation of the combination in the Phase 1/2a clinical setting, including evaluating potential response rates in specific tumor and prior anti-PD-1 defined expansion cohorts at combination doses shown to be tolerated.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the IB or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed Health Insurance Portability and Accountability Act (HIPAA) Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

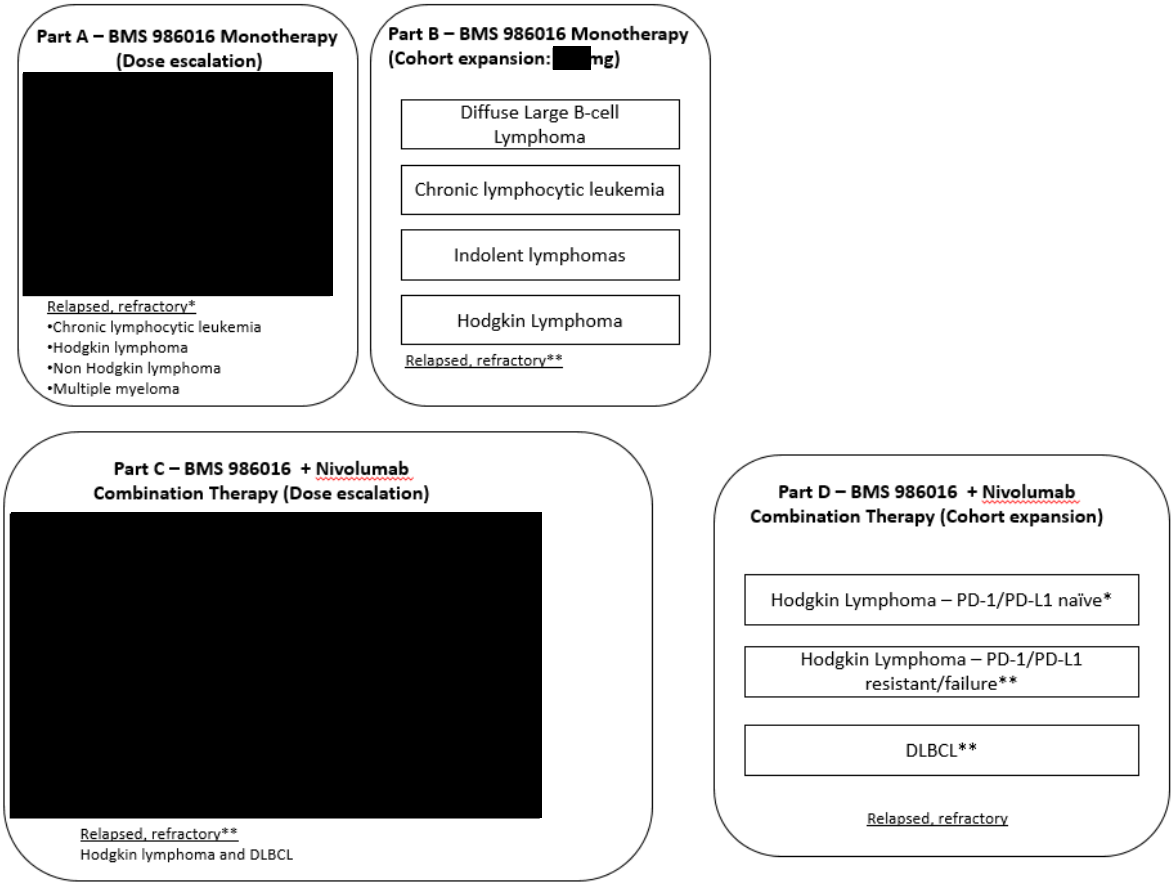
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 1/2a, open-label study of relatlimab administered as monotherapy or in combination with nivolumab to subjects with advanced relapsed or refractory B-cell malignancies. The study will be conducted in 4 parts. Part A consists of a 3 + 3 + 3 dose escalation design in subjects with relapsed or refractory CLL, HL, NHL, and multiple myeloma with relatlimab administered as monotherapy. Part B consists of cohort expansion in 4 disease-restricted populations of [redacted] to [redacted] subjects each with relatlimab administered as monotherapy. Part C consists of a 3+3+3 dose escalation design in subjects with advanced HL and DLBCL with relatlimab administered in combination with nivolumab. Part D consists of cohort expansion in three disease-restricted populations of approximately [redacted] to [redacted] subjects each with relatlimab administered in combination with nivolumab (Figure 3.1-1).

Figure 3.1-1: Study Design Schematic



* In Part A and selected cohort in Part D (ie, Hodgkin Lymphoma PD-1/PD-L1 naive cohort), subjects will be naive to immune cell-modulating antibody regimens (ICMARs), such as but not limited to anti PD-1, anti PD-L1, anti PD-L2, anti CTLA-4, anti-KIR, and/or anti-OX40 antibodies. Prior anti-CD20, alemtuzumab, and/or anti-CD30 antibody therapy are allowed.

** In Part B, Part C, and selected cohorts in Part D (ie, Hodgkin Lymphoma anti-PD-1/PD-L1 resistant/failure cohort and Diffuse Large B-Cell Lymphoma cohort),subjects will be naive to immune cell-modulating antibody regimens

(ICMARs), such as, but not limited to anti CTLA-4, anti PD-L2, anti-KIR, and/or anti-OX40 antibodies. Prior anti-PD-1, anti-PD-L1, anti-CD137, anti-CD20, alemtuzumab, and/or anti-CD30 antibody therapy are allowed.

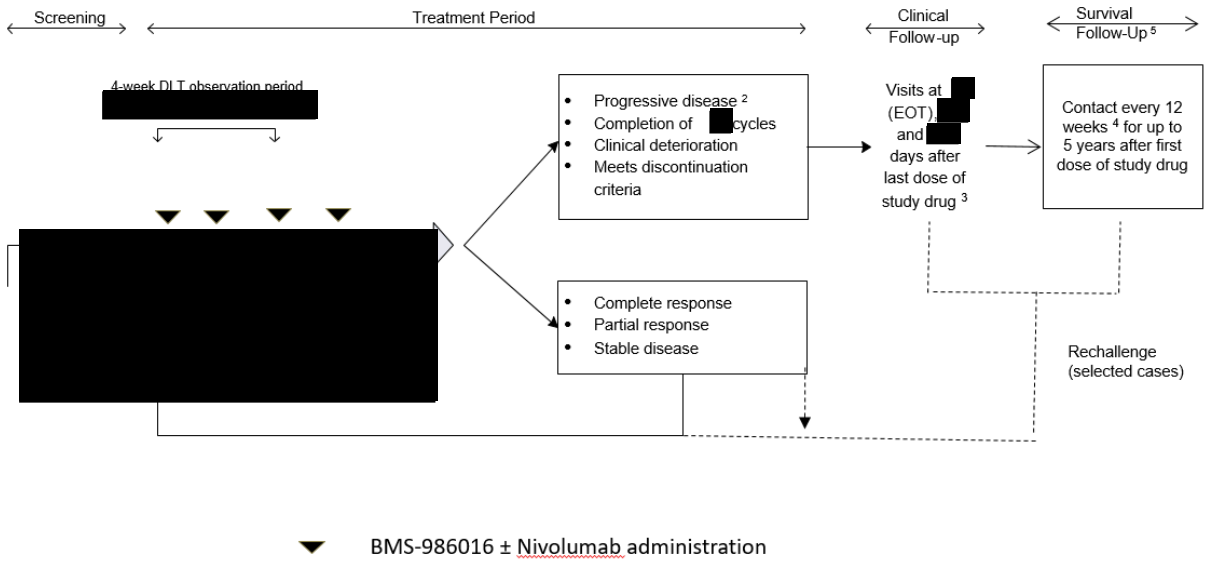
Subjects will complete up to 4 periods of the study: **Screening** (up to 28 days), **Treatment** (up to a maximum of twelve 8-week cycles of study therapy), **Clinical Follow-up** (135 days following the last dose of study drug; and **Survival Follow-up** (up to 5 years following the first dose of study drug).WOCBP will have additional follow-up assessments through Day 165 for home pregnancy tests. Survival follow-up will be conducted for HL patients in Part C and D only, if appropriate.

The **Treatment Period** consists of up to twelve 8-week treatment cycles. Each treatment cycle comprises 4 doses of relatlimab administered on Days [redacted]. Subjects will be allowed to continue study therapy until the first occurrence of either: (1) meeting criteria for discontinuation as described in Section 4.3.5, (2) completion of the maximum number of twelve [redacted] cycles, (3) confirmed progressive disease (PD), or (4) clinical deterioration. Subjects who discontinue treatment will enter a 135-day **Clinical Follow-Up** Period. After completion of the **Clinical Follow-Up period**, HL patients in Parts C and D will enter the **Survival Follow-Up period**. For participants who discontinue study treatment prior to disease progression, diagnostic imaging will be obtained every 6 months after the first clinical follow-up in year 1 and in year 2, and annually thereafter for a total of 5 years maximum (since the first dose of the study drug) until disease progression. **Re-Challenge** may be conducted in selected cases at progression.

If subjects progress during the clinical follow-up period or the survival follow-up period, they could further receive therapy with relatlimab alone or in combination with nivolumab (Re-Challenge period) as long as the risk:benefit ratio is considered favorable by the Investigator and the Medical Monitor and eligibility criteria is met (Section 3.3). The original dose and schedule and protocol rules would apply accordingly. Thus, subjects could receive therapy for up to [redacted] additional eight-week cycles. Subjects will not be re-challenged a second time. Collection of archival tissue (baseline) and tumor biopsies (baseline and on-treatment) will be optional for subjects enrolled for re-challenge. PK and biomarker monitoring will be limited (Sections 5.5 and 5.7).

A study schematic is shown in Figure 3.1-2.

Figure 3.1-2: Study Schematic for Parts A,[1] B, C, and D



1 Part A DLT period: 8 weeks

2 Treatment beyond progression may be considered in selected subjects as described in Protocol Section 4.3.4

3 WOCBP will have additional follow-up assessments through Day 165 for home pregnancy tests

4 For participants who discontinue study treatment prior to disease progression, diagnostic imaging will be obtained every 6 months after the first clinical follow-up in year 1 and in year 2, and annually thereafter for a total of 5 years maximum (since the first dose of the study drug) until disease progression.

5 Survival follow up is for HL patients recruited in Parts C and D only

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), pulse oximetry, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Subjects will be closely monitored for AEs throughout the study. Blood will be collected following the start of study drug administration for pharmacokinetic (PK) analysis as described in Section 5.5.

Subjects will be allowed to continue on therapy for up to twelve 8-week cycles, or, confirmed PD, or until meeting criteria for discontinuation as described in Section 4.3.5. Treatment beyond progression maybe considered in select subjects as described in Section 4.3.4. Subjects may be on study for a total of up to approximately 5 years, including a 28-day screening period, up to twelve 8-week cycles of treatment, a 135-day clinical follow-up period and up to 5 years of follow-up for survival (beginning from the first dose of study drug). The study will end once survival follow-up has concluded. The total duration of the study is expected to be approximately 9 to 10 years from the time of the first visit of the first subject to the required survival follow-up of the last subject enrolled.

3.1.1 Part A - Dose Escalation

In Part A, a 3 + 3 + 3 design will be used to assess the safety of relatlimab. The dose levels evaluated during dose escalation are provided in Table 3.1.1-1. Dose escalation rules are outlined below. Three subjects will initially be treated in each dose cohort; in Dose Cohort 1, the first 3 subjects will be designated as sentinel subjects and will begin treatment at least 5 days apart. Subjects in subsequent cohorts will not be required to observe the 5-day interval between treatment start dates.

Dose escalation will be based on the number of DLTs experienced during the DLT evaluation interval as determined by the Medical Monitor and Investigators (see Section 3.1.3 for DLT criteria). The DLT evaluation interval begins on the first day of treatment and continues for 8 weeks, ie, through Day [redacted] of the first cycle. Subjects who receive at least 1 dose of study drug during the 8-week evaluation interval will be considered evaluable for DLT determination. In consultation with Investigators, the Sponsor has the option to investigate dose levels intermediate to those defined in the protocol.

Dose escalation in Part A (Table 3.1.1-1) will proceed as follows:

- If none of the first [redacted] evaluable subjects in a dose cohort experiences a DLT within the DLT evaluation interval, then the next [redacted] subjects will be treated at the next higher dose cohort.
- If 1 of the first [redacted] evaluable subjects in a cohort experiences a DLT within the DLT evaluation interval, then [redacted] additional subjects will be treated in that dose cohort.
  - If no more than [redacted] of the first [redacted] evaluable subjects experiences a DLT during the DLT evaluation interval, then the next [redacted] subjects will be enrolled at the next higher dose cohort.
  - If [redacted] of the first [redacted] evaluable subjects in a cohort experience a DLT, that cohort will be expanded to [redacted] evaluable subjects.
- If ≥ [redacted] of the first [redacted] evaluable subjects, ≥ [redacted] of the first [redacted] evaluable subjects, or ≥ [redacted] of the first [redacted] evaluable subjects in a cohort experience a DLT within the DLT evaluation interval, that dose level will have exceeded the MTD and dose escalation will be terminated.

Table 3.1.1-1: Dose Escalation Schedule for Part A - Relatlimab Monotherapy

Dose Cohort Number	Relatlimab Dose (IV; mg)	Total Subjects
1	[redacted]	n = approximately [redacted]
2		n = approximately [redacted]
3		n = approximately [redacted]
4		n = approximately [redacted]
Total		N = approximately [redacted]

In consultation with Investigators, the Sponsor may investigate dose levels intermediate to those defined in the protocol. Prior to declaring the MTD (or MAD), and in consultation with

Investigators, the Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Dose escalation rules (cohort size, DLT evaluation interval, cohort expansion criteria, etc.) will apply to the additional cohorts. A maximum of [redacted] subjects will be enrolled in any additional dose cohorts.

3.1.2 Part B - [redacted] mg Cohort Expansion

The purpose of this cohort expansion is to gather additional safety, tolerability, PK, and pharmacodynamic information regarding relatlimab dosed at [redacted] mg.

The dose selected for Part B has not exceeded the MTD in Part A (see rationale for dose selection in Section 1.1.8.4).

Four expansion cohorts will be restricted to the tumor types listed in Figure 3.1-1 and Table 3.1.2-1. Continuous evaluation of toxicity events will be assessed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds [redacted] across all subjects treated in Part B cohort expansions, the findings will be discussed with the Medical Monitor and Investigators; further enrollment may be interrupted. Depending on the nature and grade of the toxicity and after assessing the risk/benefit ratio, the dose for all or for select cohorts may be reduced.

Table 3.1.2-1: Tumor Types Eligible For Part B - Cohort Expansion Relatlimab Monotherapy

Tumor Type[a]	Total Subjects
Chronic Lymphocytic Leukemia (CLL)	n=approximately [redacted]
Diffuse Large B-Cell Lymphoma (DLBCL)	n=approximately [redacted]
Indolent non-Hodgkin Lymphoma (i-NHL)	n=approximately [redacted]
Hodgkin Lymphoma (HL)	n=approximately [redacted]
Total	n=approximately [redacted]

[a] All subjects in Part B will be naive to immune cell-modulating antibody regimens (ICMARs), such as, but not limited to anti-CTLA-4, anti PD-L2, anti-KIR, and/or anti-OX40 antibodies except for anti-PD-1, anti-PD-L1, anti-CD137, anti-CD20, alemtuzumab, or anti-CD30 antibody therapy.

3.1.3 Part C - Dose Escalation Combination Therapy

As in Part A, a 3 + 3 + 3 design will also be used in Part C to assess the safety of relatlimab given in combination with nivolumab as a sequential infusion. A fourth subject may be enrolled at the beginning of a dose escalation cohort following agreement between the Investigator and the Sponsor/Medical Monitor, if subject is able to start the first day of dosing within approximately one week of the third subject in the same dose escalation cohort.

The dosages during dose escalation are provided in Table 3.1.3-1.

Treatment in Part C will be initiated after the decision is made to escalate to the fourth dose cohort ([redacted] mg anti-Lag-3 in combination with [redacted] mg anti-PD-1) in CA224020 study. At no point will the dose of relatlimab administered in combination with nivolumab (Part C) exceed doses of relatlimab that have been demonstrated previously to be safe on the monotherapy dose escalation arm (Part A). The escalation cohorts in Part C will be restricted to subjects with HL (naive to anti-PD-1/PD-L1 or whose disease progresses while-on or within 3 months of treatment with anti-PD-1 or anti-PD-L1 antibody) and DLBCL.

Dose escalation in Part C will proceed as described for Part A with the exception that the DLT observation period will be reduced from 8 weeks to 4 weeks. The rationale for the shorter observation period is presented in Section 3.1.6.1. If no MTD is reached through Dose Cohort 3, then additional cohorts of relatlimab given in combination with nivolumab may be considered based on the aggregate safety experience during dose escalation. Enrollment of additional cohorts will be implemented upon consultation and agreement between Investigators and the Sponsor via a protocol amendment.

Prior to declaring the MTD (or MAD), and in consultation with Investigators, the Sponsor has the option to expand any cohort previously established to be safe in order to obtain additional experience or to investigate dose levels intermediate to those defined in the protocol. Dose escalation rules (cohort size, DLT evaluation interval, cohort expansion criteria, etc.) will apply to these expanded or additional cohorts. A maximum of [redacted] subjects will be enrolled in any additional or expanded dose cohorts.

After completion of the relatlimab (anti-LAG-3) [redacted] mg and nivolumab [redacted] mg cohort, the intermediate dose combination of anti-LAG-3 [redacted] mg and nivolumab [redacted] mg was investigated in Part C. The dose combination ([redacted] mg anti-LAG-3/[redacted] mg nivolumab) was well-tolerated in Part C and therefore selected for Part D (expansion).

No within-subject dose escalations will be permitted. If a dose level is found to exceed the MTD, subjects enrolled in that dose level may be reduced to a lower dose following consultation and agreement between Investigators and the Sponsor.

Table 3.1.3-1: Dose Escalation Schedule for Part C - Relatlimab in Combination with Nivolumab

Dose Cohort Number	Total Subjects	Relatlimab Dose (IV; mg)	Nivolumab Dose (IV; mg)
1	n = approximately [redacted]	[redacted]	[redacted]
2	n = approximately [redacted]		
3	n = approximately [redacted]		
Total	N = approximately [redacted]		

Note: Part C will be limited to subjects with HL (naive to anti-PD-1/PD-L1 or whose disease progresses while-on or within 3 months after treatment with anti-PD-1 or anti-PD-L1 antibody) and DLBCL.

3.1.4 Part D - Dose Expansion Combination Therapy

The purpose of cohort expansion is to gather additional safety, tolerability, preliminary efficacy, PK, and pharmacodynamic information in subjects treated with sequential infusion of nivolumab followed by administration of relatlimab. The doses selected for Part D will not exceed the MTD (or MAD if no MTD is determined) in Part C, but may incorporate assessment of other data including toxicities, PK, and pharmacodynamic data from Parts A, B and C and from the CA224020 study. The dose selected can be chosen while additional Part C dose escalation cohorts continue to be explored. Doses to be considered may include doses intermediate to those evaluated in Part C if recommended by the Investigators and the Sponsor. The intermediate dose of relatlimab (anti-lag-3) [redacted] mg and nivolumab [redacted] mg dose was well tolerated, and was thus selected for extension. Modeling may be used to help inform the selection of the combination dose level to carry forward in Part D if a dose below the MTD is chosen. Three expansion cohorts will be restricted to the tumor types listed in Table 3.1.4-1. Continuous evaluation of toxicity events will be assessed throughout enrollment in the expansion cohorts. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds [redacted] across all subjects treated in the Part D cohort expansions, the findings will be discussed with the Medical Monitor and Investigators; further enrollment may be interrupted. Depending on the nature and grade of the toxicity and after assessing the risk:benefit ratio, the dose for all or for select cohorts may be reduced. See Section 8.1.3.

Table 3.1.4-1: Tumor Types Eligible For Part D - Cohort Expansion Relatlimab in Combination with Nivolumab

Tumor Type	Total Subjects
Hodgkin Lymphoma - anti-PD-1/PD-L1 naive	n=approximately [redacted]
Hodgkin Lymphoma - anti-PD-1/PD-L1 progressed	n=approximately [redacted]
Diffuse Large B-Cell Lymphoma	n=approximately [redacted]
Total	n=approximately [redacted]

3.1.5 Re-challenge in Dose Escalation (Part C) and Cohort Expansion (Part D)

If subjects progress during the clinical follow-up period or the survival follow-up period, they could further receive therapy with relatlimab alone or in combination therapy (Re-challenge) as long as the risk:benefit ratio is considered favorable by the Investigator and the Medical Monitor and the following eligibility criteria are met: 1) Subject has confirmed disease progression; 2) Subject has not experienced relatlimab related adverse events leading to permanent discontinuation. The original dose and schedule of therapy and protocol rules will apply. Thus subjects could receive therapy for up to [redacted] additional eight-week cycles. Subjects who are re-challenged and who subsequently have an objective response will not be included in the primary analysis of efficacy. Responses to re-challenge will be evaluated in a separate analysis. Subjects will not be re-challenged a second time.

3.1.6 Dose-Limiting Toxicities

For the purpose of guiding decisions regarding dose escalation in Part A, dose-limiting toxicity (DLT) will be determined based on the incidence, intensity, and duration of AEs that are related to study drug and that occur within 8 weeks of initiation of study drug (ie, the DLT evaluation interval which begins on the first day of treatment and ends on Day [redacted] of the first cycle).

For the purpose of guiding decision in combination dose escalation in Part C, dose-limiting toxicity (DLT) will be determined based on the incidence, intensity, and duration of AEs that are related to study drug and that occur within 4 weeks of initiation of study drug (ie, the DLT evaluation interval which begins on the first day of treatment and ends on Day [redacted] of the first cycle).

The severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

For the purpose of subject management, DLTs that occur at any time, whether during dose escalation (Part A or C) or cohort expansion (Part B or D) will result in study drug being held pending evaluation of the event's relatedness to study drug in accordance with Section 4.3.2. Subjects must meet criteria for re-treatment prior to re-initiation of study treatment (see Section 4.3.3).

3.1.6.1 Rationale for 4-week DLT Period in Part C

The identification of acute dose limiting toxicities that occur after administration of a study drug is crucial for the safety of the patients enrolled in a clinical trial. The length of the DLT is usually established based on the availability of pre-clinical data. When clinical data are available, the risk/benefit evaluation used to define the appropriate DLT period must be reassessed and should incorporate a critical analysis of all, clinical and pre-clinical data.

In Part C, the DLT period will be reduced from [redacted] weeks to [redacted] weeks in light of the availability of preliminary clinical data from the 2 ongoing clinical studies. This decision was made after reviewing the incidence of severe adverse event in monotherapy and in combination between Weeks [redacted] to [redacted] and after Week [redacted] and the effect of a prolonged DLT on a population with advance cancers, as reported below.

Correlation between AEs and duration of treatment

The safety profile of relatlimab as monotherapy is well manageable and generally consistent across the 2 ongoing clinical studies with no MTD reached at the [redacted] doses tested, up to [redacted] mg in dose escalation monotherapy. Only [redacted] subject experienced a related high-grade AE (asymptomatic Grade 3 lipase increased), [redacted] days post the first administration of the study drug in CA224020. There were no related SAEs reported in the monotherapy in either study.

A preliminary analysis of the clinical data from the combination arm of Study CA224020 in which [redacted] subjects were treated with relatlimab in combination with nivolumab showed that there was no relationship between the incidence, severity, or causality of AEs and the dose level of study drugs. Seven subjects received [redacted] mg relatlimab/[redacted] mg nivolumab, nine subjects were treated with [redacted] mg relatlimab/[redacted] mg nivolumab and eight subjects received [redacted] mg relatlimab/[redacted] mg nivolumab.

Four acute treatment related AEs were observed (2 SAE and 2 AEs), three of them occurred during the first [redacted] weeks of treatment, [redacted] event occurred at Week 6 and no treatment related AEs were documented after Week [redacted]. The treatment-emergent SAE reported at Week [redacted] (day [redacted] post first dose) was a Grade 4 ventricular fibrillation that occurred in a subject with [redacted] cancer that receive [redacted] mg relatlimab/[redacted] mg nivolumab combination therapy. The event occurred spontaneously while the subject was shopping, and CPR was administered by paramedics for 10 minutes. At the initial clinical assessment, the subject showed no evidence of coronary artery abnormality, myocardial infarction, myocarditis, or pulmonary embolism. A previous peri-infusional Holter electrocardiogram (ECG) recording on Cycle 1, Day 1 did not show an arrhythmia. The subject's history of cannabinoid ingestion, tobacco smoking, hypertension, chlorphenamine and caffeine use, and a prior episode of loss of consciousness were considered potential contributing factors for the event and suggested pre-existing cardiac disease or an arrhythmia, but in the absence of a clearly identified etiology, contribution from relatlimab and nivolumab could not be excluded. Study drug was discontinued, and defibrillator was successfully implanted. Of note, despite to possible immuno-related mechanism, the patient never received steroids for the treatment of this AE. The subject has fully recovered with no sequelae and achieved a complete response after [redacted] doses of study drug. Due to the important role that the cannabinoids may have had is this event, the use of cannabinoids is now part of the exclusion criteria

Effects of prolonged DLT period in a population with advanced cancer

The target populations for phase 1/2a oncology studies are characterized by a high frequency of patients with advanced stage disease. As a consequence, a relevant group of patients will progress rapidly after initiation of study drug. Across the 2 ongoing studies with relatlimab, administered as monotherapy or in combination with nivolumab, [redacted] of the subjects enrolled in dose escalation cohorts experienced disease progression between Weeks 4 and 8 of the DLT period while only [redacted] of the subjects progressed between Weeks 1 and 4. It is important to note that a subject that progresses during the DLT period is no longer evaluable for the purposes of safety adjudication and a new replacement subject must be enrolled at the same dose in order to complete the safety evaluation at that dose level. As a consequence, to date, nine additional patients have been exposed to safe but clinical suboptimal doses of relatlimab alone or in combination with nivolumab.

In summary, the review of the safety data from the 2 ongoing studies strongly suggests that a 4 weeks DLT period will provide an appropriate window to capture the acute, treatment related AEs and to ensure the safety of the patients enrolled in this clinical trial. Furthermore will limits the number of patients exposed to safe but suboptimal doses of the drugs due to progressive disease between Weeks 4 and 8.

Hepatic, non-hematologic, and hematologic DLTs are defined separately as outlined below.

Hepatic DLT

Any of the following drug-related events will be considered a hepatic DLT:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 8 × ULN, regardless of duration.

- ALT or AST > 5 × and ≤ 8 × ULN, that fails to return to ≤ Grade 1 within 2 weeks despite medical intervention.
- Total bilirubin > 5 × ULN.
- ALT or AST > 3 × ULN and concurrent total bilirubin > 2 × ULN.

Non-Hematologic DLT

Any of the following drug-related events will be considered a non-hematologic DLT:

- Grade 2 immune related-eye pain or reduction in visual acuity that requires systemic treatment, or
- Grade 2 eye pain or reduction in visual acuity that does not respond to topical therapy and that does not improve to Grade 1 within 2 weeks of initiation of topical therapy, or
- ≥ Grade 3 non-hepatic or non-hematologic toxicity with the exceptions noted below.

The following Grade 3 or 4 non-hematologic events **will not** be considered DLTs:

- Grade 3 electrolyte abnormality (and grade 4 hyperglycemia) that lasts < 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention.
- Grade 3 or 4 increase in amylase or lipase that is not associated with symptoms, clinical manifestations, or radiographic evidence of pancreatitis.
- Grade 3 nausea or vomiting that lasts < 48 hours and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention.
- Grade 3 diarrhea that lasts < 24 hours, does not result in hospitalization, and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention.
- Grade 3 or 4 fever that lasts < 72 hours and is not associated with hemodynamic compromise (including hypotension, or clinical or laboratory evidence of end organ perfusion impairment).
- Grade 3 endocrinopathy that is well controlled by hormone replacement.
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor).
- Grade 3 fatigue for less than 7 days.
- Grade 3 rash meeting the following criteria: 1) improves to grade 1 within 2 weeks, 2) does not limit self-care, and 3) is not associated with infection.
- Grade 3 troponin not associated with any other sign of cardiac toxicity (as determined by a cardiac evaluation).

Hematologic DLT

Any of the following drug-related events will be considered a hematologic DLT:

- Grade 4 anemia.

- Grade 4 febrile neutropenia of any duration.
- Grade 4 neutropenia that does not resolve to Grade 3 or less within 5 days of initiation of granulocyte colony stimulating factor (G-CSF).
- Platelet transfusion or a platelet count < 10,000/μL.
- Grade 3 thrombocytopenia associated with clinically significant bleeding.
- Grade 3 hemolysis.

In Part A, subjects who receive at least 1 dose of relatlimab during the 8-week evaluation interval will be considered evaluable for DLT determination. In Part C, subjects who receive at least 2 doses of relatlimab and nivolumab during the 4-week evaluation interval will be considered evaluable for DLT determination In the event that study drug cannot be administered at a scheduled visit during the DLT evaluation interval, it must be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the originally scheduled visit should be performed and subjects will be considered evaluable for DLT determination. If the delay is more than 7 days, the dose will be considered missed and will not be replaced. Subjects with a delay of more than 7 days will not be considered evaluable for DLT determination. Unevaluable subjects may be replaced at the same dose level. Subjects who miss a dose during the DLT evaluation period may continue on treatment if the subject does not otherwise meet the criteria for permanent discontinuation in Section 4.3.5.

3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to supply study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The subject must sign and date the IRB/IEC-approved written informed consent form prior to the performance of any study-related procedures that are not considered part of standard of care.

b) Consent for biopsy samples in subjects with Lymphoma.

i) Subjects must consent to allow a pre-treatment tumor biopsy (eg, lymph node) to be performed (all subjects). If a pre-treatment tumor biopsy is not clinically feasible, subject must consent to allow the acquisition of an archived tumor sample (eg, primary tumor, lymph node, etc). Subjects unable to provide a fresh pre-treatment tumor biopsy or archived tumor sample must seek approval of the BMS Medical Monitor before

enrolling. Subjects whose pre-treatment biopsy yields inadequate tissue quantity or quality will not be ineligible on this basis alone.

ii) Subjects enrolled in Part B and C with Hodgkin lymphoma whose disease progresses while-on or within 3 months of treatment with anti-PD-1 or anti-PD-L1 antibody must consent to allow a pre-treatment tumor biopsy (eg, lymph node) to be performed. If a pre-treatment tumor biopsy is not clinically feasible, subject must consent to allow the acquisition of an archived tumor sample (eg, primary tumor, lymph node, etc) collected after the most recent therapy. Subjects unable to provide a fresh pre-treatment tumor biopsy or archived tumor sample must seek approval of the BMS Medical Monitor. Subjects whose pre-treatment biopsy yields inadequate tissue quantity or quality will not be ineligible on this basis alone.

iii) The first three subjects in each cohort enrolled in the Part C, dose escalation, must consent to allow on-treatment tumor biopsy (eg, lymph node) to be performed at Week 4 during cycle 1 independently of the disease status. Subjects unable to provide a fresh on-treatment tumor biopsy must seek approval of the BMS Medical Monitor.

iv) All subjects in Part D must consent to allow on-treatment tumor biopsy (eg, lymph node) to be performed at Week 4 during cycle 1 independently of the disease status. Note: If a fresh pre-treatment tumor biopsy was not medically feasible and enrollment was approved by the Medical Monitor, the on-treatment tumor biopsy will not be required.

v) Subjects enrolled in Part A and B must consent to allow a pre-treatment unilateral bone marrow biopsy and/or aspirate to be performed (all subjects). Subjects who had a bone marrow biopsy and/or aspirate since completion of their last therapy may not use those results in lieu of the required baseline bone marrow biopsy.

vi) Subjects enrolled in the [redacted] mg monotherapy escalation cohort must consent to allow on-treatment unilateral bone marrow biopsy and/or aspirate to be performed at Week 4 during cycle 1 independently of the disease status. Subjects unable to provide a fresh on-treatment tumor biopsy are not eligible.

vii) Subjects enrolled in the [redacted] mg monotherapy escalation cohort must consent to allow on treatment unilateral bone marrow biopsy and/or aspirate to be performed to document complete response (CR), partial response (PR), or progressive disease (PD) shall be performed as clinically indicated.

viii) Subjects enrolled in Part B, expansion monotherapy cohort, must consent to allow on-treatment unilateral bone marrow biopsy and/or aspirate to be performed (first three subjects in each cohort) at Week 4 during cycle 1 independently of the disease status. Subjects unable to provide a fresh on-treatment tumor biopsy are not eligible.

ix) Subjects enrolled in Part B, expansion monotherapy, must consent to allow on treatment unilateral bone marrow biopsy and/or aspirate to be performed to document

complete response (CR), partial response (PR), or progressive disease (PD) shall be performed as clinically indicated.

c) Consent for biopsy samples in subjects with Multiple Myeloma.

i) Subjects must consent to allow a pre-treatment unilateral bone marrow biopsy and/or aspirate to be performed (all subjects).

2) Target Population

a) Subjects must have histologic or cytologic confirmation of chronic lymphocytic leukemia, Hodgkin lymphoma, Non-Hodgkin lymphoma, or Multiple Myeloma and have relapsed following prior treatment or been refractory to prior treatment.

b) Part A Dose Escalation Relatlimab Monotherapy.

i) Chronic lymphocytic leukemia.

ii) Hodgkin lymphoma.

iii) Non-Hodgkin lymphoma.

iv) Multiple Myeloma by modified IMWG Criteria[63] (Appendix 6).

c) Part B Cohort Expansion Relatlimab Monotherapy [redacted] mg.

i) Chronic lymphocytic leukemia.

ii) Diffuse large B-cell lymphoma.

iii) Indolent non-Hodgkin lymphoma.

iv) Hodgkin Lymphoma.

d) Part C Dose Escalation Relatlimab in Combination with Nivolumab.

i) Hodgkin Lymphoma.

ii) Diffuse Large B-Cell Lymphoma.

e) Part D Dose Expansion Relatlimab in Combination with Nivolumab.

i) Hodgkin Lymphoma naive to anti-PD-1/PD-L1.

ii) Hodgkin Lymphoma whose disease progresses while-on or within 3 months of treatment with anti-PD-1 or anti-PD-L1 antibody as most recent therapy.

iii) Diffuse Large B-Cell Lymphoma.

f) In Part A, and selected cohort in Part D, (ie, Hodgkin Lymphoma anti-PD-1/PD-L1 naive cohort), only subjects without prior exposure to immune cell-modulating antibody regimens (ICMARs), such as but not limited to anti PD-1, anti PD-L1, anti PD-L2, anti CTLA-4, anti-KIR, and/or anti-OX40 antibodies, are allowed. Prior anti-CD20, alemtuzumab, and/or anti-CD30 antibody therapy is allowed.

In Part B, Part C, and selected cohort in Part D (ie Hodgkin Lymphoma subjects who progresses while on or within 3 months of treatment with anti PD-1/PD-L1 as most recent

therapy and Diffuse Large B-Cell Lymphoma subjects), only subjects without prior exposure to immune cell-modulating antibody regimens (ICMARs), such as, but not limited to anti-CTLA-4, anti-CD137, anti PD-L2, anti-KIR, and/or anti-OX40 antibodies are allowed. Prior anti-PD-1, anti-PD-L1, anti-CD20, alemtuzumab, and/or anti-CD30 antibody therapy is allowed.

g) Definition of Measurable Disease.

   i) Subjects with lymphomas and CLL must have at least one measureable lesion > 1.5 cm as defined by the Lymphoma (Revised Response Criteria for Malignant Lymphoma)[63] and CLL (Guidelines for the Diagnosis and Treatment of Chronic Lymphocytic Leukemia)[62] response criteria (Appendices 1 and 2). Tumor sites that are considered measureable must not have received prior radiation therapy.

h) Subjects must have progressed or been refractory to, at least one prior standard therapy, including radiation, immunomodulatory agents (eg, lenalidomide), immunotherapy, cytotoxic chemotherapy, and select antibody (anti-CD20, alemtuzumab, or anti-CD30) therapy. The following are not considered separate lines of treatment: addition of a compound to an ongoing regimen, restarting the same regimen after a drug holiday, or switching from IV to oral therapy.

i) Subjects are not eligible for transplantation or any standard therapy known to be life-prolonging or life-saving. (Subjects who are eligible for transplantation or any standard therapy known to be life-prolonging or life-saving and who have declined transplantation or any standard therapy known to be life-prolonging or life-saving are eligible for the study.)

j) Subjects must be more than 100 days post autologous transplant.

k) Eastern Cooperative Oncology Group (ECOG) status of 0 or 1.

l) Life expectancy of ≥ 10 weeks at the time of informed consent per Investigator assessment.

m) Adequate organ function as defined by the following:

   i) Neutrophils ≥ 750/μL (stable off any growth factor within 2 weeks of first study drug administration).

   ii) Platelets ≥ 50 × 10^3/μL (transfusion to achieve this level is not permitted within 2 weeks of first study drug administration).

   iii) Hemoglobin ≥ 8.5 g/dL (transfusion to achieve this level is not permitted within 1 week of first study drug administration).

   iv) Creatinine < 1.5 × ULN or creatinine clearance ≥ 40 mL/min (Cockcroft-Gault formula).

   v) ALT and AST ≤ 3 × ULN.

vi) Total bilirubin ≤ 1.5 x ULN (except subjects with Gilbert's syndrome who must have a total bilirubin level of < 3.0 x ULN).

vii) Normal thyroid function, or stable on hormone supplementation per Investigator assessment.

n) Ability to comply with treatment, PK, and pharmacodynamic sample collection and required study follow-up.

o) Subject re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized or treated). If re-enrolled, the subject must be re-consented.

p) Adequate cardiac function as defined by the following:

i) LVEF ≥ 50% by either TTE or MUGA (TTE preferred test) within 6 months of first drug administration.

3) Age and Reproductive Status

a) Men and women, ages ≥ 18 years at the time of informed consent.

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with relatlimab plus 5 half-lives of relatlimab (135 days) plus 30 days (duration of ovulatory cycle) for a total of 165 days (24 weeks) after completion of treatment. The terminal half-life of nivolumab is up to 25 days. WOCBP who are treated with combination of relatlimab and nivolumab should follow the requirements for relatlimab which has a slightly longer half-life than nivolumab.

e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with relatlimab plus 5 half-lives of relatlimab (135 days) plus 90 days (duration of sperm turnover) for a total of 225 days (33 weeks) after completion of treatment. Those treated with the combination of relatlimab and nivolumab should follow the requirements for relatlimab which has a slightly longer half-life than nivolumab.

f) Azoospremic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP who abstain from heterosexual activity on a continuous basis must still undergo pregnancy testing as described in this protocol.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the

use of highly effective methods of contraception. Highly effective methods of contraception (Appendix 3) have a failure rate of < 1% per year when used consistently and correctly.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Lymphomas and Multiple Myeloma.

i) Subjects with primary cutaneous lymphoma, lymphoproliferative diseases associated with primary immune deficiencies, and lymphomas associated with human immunodeficiency virus (HIV) infection are excluded.

ii) Solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia.

iii) Monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma or Waldenström's macroglobulinemia.

iv) Active plasma cell leukemia (defined as either 20% of peripheral WBC comprised of plasma/CD138+ cells or an absolute plasma cell count of 2 x 109 /L).

b) Subjects with known or suspected central nervous system (CNS) metastases or with the CNS as the only site of active disease are excluded:

i) Subjects with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as those with no radiographic progression for at least 4 weeks after radiation or surgical treatment at the time of consent. Subjects must have been off steroids for at least 2 weeks prior to informed consent and have no new or progressive neurological signs and symptoms.

ii) Subjects with signs or symptoms of brain metastases are not eligible unless brain metastases are ruled out by computed tomography (CT) or magnetic resonance imaging (MRI).

2) Medical History and Concurrent Diseases

a) Subjects with a prior malignancy are excluded, except adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix or of the bladder, or in situ ductal or lobular carcinoma of the breast. Subjects with other prior malignancies diagnosed more than 2 years previously (at the time of informed consent) who have received therapy with curative intent with no evidence of disease during the interval and who are considered by the Investigator to present a low risk for recurrence will be eligible.

b) Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitis, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. Subjects with well-controlled asthma and/or mild allergic rhinitis (seasonal allergies) are eligible.

c) Subject has autoimmune hemolytic anemia (AIHA) or autoimmune thrombocytopenia (ITP) requiring therapeutic doses of systemic steroids.

d) Subject has undergone any allogeneic transplant.

e) Subject has received autologous/allogeneic T-cells transfer.

f) A known or underlying medical condition that, in the opinion of the Investigator or Sponsor, could make the administration of study drug hazardous to the subject or could adversely affect the ability of the subject to comply with or tolerate study procedures and/or study therapy, or confound the ability to interpret the tolerability of relatlimab in treated subjects.

g) Requirement for daily supplemental oxygen.

h) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:

   i) Myocardial infarction (MI) or stroke/transient ischemic attack (TIA) within the 6 months prior to consent.

   ii) Uncontrolled angina within the 3 months prior to consent.

   iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes).

   iv) QTc prolongation > 480 msec.

   v) History of other clinically significant cardiovascular disease (ie, cardiomyopathy, congestive heart failure with New York Heart Association [NYHA] functional classification III-IV, pericarditis, significant pericardial effusion, significant coronary stent occlusion, deep venous thrombosis, etc).

   vi) Cardiovascular disease-related requirement for daily supplemental oxygen.

   vii) ***Not applicable per Revised Protocol 07****. See criteria xi) below for cardiac troponin*. Cardiac Troponin T (cTnT) or I (cTnI) ≥ 2 × institutional ULN. Subjects with cTnT or cTnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤ 1 ULN.

      (1) If cTnT or cTnI levels are > 1 ULN at 24 hours, the subject may undergo a cardiac evaluation and be considered for treatment, following a discussion with the BMS Medical Monitor or designee.

   viii) History of myocarditis, regardless of etiology.

   ix) History of two or more MIs or two or more coronary revascularization procedures.

   x) A confirmed history of encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.

   xi) Troponin T (TnT) or I (TnI) > 2 × institutional ULN.

      Note: Subjects with TnT or TnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤ 1 x ULN. If TnT or TnI levels are >1 to 2 × ULN within 24 hours, the subject may undergo a cardiac evaluation and be considered for

treatment, following a discussion with the BMS Medical Monitor or designee. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible. If TnT or TnI repeat levels beyond 24 hours are < 2 x ULN, the subject may undergo a cardiac evaluation and be considered for treatment, following a discussion with the BMS Medical Monitor or designee.

i) Positive blood screen for HIV or known acquired immunodeficiency syndrome (AIDS).

j) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg), Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).

k) Evidence of active infection that requires systemic antibacterial, antiviral, or antifungal therapy ≤ 7 days prior to initiation of study drug therapy.

l) Any other significant acute or chronic medical illness.

m) Subjects who are unable to undergo venipuncture and/or tolerate venous access.

n) Any other sound medical, psychiatric, and/or social reason as determined by the Investigator.

o) Subjects with history of life-threatening toxicity related to prior immune therapy (eg. anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hormone replacement after endocrinopathy).

p) Any of the following procedures or medications:

   i) Within 2 weeks prior to study drug administration:

      (1) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of relatlimab administered as monotherapy or in combination with nivolumab. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

   ii) Within 4 weeks prior to study drug administration:

      (1) Any investigational drug or placebo.

      (2) Any anticancer therapy (IMIDs [eg, lenalidomide], proteasome inhibitors, chemotherapy, monoclonal antibody for antineoplastic intent [eg, anti-CTLA-4, anti PD-1, anti PL-1, anti PDL-2, anti-CD20, anti-CD30, or alemtuzumab antibody therapy], therapeutic vaccines, radiotherapy, or hormonal treatment).

      (3) Non-oncology vaccines containing live / attenuated virus within 30 days of first treatment.

      (4) Allergen hyposensitization therapy.

      (5) Major surgery.

iii) Within 6 weeks prior to study drug administration:

(1) Nitrosureas, fludarabine.

iv) Within 10 weeks prior to study drug administration:

q) Radio-immunoconjugates.

3) Allergies and Adverse Drug Reaction

a) History of allergy to anti–PD-1 or anti–PD-L1 antibody therapy or to other monoclonal antibodies or related compounds or to any of their components (eg, history of severe hypersensitivity reactions to drugs formulated with polysorbate 80).

4) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated (Note: under specific circumstances, and only in countries where local regulations permit, a person who has been imprisoned may be included as a participant. Strict conditions apply and Bristol-Myers Squibb [BMS] approval is required).

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In additional, women under the age of 55 must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is >40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

- 1 week minimum for vaginal hormonal products, (rings, creams, gels).
- 4 week minimum for transdermal products.
- 8 week minimum for oral products.

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents unless they are utilized to treat an AE or as specified in Section 3.4.3.
- Concurrent administration of any anticancer therapies (investigational or approved) with the exception of subjects in the survival period of the study.
- Use of allergen hyposensitization therapy.
- Use of growth factors unless prior discussion and agreement with BMS Medical Monitor.
- Use of cannabis or other recreational drugs.
- Any live / attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.

Palliative radiotherapy is permitted only under certain conditions as described in Section 3.4.3.

3.4.2 Other Restrictions and Precautions

3.4.2.1 Vaccinations

Any vaccination containing attenuated or inactivated virus may be permitted if clinically indicated. However, this must be discussed and documented with the BMS Medical Monitor **prior to administration** and may require a study drug washout period prior to and after administration of the vaccine. Inactivated influenza vaccination will be permitted on study without restriction. Any vaccination containing live virus is prohibited.

3.4.2.2 Imaging Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

3.4.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Immunosuppressive agents and the use of systemic corticosteroids are permitted in the context of treating AEs, prophylaxis prior to a diagnostic procedure (eg contrast MRI/CT scans) or as specified in Section 3.4.4. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) is permitted after discussion with the BMS Medical Monitor.

Subjects may continue to receive HRT.

Oral antiviral therapy (acyclovir or equivalent) may be required to reduce the risk of herpes zoster reactivation. Discussion with medical monitor is required for any subject planned to receive oral anti-viral therapy.

Palliative and supportive care for disease-related symptoms may be offered to all subjects on the trial; however, Investigators should consult with the BMS Medical Monitor prior to initiating palliative radiation in subjects who have not yet completed the DLT evaluation interval (Part A).

The potential for overlapping toxicities with radiotherapy and relatlimab administered as monotherapy or in combination with nivolumab is currently not known. Therefore, palliative radiotherapy is not recommended while receiving any of these drugs, alone or in combination. If palliative radiotherapy in short courses and for isolated fields is required to control symptoms not clearly related to disease progression, then drug administration should be withheld, if possible, for at least 1 week before radiation and for at least 2 weeks after its completion. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy. Prior to resuming study drug treatment, radiotherapy-related AEs should resolve to ≤ Grade 1 or baseline and subjects must meet relevant eligibility criteria as determined by the BMS Medical Monitor in discussion with the Investigator. The BMS Medical Monitor must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after the last dose.

Details of palliative radiotherapy should be documented in the source records and electronic case report form (CRF). Details in the source records should include dates of treatment, anatomical site, dose administered and fractionation schedule, and AEs. Symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression. Administration of additional relatlimab, as monotherapy or in combination with nivolumab to subjects who receive limited-field palliative radiation, should follow guidelines specified in Section 4.3.5. Subjects receiving palliative radiation of index lesions will have the evaluation of ORR just prior to radiotherapy but such subjects will no longer be evaluable for determination of response subsequent to the date palliative radiation occurs.

For subjects who need to undergo elective surgery (not tumor-related) during the study, it is recommended to hold study drug for at least 2 weeks before and 2 weeks after surgery, or until the subject recovers from the procedure, whichever is longer. Prior to resuming study drug treatment, surgically related AEs should resolve to ≤ Grade 1 or baseline and subjects must meet relevant eligibility criteria as determined by the BMS Medical Monitor in consultation with the

Investigator. The BMS Medical Monitor must be consulted prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after the last dose.

3.4.4 Treatment of Relatlimab or Nivolumab-Related Infusion Reactions

Since relatlimab and nivolumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE version 4.0 guidelines. If a subject has an infusion reaction with nivolumab, the relatlimab infusion can be given (without prophylactic medications) if the infusion reaction resolves within 3 hours. For scheduling purposes after a nivolumab infusion reaction, the relatlimab infusion may be given the next day. Prophylactic pre-infusion medications should be given prior to all subsequent nivolumab infusions.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

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

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional study drug administrations.

For Grade 2 symptoms (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours).

- Stop the infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further study drug will be administered at that visit.

For future infusions, the following prophylactic premedications are recommended:

- Diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before study drug infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Life-threatening, Grade 4: pressor or ventilatory support indicated).

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous (SC) administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Treatment with study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

Please refer to Appendix 4 for a complete list of the Nivolumab Management Algorithms.

3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment.
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Pregnancy.
- Termination of the study by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances, and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required).
- Inability to comply with protocol requirements.
- Progressive disease (PD; see also Section 4.3.4 for details regarding continuing treatment beyond initial assessment of PD).
- Clinical deterioration as assessed by the investigator.
- Protocol-defined reasons for discontinuation (Section 4.3.5).

All subjects who discontinue investigational product should comply with protocol-specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

3.6 Post Treatment Study Follow-Up

In this study, overall survival is an exploratory endpoint of the study. Post-treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other

public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

All protocol-specified investigational and non-investigational products are considered study drug.

4.1 Study Treatments

Product description and storage information is described in Table 4.1-1. Preparation and administration instructions will be provided separately via site training materials.

For study drugs not provided by BMS and obtained commercially by the site, storage should be in accordance with the package insert, summary of product characteristics (SmPC), or similar documentation.

Table 4.1-1: Product Description and Dosage Form

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-986016-01[a] Relatlimab Injection, [redacted] mg/vial or [redacted] mg/vial ([redacted] mg/mL)	[redacted] mg/mL	[redacted] mL or [redacted] mL vial/open label	[redacted] vials/carton/open label	A clear to slightly opalescent, colorless to pale yellow liquid. May contain particles	Store refrigerated, 2-8 °C (36-46 °F) Protect from light Protect from freezing
BMS-936558-01[b] Nivolumab Injection, [redacted] mg/vial ([redacted] mg/mL)	[redacted] mg/mL	[redacted] mL vial/open label	[redacted] or [redacted] vials/carton/open label	Clear to opalescent, colorless to pale yellow liquid. May contain particles	Store refrigerated, 2-8 °C (36-46 °F) Protect from light Protect from freezing

[a] Relatlimab; designated as BMS-986016 in the protocol

[b] Nivolumab; designated as BMS-936558 in the protocol

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are: relatlimab (BMS-986016) and nivolumab (BMS-936558).

4.1.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this study, non-investigational product(s) are not applicable.

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For treatment visits in Parts C, and D, where both relatlimab and nivolumab are administered, nivolumab will be administered first followed by relatlimab within 30 minutes after completion of the nivolumab infusion. Nivolumab infusion will be administered over 30 minutes. Further details regarding preparation and administration will be provided separately in site/pharmacy training materials.

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, SmPC, or similar.

4.2 Method of Assigning Subject Identification

This is an open-label study. All subjects will be assigned a subject number upon providing signed written informed consent. The investigative site will call into the enrollment option of the Interactive Voice Response System (IVRS) designated by BMS for assignment of a 5-digit subject number that will be unique across all sites. Enrolled subjects, including those not dosed, will be

assigned sequential subject numbers starting with [redacted]. The patient identification number (PID) will ultimately be comprised of the site number and subject number. For example, the first subject screened (ie, enrolled) at site number 1, will have a PID of [redacted]. Specific instructions for using IVRS will be provided to the investigative sites in a separate document.

Once it is determined that the subject meets the eligibility criteria, the investigative site will call the IVRS prior to first study drug administration for the subject to be either:

- Assigned to a part (Parts A, D) and dose cohort in the dose escalation portion of the study.
- Assigned to an expansion cohort in the cohort expansion portion (Part B and D) of the study.

During dose escalation (Part A and C), subjects who are not evaluable for DLT determination may be replaced. Replacement subjects will be assigned to the same dose cohort, but will be assigned a new subject number.

4.3 Selection and Timing of Dose for Each Subject

4.3.1 Guidelines for Dose Modification

4.3.1.1 Intrasubject Dose Escalation

Intrasubject dose escalation of relatlimab or nivolumab is not permitted in this study.

4.3.1.2 Dose Reductions

With the possible exception of subjects being treated at a dose level that is subsequently deemed to exceed the MTD, intrasubject dose reduction of relatlimab or nivolumab is not permitted.

4.3.2 Dose Delay Criteria

In some cases, the natural history of select AEs associated with immunotherapy can differ from and be more severe than AEs caused by other therapeutic classes. Early recognition and management may mitigate severe toxicity.

Guidance for Investigators is provided in the current relatlimab and nivolumab Investigator's Brochures.[58.14] Additionally, management algorithms have been developed to assist Investigators with select toxicities and can be found in Appendix 4.

Toxicities for which management algorithms have been developed include:

- Pulmonary.
- Gastrointestinal.
- Hepatic.
- Endocrine.
- Renal.
- Dermatologic.
- Neurologic.
- Myocarditis.

Subjects who experience the following must have all study drugs(s) delayed:

- Potential DLTs (per definition, are related to study drug) until DLT relatedness is defined.
- Select drug-related AEs and drug-related laboratory abnormalities:
  - ≥ Grade 1 pneumonitis.
  - ≥ Grade 1 myocarditis.
  - All troponin elevations require a dose delay to allow for prompt cardiac evaluation.
  - ≥ Single grade increase shift from baseline (at least to Grade 2) of AST, ALT, and total bilirubin.
  - ≥ Grade 2 creatinine.
  - ≥ Grade 2 diarrhea or colitis.
  - ≥ Grade 2 neurological AE.
  - Grade 4 amylase and/or lipase abnormalities regardless of symptoms or clinical manifestations.
- Any AE, laboratory abnormality, or intercurrent illness, which in the judgment of the Investigator, warrants delaying the dose of study medication.

Subjects may be dosed no less than [redacted] days from the previous dose and no more than [redacted] days from scheduled dose. If an infusion cannot be administered at a scheduled visit, it should be administered as soon as possible. Subsequent dosing visits will follow every [redacted] weeks after the delayed dose. A dose given more than [redacted] days after the intended dose date will be considered a delay. A maximum delay of [redacted] weeks between doses is allowed. Longer delays may be allowed following discussion with the Medical Monitor. Subjects who meet criteria listed in Section 4.3.5 are required to permanently discontinue study drug. All other subjects will be permitted to resume therapy with study drug at the same dose level(s) following resolution of the AE as described in Section 4.3.3.

4.3.3 Criteria to Resume Treatment after Dose Delay

Subjects will be permitted to resume therapy at the same dose level(s) following resolution of the AE to ≤ Grade 1 or to baseline within 6 weeks after last dose, with the exception of subjects who meet criteria for permanent discontinuation as specified in Section 4.3.5. Subjects who meet criteria for permanent discontinuation should receive no further study therapy. The following exceptions apply:

- If the toxicity resolves to ≤ Grade 1 or baseline > 6 weeks after last dose, but the subject does not otherwise meet the criteria for permanent discontinuation (see Section 4.3.5), and the Investigator believes that the subject is deriving clinical benefit, then the subject may be eligible to resume the study drug(s) following the approval of the BMS Medical Monitor.
- Subjects with a Grade 4 drug-related amylase and/or lipase increase that is not associated with symptoms or clinical manifestations of pancreatitis can be restarted on therapy once the levels have recovered to grade 3 or less, and after consultation with the BMS Medical Monitor.

- Subjects with baseline Grade 1 AST, ALT, or total bilirubin who require dose delays for reasons other than a drug-related hepatic event may resume treatment in the presence of Grade 2 AST, ALT, or total bilirubin.
- Subjects who require dose delays for drug-related elevations in AST, ALT, or total bilirubin may resume treatment when these values have returned to their baseline CTCAE Grade or normal and management with corticosteroids, if needed, is complete, provided the criteria for permanent discontinuation are not met.
- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- Troponin elevations will require the participants to undergo a cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discussion with the BMS Medical Monitor or designee.

4.3.4 Treatment Beyond Disease Progression

Accumulating evidence indicates that a subset of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Participants treated with relatlimab + nivolumab or with relatlimab alone, will be permitted to continue their study treatment beyond initial investigator assessment of progression, provided the following criteria are met:

- Subject is deriving clinical benefit as assessed by the Investigator.
- Disease progression is not rapid as assessed by the Investigator.
- Subject continues to meet relevant eligibility criteria as determined by the BMS Medical Monitor in discussion with the Investigator.
- Subject tolerates study drug.
- Subject has stable performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).
- Subjects have provided written informed consent prior to receiving additional study drug.

The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment. If the Investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the study and continue to receive monitoring according to the Time and Events Schedule (Table 5.1-2). The decision to continue treatment should be discussed with the BMS Medical Monitor and documented in the study records.

Subjects that meet the above criteria and continue on study therapy beyond initial PD. must discontinue relatlimab (and nivolumab, if part of the combination cohorts) upon the next documented event of PD. A follow-up efficacy assessment should be performed at the next

scheduled evaluation 8 weeks later (but no sooner than 4 weeks later) to determine whether there is continued PD.

4.3.5 Guidelines for Permanent Discontinuation

Subjects meeting any of the following criteria will be required to permanently discontinue all study drug(s) (relatlimab in Part A and B; relatlimab and nivolumab in Parts C and D):

- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies.
- Grade 3 drug-related myocarditis, uveitis, pneumonitis, bronchospasm, or hypersensitvity reaction of any duration.
- Grade 3 infusion reaction that does not return to Grade 1 in 6 hours or less.
- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 neutropenia ≤ 7 days in duration.
  - Grade 4 lymphopenia or leukopenia.
  - Isolated Grade 4 lipase and/or amylase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Grade 3 drug-related laboratory abnormalities do **not** require treatment discontinuation **except**:
  - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
  - AST, ALT, or bilirubin abnormalities that meet DLT criteria (Section 3.1.6) (In most cases of AST or ALT elevation meeting DLT criteria study drugs will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drugs, a discussion between the investigator and the BMS Medical Monitor/designee must occur).
  - Elevated troponin that meets DLT criteria (Section 3.1.6).

- Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
- Any event that leads to dosing delays lasting > 6 weeks from the previous dose **requires discontinuation** with the following **exceptions**:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks after the previous dose the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks from the previous dose, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed and subjects must otherwise meet the criteria for continued treatment at the time re-initiation of study therapy is considered. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued relatlimab or nivolumab dosing.
- PD (see also Section 4.3.4 for details regarding continuing treatment beyond initial assessment of PD).
- Clinical deterioration as assessed by the Investigator.
- Completion of the maximum number of twelve 8-week cycles.

The consideration to re-initiate study therapy in selected cases at any time point after discontinuation could be made on a case-by-case basis after considering the overall benefit/risk profile and in consultation between the Investigator and the study Sponsor. The selected subjects will need to meet eligibility criteria. The original dose and schedule and protocol rules would apply accordingly.

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

Study drug will be administered in the clinical facility by trained medical personnel. Treatment compliance will be monitored by drug accountability, as well as by recording relatlimab and nivolumab administration in subjects' medical records and CRF.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1 (screening), Table 5.1-2 (on-treatment), and Table 5.1-3 (follow-up).

Table 5.1-1: Screening Procedural Outline (CA224022)

Procedure	[redacted]
Eligibility Assessments	
Informed consent	
Inclusion/exclusion criteria	
Medical history	
Safety Assessments	
Physical examination (PE)	
Performance status	
Physical measurements	
Vital signs	
Oxygen saturation	
Electrocardiogram (ECG)	
LVEF Assessment (either TTE or MUGA)	
Cardiac Troponin T (cTnt) or I (cTnI)	
Chest radiograph	

Table 5.1-1: Screening Procedural Outline (CA224022)

Procedure	[redacted]
Safety laboratory tests	
Pregnancy test	
Follicle-stimulating hormone (FSH)	
Concomitant medications	
Clinical complaints	
Adverse Event Reporting	
Monitor for serious adverse events	

Table 5.1-1: Screening Procedural Outline (CA224022)

Procedure	[redacted]
Baseline Assessments Lymphomas and CLL	
Tumor tissue sample (eg, primary tumor, lymph node)	
Bone marrow biopsy and/or aspirate	
Diagnostic Imaging	

Table 5.1-1: Screening Procedural Outline (CA224022)

Procedure	[redacted]
Brain imaging	
PET or PET/CT scan	
Photography	
Baseline Assessments Myeloma	
Skeletal survey	
Documentation of extramedullary soft tissue plasmacytomas, if clinically indicated	
Bone Marrow Aspiration/Biopsy	
Myeloma serum tests	
Myeloma urine tests	

Note: Re-challenge subjects must be screened.

Table 5.1-2: On-Treatment Procedural Outline

Procedure	[redacted]
IVRS Assignment	
IVRS assignment	
Safety Assessments	
Physical examination (PE)	
Neurological Exam (NE)	
Performance status	
Weight	
Vital signs	

Table 5.1-2: On-Treatment Procedural Outline

Procedure	[redacted]
12-lead electrocardiogram (ECG)	
Cardiac Troponin T (cTnt) or I (cTnI)	
Oxygen saturation	

Table 5.1-2: On-Treatment Procedural Outline

Procedure	[redacted]
Safety laboratory tests	
Endocrine Panel	
Immunoglobulins and Complement	
Cytogenetics	

Table 5.1-2: On-Treatment Procedural Outline

Procedure	[redacted]
Mutations & molecular markers	
Pregnancy test (WOCBP)	
Assess adequate contraceptive use	

Table 5.1-2: On-Treatment Procedural Outline

Procedure	[redacted]
Adverse Event and Con Med Assessment	
Monitor for non-serious adverse events	
Monitor for serious adverse events	
Con Med assessment	
Sample Collection	
Pharmacokinetic (PK) assessments	
Immunogenicity assessments	

Table 5.1-2: On-Treatment Procedural Outline

Procedure	[redacted]
Biomarker assessments	
On-treatment tumor or lymph node biopsy	
Efficacy Assessments Lymphomas and CLL	
Diagnostic Imaging	
Brain imaging	

Table 5.1-2: On-Treatment Procedural Outline

Procedure	[redacted]
Photography	
Bone marrow biopsy and/or aspirate	
Response assessment	
Efficacy Assessments **Myeloma**	
Skeletal survey	
Documentation of extramedullary soft tissue plasmacytoma	
Bone Marrow Aspiration/ Biopsy	
Flow cytometry	
Myeloma tests in serum	

Table 5.1-2: On-Treatment Procedural Outline

Procedure	[redacted]
Myeloma tests in urine	
Study Drug Administration	
Relatlimab (BMS-986016) administration	
Nivolumab (BMS 936558) administration	

[redacted]

Table 5.1-3: Follow-Up Procedural Outline (CA224022)

Procedure	[redacted]
Safety Assessments	
Physical examination (PE)	
Performance status	
Weight	
Vital signs	
12-lead electrocardiogram (ECG)	
Oxygen saturation	
Safety Laboratory tests	

Table 5.1-3: Follow-Up Procedural Outline (CA224022)

Procedure	[redacted]
Pregnancy test	
Assess adequate contraceptive use	
Adverse Event and Con Med Assessment	
Monitor for non-serious adverse events	
Monitor for serious adverse events	
Con Med assessment	

Table 5.1-3: Follow-Up Procedural Outline (CA224022)

Procedure	[redacted]
Sample Collection	
Pharmacokinetic (PK) assessments	
Immunogenicity (ADA) assessments	
Efficacy Assessments Lymphomas and CLL	
Diagnostic Imaging	
Brain Imaging	
Response assessment	

Table 5.1-3: Follow-Up Procedural Outline (CA224022)

Procedure	[redacted]
Efficacy Assessments	
Myeloma	
Documentation of extramedullary soft tissue plasmacytoma	
Myeloma tests in serum	
Myeloma tests in urine	

Table 5.1-3: Follow-Up Procedural Outline (CA224022)

Procedure	[redacted]
Survival Status	
Assessment of subject survival status	

In the event of multiple procedures are required at a single time point, the following is a list of procedures from highest to lowest priority:

1) Safety (ECG).
2) Pharmacokinetic Sampling.
3) Safety (clinical labs).
4) Oxygen saturation.

5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.0.
- Relatlimab and BMS-936558 IBs.
- Pharmacy Binder.
- Laboratory kits and manuals for collection and handling of blood (including PK, immunogenicity, and biomarkers) and tissue specimens.
- Holter monitor, associated supplies, and manual.
- IVRS manual.
- Enrollment Worksheets.
- Serious Adverse Event Forms.
- Pregnancy Surveillance Forms.

5.3 Safety Assessments

Adverse events will be assessed continuously during the study and for 135 days after the last treatment. Adverse events will be evaluated according to NCI CTCAE version 4.0 and should be followed per requirements in Sections 6.1.1 and 6.2.1. Adverse events will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and reviewed for potential significance and importance.

Protocol-specified assessments are described in Table 5.1-1 (Screening Procedural Outline), Table 5.1-2 (On-Treatment Procedural Outline), and Table 5.1-3 (Follow-Up Procedural Outline).

5.3.1 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

5.3.2 Genomic Analysis

In order to identify potential polymorphisms associated with safety and efficacy of relatlimab, selected genes will be evaluated for single nucleotide polymorphisms (SNP). Analysis will include but not be limited to sequence polymorphisms linked to genes and pathways associated with [redacted] and [redacted]

[redacted] DNA may also be utilized for DNA sequencing to identify germline sequences to compare with tumor sequences.

5.3.3 Laboratory Test Assessments

A central/local laboratory will perform the analyses and will provide reference ranges for these tests.

Clinical laboratories will be assessed at the time points indicated in Table 5.1-1 (Screening Procedural Outline), Table 5.1-2 (On-Treatment Procedural Outline), and Table 5.1-3 (Follow-Up Procedural Outline).

At screening, sites should collect samples during the timeframes indicated in Table 5.1-1 and ensure that results required for eligibility are verified prior to registration. During treatment, unless otherwise indicated in Table 5.1-2, results of clinical laboratory test must be reviewed prior to dosing.

The following clinical laboratory tests will be performed:

Hematology (Local Laboratory)

Complete blood count (CBC) with differential
Platelet count
INR (screening only)

Serum Chemistry (Local Laboratory)

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total bilirubin
Alkaline phosphatase
Lactate dehydrogenase (LDH)
Creatinine
Blood urea nitrogen (BUN)
Uric acid
Fasting or non-fasting glucose
Amylase
Lipase
Cardiac Troponin T (cTnT) or Cardiac Troponin I cTnI
C-reactive protein
Albumin
Sodium
Potassium
Chloride
CO_2
Calcium
Magnesium
Phosphorus
Creatine clearance (CLcr)* - screening only *Cockcroft-Gault formula

For those subjects receiving on-going treatment with relatlimab and nivolumab, troponin elevations will require the subject to undergo a cardiac evaluation. Following this evaluation, determination of further treatment will be based on the discussion with the BMS Medical Monitor or designee.

Endocrine Panel (Local Laboratory)

Thyroid-stimulating hormone (TSH) with reflex to free T3 and free T4 as applicable. Subjects with controlled hyperthyroidism must be negative for thyroglobulin and thyroid peroxidase antibodies with thyroid stimulating immunoglobulin (screening only).

Urinalysis (Local Laboratory)

Total protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick

Serology (Local Laboratory)

Hepatitis B surface antigen (HBsAg) and/or hepatitis B core antigen
Qualitative hepatitis C viral load by PCR
HIV-1,-2 antibody

Immunoglobulins and Complement (Local Laboratory)

[redacted]

Mutation and Molecular Markers (Local Laboratory)

[redacted] expression
[redacted] expression
[redacted]

Cytogenetics Analysis (Local Laboratory)

[redacted]

Cytogenetics Analysis (Central Laboratory)

[redacted]

Multiple Myeloma Tests

- Serum: specific alkaline phosphatase, total serum protein, immunoglobulin assay, serum protein electrophoresis (SPEP) with M-protein quantitation and serum free light chain. Serum immunofixation as indicated in Table 5.1-2
- Urine: 24-hour urine collection for creatinine (spot urine is not acceptable), total urine proteins, and UPEP with M-protein (urinary light chain) quantitation. Urine immunofixation as indicated in Table 5.1-2.
- Bone marrow: flow cytometry evaluation of percentage [redacted] cells and clonality (based on [redacted]) to confirm [redacted].

Reproductive Analyses (Local Laboratory)

Pregnancy testing:

- Clinic: serum or urine (urine pregnancy test: minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG])
- Home pregnancy test kits

Follicle-stimulating hormone (FSH); if needed to document post-menopausal status as defined in Section 3.3.3)

Other Analyses

Additional measures including non-study required laboratory tests should be performed as clinically indicated.

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal

laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3).

5.4 Efficacy Assessments

Study evaluations will take place in accordance with the Schedule of Activities in Section 5.1.

Efficacy assessments will be conducted and reported by the investigator on the CRF using the appropriate efficacy assessment based on tumor type.

- Subjects with NHL or HL will be evaluated using the 2007 IWG Response Criteria for Malignant Lymphoma[62] (Appendix 1). Disease assessments for subjects with HL and DLBCL will occur between Days [redacted] and [redacted] of each treatment cycle [redacted] cycles) and at the [redacted].
- Since the conception of this protocol, new response criteria known as Lugano 2014 criteria (Appendix 7) have been developed to refine tumor metabolic response. A retrospective exploratory assessment of tumor metabolic response will be evaluated according to the Lugano 2014 criteria using the Deauville 5-point scale on Part D subjects with NHL or HL who had fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans performed in the pre-treatment period (defined as within 60 days before the first dose, providing no other therapy was given during this time) and during this study.
  - For these PET-based assessments, a response of complete metabolic response (CMR), partial metabolic response (PMR), no metabolic response, or progressive metabolic disease (PMD) will be determined. The PET scan metabolic uptake will be graded using the Deauville 5-point scale, with a score of 1, 2, or 3 considered to represent a CMR (see Appendix 7). Assessments will be performed by PET scan with CT/MRI of diagnostic quality, with disease involvement determined by focal FDG uptake in nodal and extranodal lesions (including the spleen and liver).
- Subjects with CLL will be evaluated using the 2008 IWG Response Criteria for CLL with Modifications[64] (Appendix 2). Disease assessments for subjects with CLL will occur between Days [redacted] and [redacted] of each treatment cycle (up to twelve 8-week treatment cycles) and at the [redacted].
- Subjects with MM will be evaluated using Response Criteria Modified from IMWG for Multiple Myeloma[63] (Appendix 6). [65,66] Disease assessments for subjects with MM will occur on Day [redacted] and Day [redacted] of each cycle and at the [redacted]. According to study design, the results on [redacted] will be used to define continuation of therapy or not in all subjects.

5.5 Pharmacokinetic Assessments

Serum samples for relatlimab and nivolumab PK and anti-drug antibody (ADA) assessments will be collected for all subjects.

5.5.1 Pharmacokinetics - Collection and Processing

Pharmacokinetic blood samples will be drawn from study subjects receiving relatlimab as monotherapy or in combination with nivolumab at the time points indicated in Table 5.5.1-1 and Table 5.5.1-2. All time points are relative to the start of study drug administration. All samples collected pre-dose should be taken within 30 minutes before the start of dose administration. End-of-infusion samples should be taken just prior to the end of infusion (preferably within 2 minutes) from the contralateral arm (ie, the arm not used for the infusion). On-treatment samples are intended to be drawn relative to actual dosing days. If a dose occurs on a different day within the cycle due to minor schedule adjustments or dose delays, PK samples should be adjusted accordingly. Further details of sample collection, processing, and shipment will be provided in the Laboratory Procedures Manual.

Table 5.5.1-1: PK and ADA Sampling Schedule for Relatlimab and Nivolumab in all Subjects in Part A, B, C and [redacted] Subjects in Part D and for Cohorts with Re-Challenge

Study Day of Sample Collection (1 Cycle = 56 Days [8 Weeks])	Event	Time (Relative to Start of Infusion) Hour: Min	Relatlimab PK Sample (All Subjects)	Relatlimab ADA Sample (All Subjects)	Nivolumab PK Sample (Part C & D Only)	Nivolumab ADA Sample (Part C & D Only)
Cycle 1						
1	predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00	X		X	
1		04:00	X			
2		24:00	X			
3-5		48:00 - 96:00[c]	X			
7-9		144:00 - 192:00[c]	X			
15	predose[a]	00:00	X	X	X	X
29	predose[a]	00:00	X	X	X	X
43	predose[a]	00:00	X		X	
Cycle 2						
1	predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00	X		X	
15	predose[a]	00:00	X		X	
29	predose[a]	00:00	X		X	
Cycle 3						
1	predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00	X		X	

Table 5.5.1-1: PK and ADA Sampling Schedule for Relatlimab and Nivolumab in all Subjects in Part A, B, C and [redacted] Subjects in Part D and for Cohorts with Re-Challenge

Study Day of Sample Collection (1 Cycle = 56 Days [8 Weeks])	Event	Time (Relative to Start of Infusion) Hour: Min	Relatlimab PK Sample (All Subjects)	Relatlimab ADA Sample (All Subjects)	Nivolumab PK Sample (Part C & D Only)	Nivolumab ADA Sample (Part C & D Only)
1		04:00	X			
2		24:00	X			
3-5		48:00 - 96:00[b]	X			
7-9		144:00 - 192:00[b]	X			
15	predose[a]	00:00	X		X	
Subsequent Odd # Treatment Cycles						
1	predose[a]	00:00	X	X	X	X
Follow-up Period						
FU2[d]	FU2		X	X	X	X
FU3[d]	FU3		X	X	X	X

[a] Predose: All predose samples for relatlimab and nivolumab should be collected within 30 minutes prior to the start of nivolumab infusion.

[b] EOI: End of Infusion. For subjects receiving relatlimab in combination with nivolumab, EOI samples for both relatlimab and nivolumab should be collected after the end of relatlimab infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as drug was administered; refer to the Laboratory Procedures Manual for additional restrictions.

[c] A single PK sample is to be drawn during this time range.

[d] FU2 and FU3 corresponds to 60 and 135 day follow up visit, respectively.

Table 5.5.1-2: PK and ADA Sampling Schedule for Relatlimab and Nivolumab for Dose Expansion Part D after [redacted] Subjects

Study Day of Sample Collection (1 Cycle = 56 Days [8 Weeks])	Event	Time (Relative to Start of Infusion) Hour: Min	Relatlimab PK Sample (All Subjects)	Relatlimab ADA Sample (All Subjects)	Nivolumab PK Sample (Part C & D Only)	Nivolumab ADA Sample (Part C & D Only)
Cycle 1						
1	predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00	X		X	
15	predose[a]	00:00	X	X	X	X
29	predose[a]	00:00	X	X	X	X
43	predose[a]	00:00	X		X	
Cycle 2						
1	predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00	X		X	
15	predose[a]	00:00	X		X	
Cycle 3						
1	predose[a]	00:00	X	X	X	X
1	EOI[b]	01:00	X		X	
15	predose[a]	00:00	X		X	
Subsequent Odd # Treatment Cycles						
1	predose[a]	00:00	X	X	X	X
Follow-up Period						
FU2[c]	FU2		X	X	X	X
FU3[c]	FU3		X	X	X	X

[a] Predose: For subjects receiving relatlimab in combination with nivolumab, all predose samples for relatlimab and nivolumab should be collected within 30 minutes prior to the start of nivolumab infusion.

[b] EOI: End of Infusion. For subjects receiving relatlimab in combination with nivolumab, EOI samples for both relatlimab and nivolumab should be collected after the end of relatlimab infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as drug was administered; refer to the Laboratory Procedures Manual for additional restrictions.

[c] FU2 and FU3 corresponds to 60 and 135 day follow up visit, respectively.

5.5.2 Pharmacokinetic Sample Analyses

The serum samples will be analyzed for relatlimab and nivolumab concentrations by a validated immunoassay. In addition, selected serum samples may be analyzed by an exploratory orthogonal method (eg, liquid chromatography [LC]-mass spectrometry [MS]/MS) that measures total relatlimab and/or nivolumab, but the generated data will not be reported. Only results generated from the validated immunoassay method will be reported. Potential results generated from any orthogonal method are intended as informational for technology exploration purposes and will not be reported.

5.5.3 Labeling and Shipping of Biological Samples

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the Laboratory Procedures Manual.

5.6 Biomarker Assessments

Not applicable.

5.7 Exploratory Biomarker Assessments

Tumor tissue will be collected prior to therapy and at selected time points on treatment in all subjects in Parts A, B, C, and D. Bone Marrow and/or aspirate will be collected prior to therapy and at selected time points on treatment in all subjects in Parts A and B. Peripheral blood will be collected prior to therapy and at selected time points on treatment in up to [redacted] subjects enrolled in each dose level in Part A and in all subjects in Part B, C, and D. If biomarker samples are drawn but study drug is not administered, samples will be retained. A schedule of pharmacodynamic evaluations is provided in Table 5.7-1 and detailed descriptions of each assay system are provided in the sections that follow.

Table 5.7-1: Biomarker Sampling Schedule

5.7.1 Soluble Biomarkers

Soluble factors, including but not limited to cytokines, chemokines, soluble receptors, and antibodies to tumor antigens will be characterized and quantified by immunoassays in serum. Analyses may include, but not necessarily be limited to, [redacted]. Collected serum samples may also be used for the assessment of tumor antigen-specific antibody responses elicited following treatment.

5.7.2 Immunophenotyping of PBMC and Bone Marrow Aspirates

The proportion of specific lymphocyte subsets and expression levels of T-cell co-stimulatory markers in PBMC preparations will be quantified by cytometry. Analyses may include, but not necessarily be limited to, [redacted]

5.7.3 Ex Vivo Functional Assays

To explore whether relatlimab alone or with nivolumab will [redacted]

5.7.4 Peripheral Blood Gene Expression

The expression level of genes related to response to relatlimab will be quantified using molecular methods including but not limited to [redacted]

5.7.5 Relatlimab Receptor Occupancy

[redacted] Samples will be taken prior to treatment to define a baseline and at the time of bone marrow aspirate collection. Analysis of peripheral blood and bone marrow aspirates will be done in fresh samples; therefore, it is critical that samples be shipped promptly after collection.

[redacted]

5.7.7 Tumor-Based Biomarker Measures

Tumor biopsy specimens (eg, primary tumor, lymph nodes) will be obtained prior to and after treatment with relatlimab alone or with nivolumab to characterize [redacted] and expression of selected tumor markers.

A pre-treatment tumor biopsy (eg, primary tumor, lymph node) will be collected in all consenting subjects.

If a pre-treatment tumor biopsy is not clinically feasible, after approval by the medical monitor, an archived tumor tissue sample (eg, primary tumor, lymph node, etc), [redacted] should be provided for performance of correlative studies. If slides are submitted, the recommended tissue section thickness is 4 microns and the **slides must be positively charged**. Slides should be shipped refrigerated at 2-8°C.

The pathology report should be submitted with the archived or fresh biopsy sample. If both a fresh biopsy and an archived sample are available, both samples should be sent.

On-treatment tumor biopsies will be collected in up to [redacted] The biopsy should be obtained during [redacted] The biopsy may be coordinated with protocol-specified diagnostic imaging.

When a fresh biopsy is taken, up to 3 to 4 core biopsies, and a minimum of two are recommended. An assessment of biopsy quality by a pathologist is strongly encouraged at the time of the procedure. The tumor tissue that is obtained from these biopsies will be divided equally into [redacted]

Biopsy samples should be excisional, incisional, or core needle. Fine needle aspirates are not allowed. It is recommended that samples be fixed in [redacted].

Sample shipments should include a completed requisition form containing collection date, collection method, primary tumor and lymph node and/or metastasis, site, fixation conditions, and a copy of pathology report, if available.

The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable and feasible. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. However, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject. Subjects should have at least one lesion large enough to undergo repeated biopsies (pre- and on-treatment biopsies) via core needle (minimum size 18 gauge) or have at least [redacted] for core needle or excisional biopsies. The expected core needle length should be greater than [redacted] mm. Fine needle aspirate biopsies are not accepted. At least [redacted] biopsies will be taken at each time point, but collection of additional cores is strongly encouraged if deemed clinically safe by the investigator. **An assessment of biopsy quality by a pathologist is strongly encouraged at the time of the procedure.** All biopsies collected must have a detailed pathology report submitted with the specimen. Detailed instructions regarding the acquisition, processing, labeling, handling, storage,

and shipment of biopsy specimens will be provided in a separate procedure manual prior to study initiation.

On-treatment tumor biopsies will be collected in up to six patients treated on [redacted] The biopsy may be coordinated with protocol-specified diagnostic imaging.

Biopsy and bone marrow samples may be used for the following assessments:

- Characterization of [redacted]. Immunohistochemistry will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within tumor tissue before and after exposure to relatlimab and nivolumab. These IHC analyses will include, but not necessarily be limited to, the following markers: [redacted] be made between assays performed if deemed to be informative.
- [redacted]
- [redacted]
- Gene expression profiling. Tumor biopsies that are collected in RNAlater or similar reagent will be examined for mRNA gene expression by techniques including but not limited to [redacted]
- [redacted]
- [redacted]

Subjects whose screening biopsy yields inadequate tissue quantity or quality will be allowed to continue in the study. If on-treatment biopsy is not successful, subjects may also continue on study. Such subjects may be replaced in order to obtain 48 subjects with adequate paired tumor biopsies. If subjects have a major response to treatment, on-treatment biopsies might not be possible. In this case, subjects may also continue on study.

The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. However, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject.

Bone Marrow and/or Aspirates in Subjects enrolled in Part A and B

Unilateral bone marrow biopsy and/or aspirate will be done [redacted] Subjects who had a bone marrow aspirate and biopsy result since completion of their last therapy may not use those bone marrow results in lieu of the baseline bone marrow required for this study. [redacted] as clinically indicated, and may be coordinated with protocol-specified diagnostic imaging.

Bone marrow biopsy and/or aspirates will be obtained using institutional standards for these procedures. Detailed instructions for bone marrow biopsy and aspirate collection will be provided in the Laboratory Procedures Manual. In brief, [redacted] approximately 10 mL of aspirate will be collected in a sodium heparin tube and shipped ambiently. A second bone marrow biopsy will be harvested for RNA later. The pathology report should be submitted with the biopsy sample.

[redacted] No additional sampling is required for residual collections. Retention is mandatory for all subjects, except where prohibited by local laws or regulations. Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of specimens will be provided in a separate Laboratory Procedures Manual at the time of study initiation.

5.7.8 Additional Research Collection

This protocol will include residual sample storage for additional research (AR).

For All US sites:

Additional research participation is required for all investigational sites in the US.

For non-US Sites:

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

This collection for additional research is intended to expand the translational R&D capability at BMS, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

Sample Collection and Storage

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development (or designee) to ensure the research supports appropriate and well-defined scientific research activities.

- Residual samples from tumor biopsies and biomarker collections Table 5.7.8-1 will also be retained for additional research purposes.

Samples kept for future research will be stored at the BMS Biorepository in [redacted] USA or an independent, BMS-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

Table 5.7.8-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Time points for which residual samples will be retained
Tumor Biopsies	[redacted]
Biomarker Blood Collections	
PK Blood Collections	

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Assessments

5.9.1 Immunogenicity Assessments

Blood samples for immunogenicity analysis of relatlimab and nivolumab will be collected according to the schedule given in Table 5.5.1-1 and Table 5.5.1-2. These samples will be evaluated for the development of anti-drug antibody (ADA) for relatlimab and nivolumab by validated immunoassays. Additional characterization (eg, neutralizing antibody (NAB) assay) for any detected ADA may also be performed using a validated assay. On-treatment samples are intended to be drawn relative to actual dosing days. If a dose occurs on a different day within the cycle, immunogenicity samples should be adjusted accordingly.

Selected serum samples may be analyzed by an exploratory orthogonal method that measures anti-relatlimab or anti-nivolumab. Potential results generated from any orthogonal method are intended as informational for technology exploration purposes and will not be reported.

Selected immunogenicity samples also may be analyzed for exploratory analyses; exploratory results will not be reported.

In addition, ad hoc serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

5.10 Results of Central Assessments

The effect of relatlimab on QTc interval when administered as monotherapy or in combination with nivolumb will be evaluated by a central reader using ECG data collected via Holter monitors supplied by a core laboratory; these results will be summarized at the end of the study. For the purposes of monitoring subject safety, Investigators will review 12-lead ECGs per the protocol-specified schedule (see Table 5.1-2) using their site's standard electrocardiogram machines.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol.

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death.
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below).
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.).

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event).
- elective surgery, planned prior to signing consent.
- admissions as per protocol for a planned medical/surgical procedure.
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy).
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 135 days of discontinuation of dosing or until starting a new anti-neoplastic treatment (whichever occurs first). If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

All SAEs that occur during the screening period and within 100 days after discontinuation of dosing must be collected except in cases where a study participant has started a new anti-neoplastic treatment.

However, any SAE occurring after the start of a new anti-neoplastic treatment that is suspected to be related to study treatment by the investigator should be reported as an SAE.

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Non-serious Adverse Events

A ***non-serious adverse event*** is an AE not classified as serious.

6.2.1 Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug and for 135 days after discontinuation of dosing or until starting a new anti-neoplastic treatment (whichever occurs first). Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified non-serious AEs must be recorded and described on the non-serious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were

exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's case report form.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE.
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted.
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives + 30 days (165 days) after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

In cases where a study drug can be present in seminal fluid, at exposures sufficient to potentially cause fetal toxicity, and if any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant WOCBP partner(s), the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an informed consent form for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

All occurrences of intentional overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1) Aminotransferase (ALT or AST) elevation > 3 times upper limit of normal (ULN) AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3) No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, radiologic exams, any other potential safety assessment required or not required by protocol should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

8.1.1 Parts A and C - Dose Escalation

The sample size at each dose depends on observed toxicity and cannot be precisely determined. Part A will have [redacted] to [redacted] subjects in each cohort.

8.1.2 Part B Cohort Expansion for Monotherapy

[redacted]

8.1.3 Part D Cohort Expansion for Combination Therapy

The objective of this expansion in combination with nivolumab is, in addition to demonstrating adequate safety and tolerability, to evaluate a favorable risk/benefit assessed by signal seeking for anti-PD-1/PD-L1 progressed nivolumab HL, improvement in complete response (CR) rate for anti-PD-1/PD-L1 naive HL relative to PD-1 monotherapies, and improvement in objective response rate (ORR) for DLBCL relative to existing available therapies.

[redacted]

Table 8.1.3-1: Example of a Two-stage Design Characteristics

8.2 Populations for Analyses

- **All Enrolled Subjects:** All subjects who signed an informed consent form and were registered into the IVRS.
- **All Treated Subjects:** All subjects who received at least one dose of study medication. This is the primary population for safety and efficacy analyses.
- **Response-Evaluable Subjects:** All treated subjects with measurable disease at baseline and one of the following: 1) at least one post-baseline tumor assessment, 2) clinical progression, or 3) death (if death occurred within 135 days after last relatlimab dose).
- **Pharmacokinetic Subjects:** All subjects who received at least one dose of relatlimab or nivolumab and have evaluable plasma/serum concentration data.
- **Immunogenicity Subjects**: All treated subjects with relatlimab or nivolumab who have baseline and at least one post baseline immunogenicity assessment.
- **Biomarker Subjects**: All treated subjects with available biomarker data.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint of this Phase 1 study is safety as measured at the study level by the rate of AEs, SAEs, AEs leading to discontinuation, deaths, and laboratory abnormalities, assessed during treatment and for up to 135 days after the last treatment. All subjects who receive at least one dose of relatlimab alone or in combination with nivolumab will be analyzed for safety.

Co-primary endpoint in Part D is objective response rate (ORR) and duration of response (DOR) (see Section 8.3.2.3 for details).

8.3.2 Secondary Endpoint(s)

8.3.2.1 Pharmacokinetics

The PK of relatlimab administered both alone and in combination with nivolumab will be assessed as a secondary objective using the following endpoints derived from serum concentration versus time data at time points indicated in Table 5.5.1-1.

The PK parameters to be assessed include:

Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed serum concentration
Ctrough	Trough observed serum concentration
Ctau	Concentration at the end of a dosing interval (eg, concentration at 336 hours)
Css,avg	Average concentration over a dosing interval ([AUC(TAU)/tau]
AUC(TAU)	Area under the concentration-time curve in one dosing interval
CLT	Total body clearance
T-HALFeff AUC	Effective elimination half-life that explains the degree of AUC accumulation observed
T-HALFeff Cmax	Effective elimination half-life that explains the degree of Cmax accumulation observed
AI_AUC	Accumulation index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax accumulation index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau accumulation index; ratio of Ctau at steady state to Ctau after the first dose
DF	Degree of fluctuation or fluctuation index ([Cmax - Ctau]/Css,avg)

Individual subject PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

8.3.2.2 Immunogenicity

Incidence of ADA to either relatlimab or nivolumab will be assessed during treatment and for up to 135 days after their last treatment in post-treatment follow-up. Baseline ADA positive subject is defined as a subject with positive seroconversion detected in the last sample before initiation of treatment. ADA-positive subject is a subject with at least one ADA-positive sample relative to baseline after initiation of the treatment.

8.3.2.3 Efficacy

All efficacy analyses will be based on the all treated analysis population except otherwise stated. Co-primary, secondary and exploratory efficacy endpoints for Part D subjects are as follows:

Objective Response Rate (ORR)

ORR based on investigator assessment, according to the applicable criteria based on tumor type, will be co-primary endpoint in Part D. For the NHL and HL subjects, the ORR will be based on the IWG (2007) response criteria. In addition to the primary ORR endpoint, an exploratory endpoint of ORR based on the Lugano (2014) response criteria in the NHL and HL subjects in Part D will be assessed. For the Lugano criteria, response is defined as CMR and PMR.

Duration of Objective Response (DOR)

DOR is defined as the time between the date of first documented response (CR or PR) to the date of the first objectively documented progression as per criteria relevant to each disease type in Part D (Appendices 1, 2, and 6), or death due to any cause, whichever occurs first. For subjects who neither progress nor die, DOR will be censored on the date of their last tumor assessment. Subjects who start subsequent therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy. This endpoint will only be evaluated in subjects with objective response of CR or PR. DOR will be evaluated based on investigator assessments. DOR is a co-primary endpoint in Part D. DOR based on the Lugano (2014) response criteria, response defined as CMR or PMR, will be assessed for the NHL/HL subjects in Part D as an exploratory endpoint.

Complete Response (CR) Rate and Duration

The CR rate is defined as the number of subjects with a best overall response (BOR) of CR according to the applicable criteria based on tumor type, based on IWG criteria for NHL and HL subjects, divided by the number of treated subjects. The duration of CR (DoCR) will only be evaluated in subjects with BOR of CR and is defined as the time from first documentation of CR (the date of first negative FDG-PET scan) to the date of initial objectively documented progression as determined using the applicable criteria based on tumor type or death due to any cause, whichever occurs first. Censoring will be applied as per DOR definition. CR rate and DoCR will be evaluated based on investigator assessments. CR rate is an exploratory endpoint in this study.

Progression Free Survival (PFS) Rate

PFS is defined as the time from first dose to the date of first objectively documented progression, per applicable criteria based on tumor type or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date of first dose. Subjects who started any subsequent anti-cancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy. The PFS rate at time T is defined as the probability that a subject has not progressed and is alive at time T following first dose. PFSR will be assessed at Weeks 16, 24, 32, 40, and 100, and evaluated based on investigator assessments. PFS will be an exploratory endpoint in this study.

Overall Survival (OS) Rate

OS is defined as the time between the date of first dose and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive. The overall survival rate at time T is defined as the probability that a subject is alive at time T following first dose OS will be assessed at various time points in HL patients in Part D.

8.3.3 Exploratory Endpoint(s)

8.3.3.1 Biomarkers

Biomarkers endpoints from peripheral blood may include measures such as levels of soluble factors, as well as activation and proliferation of subsets of immune cells including but not limited to subset of T cells characterized by immunophenotyping, at each scheduled time point. Biomarker endpoints from tumor biopsies may include, but will not be limited to, [redacted]

8.3.3.3 Other Efficacy Endpoints

PFS based on Lugano (2014) Criteria:

PFS for a subject is defined as the time from the first dosing date to the date of first progressive metabolic disease or death due to any cause (death occurring after retreatment will not be considered), whichever occurs first. Subjects who died without a reported prior progression will be considered to have progressed on the date of their death. The censoring rules applied to the PFS endpoint based on the IWG criteria will also be used for this endpoint.

Complete Metabolic Response Rate based on Lugano 2014 Criteria:

The CMR rate is defined as the number of subjects with a BOR of CMR based on the Lugano (2014) criteria divided by the number of treated subjects. The duration of CMR (DoCMR) will only be evaluated in subjects with BOR of CMR and is defined as the time from first documentation of CMR (the date of first negative FDG-PET scan) to the date of initial objectively documented PMD based on the Lugano (2014) criteria or death due to any cause, whichever occurs first. Censoring will be applied using the DOR definition. CMR rate and DoCMR will be evaluated based on investigator assessments.

8.4 Analyses

Unless otherwise specified, safety data from Parts A-D will be summarized both (1) overall by dose level and across all dose levels and (2) by dose level and across all dose levels within each tumor type. Efficacy data will be summarized by dose level within each tumor type and patient population.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, height, and body mass index (BMI), and baseline laboratory results will be tabulated. Baseline disease characteristics will be summarized for expansion cohorts for different disease cohorts separately, as appropriate.

8.4.2 Efficacy Analysis

Individual ORR, CR rate, DOR, CMR, PMR, and PFS (based on IWG and Lugano criteria) will be determined. BOR outcomes will be summarized using frequency tables together with 2-sided 95% confidence intervals. Time to event distribution (eg, PFS, DOR, and DoCMR) will be estimated using Kaplan-Meier (K-M) method. When appropriate, the median along with 95% CI will be provided using Brookmeyer and Crowley methodology (using log-log transformation for constructing the confidence intervals). Rates at fixed time points (eg, PFSR 24 weeks) will be derived from the K-M estimate and corresponding confidence interval will be derived based on Greenwood formula. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method. OS data will be analyzed similarly to PFS data analysis.

8.4.3 Safety Analyses

All subjects who receive study drug therapy will be evaluated for safety endpoints. All recorded AEs will be coded according to the most current version of MedDRA and be graded using the NCI CTCAE version 4.0. AEs will be listed and subjects with AEs will be summarized based on the event with worst CTC grade by system organ class (SOC) and preferred term (PT), counting once at the PT term level and once at the SOC level, for each dose, dosing regimen, and overall. Vital signs and clinical laboratory test results will be listed and summarized by treatment. In addition, the worst grade of a laboratory measure observed on-study by the baseline grade (per CTCAE v 4) will also be generated for selected laboratory tests. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG results will be evaluated by the investigator and abnormalities, if present, will be listed.

8.4.4 Pharmacokinetic Analyses

PK parameters for relatlimab as monotherapy and in combination with nivolumab will be calculated using noncompartmental analyses. Summary statistics will be tabulated for the PK parameters of relatlimab by treatment and study day/week. To describe the dependency on dose of relatlimab, scatter plots of Cmax and AUC (TAU) versus dose may be provided for each day measured. Dose proportionality of relatlimab will also be assessed based on a power model.

Summary statistics of nivolumab exposure at trough and end of infusion will be tabulated separately.

8.4.5 Exploratory Biomarker Analyses

The pharmacodynamic effect on [redacted] in subjects who undergo biopsy will be summarized using summary statistics and plots. In addition, the correlation of [redacted] changes and tumor marker expression with measures of peripheral blood markers may be explored graphically, and using appropriate modeling approaches based on data availability. Associations of biomarker measures from peripheral blood or tumor biopsy with clinical outcomes may also be explored graphically and further assessed as needed by methods such as, but not limited to, logistic regression and characterized by appropriate statistics.

8.4.6 Outcomes Research Analyses

Not applicable.

8.4.7 Other Analyses

8.4.7.1 Immunogenicity Analyses

A listing will be provided for all available immunogenicity data. The number and percent of subjects who meet specified endpoint definitions in the statistical analysis plan (SAP) will be summarized for each drug. To examine the potential relationship between immunogenicity and safety, a table summarizing the frequency and type of AEs of special interest may be explored by immunogenicity status. In addition, potential relationships between immunogenicity and efficacy, pharmacodynamic markers, and/or PK may also be explored.

8.5 Interim Analyses

Data emerging from this open-label exploratory study may be needed for safety monitoring, and to make timely decisions about adjustments to study procedures, including potential early termination of the study. Analyses will only consist of listings, summaries, and graphs of the available data. No formal inferences requiring any adjustment to statistical significance level will be performed.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

BMS will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the

CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. For reporting purposes only, BMS also considers the occurrence of pregnancy, intentional overdose, and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
Ab	antibody
ADA	anti-drug antibody
AE	adverse event
AI	accumulation index
AI_AUC	AUC accumulation index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Ceoinf	Ceoinf accumulation index; ratio of Ceoinf at steady state to Ceoinf after the first dose
AI_Cmax	Cmax accumulation index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau accumulation index; ratio of Ctau at steady state to Ctau after the first dose
AIDS	acquired immunodeficiency virus
AIHA	autoimmune hemolytic anemia
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(TAU)	area under the concentration-time curve in one dosing interval
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BUN	blood urea nitrogen
CBC	complete blood count
Ceoinf	concentration observed at the end of infusion
CFR	Code of Federal Regulations
CHL	classical Hodgkin lymphoma
CHO	Chinese hamster ovary
CLcr	creatinine clearance
CLL	chronic lymphocytic leukemia
CLT	total body clearance
CLTp	systemic clearance

Term	Definition
Cmax	maximum observed concentration
CMV	cytomegalovirus
CMR	complete metabolic response
CNS	central nervous system
CR	complete response/complete remission
CRF	case report form, paper or electronic
CRO	contract research organization
Css,avg	average concentration over a dosing interval ([AUC(TAU)/tau]
CT	computed tomography
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte–associated antigen 4
Ctrough	trough observed serum oncentration
DF	degree of fluctuation or fluctuation index ([Cmax - Ctau]/Css,avg)
[redacted]	
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DoCMR	duration of complete metabolic response
DOR	duration of objective response
EBV	Epstein Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
FDG	fluorodeoxyglucose
[redacted]	
FSH	follicle-stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice

Term	Definition
G-CSF	granulocyte colony stimulating factor
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human equivalent dose
HepA	hepatitis A
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HNSTD	highest non-severely toxic dose
HRS	Hodgkin-Reed-Sternberg
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ICMAR	immune cell-modulating antibody regimen
IEC	Independent Ethics Committee
[redacted]	
IgG	immunoglobulin G
IGHV	immunoglobulin heavy variable
IHC	immunohistochemistry
IRB	Institutional Review Board
ITP	idiopathic thrombocytopenia purpura
IU	International Unit
IV	intravenous(ly)
IVRS	interactive voice response system
IWG	International Working Group
LAG-3	lymphocyte activation gene 3
LCMV	lymphocytic choriomeningitis virus
LDH	lactate dehydrogenase
LPHL	lymphocyte-predominant Hodgkin lymphoma

Term	Definition
mAb	monoclonal antibody
MAD	maximum administered dose
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MFI	mean fluorescent intensity
MHC	major histocompatibility complex
[redacted]	
MM	Multiple myeloma
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
N	number of subjects or observations
N/A	not applicable
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
[redacted]	
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PFSR	progression-free survival rate

Term	Definition
PID	patient identification number
PK	pharmacokinetic(s)
PMR	partial metabolic response
PPK	population pharmacokinetics
PR	partial response/partial remission
Q2W	every 2 weeks
QW	every week
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SLL	small lymphocytic leukemia
SmPC	summary of product characteristics
SOP	standard operating procedure
TGI	tumor growth inhibition
T-HALF	Terminal half-life
T-HALFeff_AUC	Effective elimination half-life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	Effective elimination half-life that explains the degree of Cmax accumulation observed)
T/HRBCL	T cell/histiocyte-rich B-cell lymphoma
TIA	transient ischemic attack
[redacted]	
Tmax	time of maximum observed concentration
TMDD	target-mediated binding and/or disposition
Treg	regulatory T cell
ULN	upper limit of normal
VGPR	Very good partial response
Vss	Volume of distribution at steady state
WHO	World Health Organization
WOCBP	women of childbearing potential

12 REFERENCES

[1] Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-723.

[2] Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus Ipilimumab in Advanced Melanoma. N Engl J Med 2013;369:122-33.

[3] American Cancer Society: Cancer Facts and Figures 2013. Atlanta, Ga: American Cancer Society, 2013. Available at: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/ documents/document/acspc-036845.pdf. [Accessed September 5, 2013].

[4] NCCN Clinical Practice Guidelines in Oncology. 2013. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. [Accessed September 2013].

[5] National Cancer Institute. Cancer Information Summaries. Available at: http://www.cancer.gov/cancertopics/pdq/adulttreatment. Bethesda, MD:2013 http://www.cancer.gov/cancertopics/pdq/treatment/CLL/healthprofessional/page1. [Accessed September 2013].

[6] Zelenetz AD, Wierda WG, Abramson JS, et al. Non-Hodgkin's Lymphomas, Version 3.2012. J Natl Compr Canc Netw 2012;10:1487-1498.

[7] Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677-704.

[8] Dong H, Zhu G, Tamada K, et al. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nat Med 1999;5:1365-1369.

[9] Terme M, Ullrich E, Aymeric L, et al. IL-18 induces PD-1-dependent immunosuppression in cancer. Cancer Res 2011;71:5393-5399.

[10] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-264.

[11] Nishimura H, Nose M, Hiai H, et al. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity 1999;11:141-151.

[12] Nishimura H., Okazaki T, Nakatani K, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science 2001;291:319-322.

[13] Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8:793-800.

[14] Nivolumab (BMS-936558, MDX1106, ONO-4538) Investigator Brochure. Bristol-Myers Squibb Pharmaceutical Research and Development., Document Control No. 930038243.

[15] Triebel F, Jitsukawa S, Baixeras E, et al. LAG-3, a novel lymphocyte activation gene closely related to CD4. J Exp Med 1990;171:1393-1405.

[16] Workman CJ, Wang Y, El Kasmi KC, et al. LAG-3 regulates plasmacytoid dendritic cell homeostasis. J Immunol 2009;182:1885-1891.

[17] Workman CJ, Vignali DA. Negative regulation of T-cell homeostasis by lymphocyte activation gene-3 (CD223). J Immunol 2005;174:688-695.

[18] Camisaschi C, Casati C, Rini F, et al. LAG-3 expression defines a subset of CD4(+)CD25(high)Foxp3(+) regulatory T cells that are expanded at tumor sites. J Immunol 2010;184:6545-6551.

[19] Huang CT, Workman CJ, Flies D, et al. Role of LAG-3 in regulatory T cells. Immunity 2004;21:503-513.

[20] Blackburn SD, Shin H, Haining WN, et al. Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection. Nat Immunol 2009;10:29-37.

[21] Grosso JF, Kelleher CC, Harris TJ, et al. LAG-3 regulates CD8+ T cell accumulation and effector function in murine self- and tumor-tolerance systems. J Clin Invest 2007;117:3383-3392.

[22] Lyford-Pike S, Peng S, Young GD, et al. Evidence for a Role of the PD-1:PD-L1 Pathway in Immune Resistance of HPV-Associated Head and Neck Squamous Cell Carcinoma. Cancer Res 2013 Mar 15;73:1733-1741.

[23] Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Res 2012;72:917-927.

[24] Okazaki T, Okazaki IM, Wang J, et al. PD-1 and LAG-3 inhibitory co-receptors act synergistically to prevent autoimmunity in mice. J Exp Med 2011;208:395-407.

[25] Bettini M, Szymczak-Workman AL, Forbes K, et al. Cutting edge: accelerated autoimmune diabetes in the absence of LAG-3. J Immunol 2011;187:3493-3498.

[26] Goding SR, Wilson KA, Xie Y, et al. Restoring Immune Function of Tumor-Specific CD4+ T Cells during Recurrence of Melanoma. J Immunol 2013;190:4899-4909.

[27] Matsuzaki J, Gnjatic S, Mhawech-Fauceglia P, et al. Tumor-infiltrating NY-ESO-1-specific CD8+ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer. Proc Natl Acad Sci U S A 2010;107:7875-7880.

[28] Gandhi MK, Lambley E, Duraiswamy J, et al. Expression of LAG-3 by tumor-infiltrating lymphocytes is coincident with the suppression of latent membrane antigen-specific CD8+ T-cell function in Hodgkin lymphoma patients. Blood 2006;108:2280-2289.

[29] Andorsky DJ, Yamada R, Steward K, et al. Expression of programmed death ligand 1 (PD-L1) by non-Hodgkin's lymphomas (NHL) and effect on tumor-associated T cells. J Clin Oncol 2009;27:15_suppl:8526. Available at: https://ascopubs.org/doi/abs/10.1200/jco.2009.27.15_suppl.8526 [Accessed on 23-Aug-2019].

[30] Muenst S, Hoeller S, Willi N, et al. Diagnostic and prognostic utility of PD-1 in B cell lymphomas. Dis Markers 2010;29:47-53.

[31] Steidl C, Gascoyne RD. The molecular pathogenesis of primary mediastinal large B-cell lymphoma. Blood 2011;118:2659-2669.

[32] Thibult ML, Mamessier E, Gertner-Dardenne J, et al. PD-1 is a novel regulator of human B-cells activation. Int Immunol 2013;25:129-137.

[33] Xerri L, Chetaille B, Serriari N, et al. Programmed death 1 is a marker of antioimmunoblastic T-cell lymphoma and B-cell small lymphocytic lymphoma/chronic lymphocytic leukemia. Human Pathol 2008;39:1050-1058.

[34] Grzywnowicz M, Zaleska J, Mertens D, et al. Programmed death-1 and its ligand are novel immunotolerant molecules expressed on leukemic B cells in chronic lymphocytic leukemia. PLoS One 2012;7:e35178.

[35] Yamamoto R, Nishikori M, Kitawaki T, et al. PD-1–PD-1 ligand interaction contributes to immunosuppressive microenvironment of Hodgkin lymphoma. Blood 2008;111:3220-3224.

[36] Green MR, Rodig S, Juszczynski P, et al. Constitutive AP-1 activity and EBV infection induce PD-L1 in Hodgkin lymphomas and posttransplant lymphoproliferative disorders: implications for targeted therapy. Clin Cancer Res 2012;18:1611-1618.

[37] Liu J, Hamrouni A, Wolowiec D, et al. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-{gamma} and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. Blood 2007;110:296-304.

[38] Hallett WH, Jing W, Drobyski WR, et al. Immunosuppressive effects of multiple myeloma are overcome by PD-L1 blockade. Biol Blood Marrow Transplant 2011;17:1133-1145.

[39] Chen BJ, Chapuy B, Ouyang J, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clin Cancer Res 2013;19:3462-3473.

[40] Bosshart H. Major histocompatibility complex class II antigen presentation in Hodgkin's disease. Leuk Lymphoma 1999;36:9-14.

[41] Muenst S, Hoeller S, Dirnhofer S, et al. Increased programmed death-1+ tumor-infiltrating lymphocytes in classical Hodgkin lymphoma substantiate reduced overall survival. Human Pathology 2009;40:1715-1722.

[42] Monti S, Savage KJ, Kutok JL, et al. Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. Blood 2005;105:1851-1861.

[43] Lukacher AE. IFN-gamma suspends the killing license of anti-tumor CTLs. J Clin Invest 2002;110:1407-1409.

[44] Castillo JJ, Beltran BE, Miranda RN, et al. Epstein-barr virus-positive diffuse large B-cell lymphoma of the elderly: what we know so far. Oncologist 2011;16:87-96.

[45] Zhang J, Xiang Y, Ding L, et al. Using gene co-expression network analysis to predict biomarkers for chronic lymphocytic leukemia. BMC Bioinformatics 2010;11 (Suppl 9);S5.

[46] Kotaskova J, Tichy B, Trbusek M, et al. High Expression of Lymphocyte-Activation Gene 3 (LAG3) in Chronic Lymphocytic Leukemia Cells is Associated with Unmutated Immunoglobulin Variable Heavy Chain Region (IGHV) Gene and Reduced Treatment-Free Survival. J Mol Diagn 2010;12:328-334.

[47] Dickinson JD, Gilmore J, Iqbal J, et al. 11q22.3 deletion in B-chronic lymphocytic leukemia is specifically associated with bulky lymphadenopathy and ZAP-70 expression but not reduced expression of adhesion/cell surface receptor molecules. Leuk Lymphoma 2006;47:231-244.

[48] Lee KM, Baris D, Zhang Y, et al. Common single nucleotide polymorphisms in immunoregulatory genes and multiple myeloma risk among women in Connecticut. Am J Hematol 2010;85:560-563.

[49] Tsimberidou AM, Keating MJ, Bueso-Ramos CE, et al. Epstein-Barr virus in patients with chronic lymphocytic leukemia: a pilot study. Leuk Lymphoma 2006;47:827-836.

[50] Ansell SM, Li CY, Lloyd RV, et al. Epstein-Barr Virus Infection in Richter's Transformation. Am J Hematol 1999;60:99-104.

[51] Dolcetti R, Carbone A. Epstein-Barr virus infection and chronic lymphocytic leukemia: a possible progression factor? Infect Agent Cancer 2010;5:22.

[52] Kanakry JA, Li H, Gellert L, et al. Plasma Epstein-Barr virus DNA predicts outcome in advanced Hodgkin lymphoma: correlative analysis from a large North American cooperative group trial. Blood 2013;121:3547-3553.

[53] Scientific Report of Study No. BDX-1408-263. Efficacy of Anti-LAG-3, Anti-PD-1, and Anti-CTLA-4 Antibodies Alone and in Combination in the Disseminated A20 B-Cell Lymphoma Model. Bristol-Myers Squibb Company; 2015. Document Control No. 930093171.

[54] Wang DD, Zhang S, Zhao H, et al. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49:1012-1024.

[55] Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51:119-135.

[56] Wong H, Choo EF, Alicke B, et al. Antitumor activity of targeted and cytotoxic agents in murine subcutaneous tumor models correlates with clinical response. Clin Cancer Res 2012;18:3846-3855.

[redacted]

58 Relatlimab (BMS-986016) Investigator Brochure. Bristol-Myers Squibb Research and Development. Document Control No. 930071620.

59 ICH Harmonised Tripartite Guideline, S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. International Conference on Harmonisation, 2011.

60 Non-Clinical Expedited Safety Report for Nivolumab (Ad Hoc CARES #54344.1). Bristol-Myers Squibb Research and Development; 2013. Document Control No. 930067627.

61 Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015;372: 311-319..

62 Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-586.

63 Durie BG, Harousseau JL, Miguel JS, et. al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-1473.

64 Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446-5456.

65 Rajkumar SV, Harousseau JL, Durie B, et al. Consensus Recommendations for the Uniform Reporting of Clinical Trials: Report of the International Myeloma Workshop Consensus Panel 1. Blood 2011; 117:4691-4695.

66 Bladé J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998;102:1115-1123.

APPENDIX 1 2007 INTERNATIONAL WORKING GROUP (IWG) RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA

2007 IWG Response Criteria for Malignant Lymphoma[1]				
Response	**Definition**	**Nodal masses**	**Spleen, Liver**	**Bone marrow**
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; residual mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses (index lesions); no increase in size of other nodes (non-index lesions) (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT	N/A	N/A
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node (index lesions), or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Key: CR = complete remission, CT = computed tomography; FDG = [18F] fluorodeoxyglucose; IWG = International Working Group; NA = Not applicable; PD = progressive disease; PET = positron-emission tomography; PR = partial remission; SD = stable disease; SPD = sum of the product of the diameters.

[1] *Cheson, BD, Pfistner, B, Juweid, ME, et al. Revised criteria for malignant lymphoma. J Clin Oncol. 2007; 25:579.*

CR (Complete Remission)

The designation of CR requires the following:

APPENDIX 1 Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms, if present before therapy.

APPENDIX 2 Typically [^{18}F] fluorodeoxyglucose (FDG)-avid lymphoma: in patients with no pretreatment positron emission tomography (PET) scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

APPENDIX 3 Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on computed tomography (CT) scan to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and > 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

APPENDIX 4 The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

APPENDIX 5 If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

PR (Partial Remission)

The designation of PR requires all of the following:

1. At least a 50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR, if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria but have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.
7. FDG:
   a. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least 1 previously involved site.
   b. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with 1 or at most 2 residual masses that have regressed by > 50% on CT; those with more than 2 residual lesions are unlikely to be PET negative and should be considered partial responders.

SD (Stable Disease)

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET scan.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

PD: Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is > 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered abnormal for relapse or progressive disease.

1. Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or PD after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered PD, a lymph node with a diameter of the short axis of < 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or > 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node > 1 cm in its short axis.
4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (e.g., a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

APPENDIX 2 2008 INTERNATIONAL WORKING GROUP (IWG) RESPONSE CRITERIA FOR CLL WITH MODIFICATIONS

2008 IWG Response Criteria for CLL with Modifications[1]

COMPLETE REMISSION (CR)

- Absence of lymphadenopathy by physical examination and appropriate radiographic techniques. Lymph nodes should not be larger than 1.5 cm in diameter.
- No hepatomegaly or splenomegaly by physical examination or appropriate radiographic techniques if in a clinical trial.
- Absence of constitutional symptoms.
- Normal CBC as exhibited by:
  - Polymorphonuclear leukocytes ≥ 1,500/μL
  - Blood lymphocytes < 4000/μL
  - Platelets > 100,000/μL
  - Hemoglobin > 11.0 g/dL (without transfusion or exogenous erythropoietin)
- Bone marrow aspirate and biopsy should be performed after clinical and laboratory results demonstrate that all of the requirements listed above have been met, to demonstrate a CR has been achieved. The bone marrow should be analyzed by flow cytometry and/or immunohistochemistry (IHC) to demonstrate that the marrow is free of clonal B-CLL cells. The marrow sample must be at least normocellular for age, with < 30% of nucleated cells being lymphocytes. Lymphoid nodules should assessed by IHC to define whether they are comprised primarily of T cells or lymphocytes other than CLL cells or of CLL cells. Cases with residual CLL cells by conventional flow cytometry or IHC are defined as partial remission (PR). If the bone marrow is hypocellular, a repeat determination should be made in 4 – 6 weeks. Samples should be re-reviewed in conjunction with the prior pathology.

Minimal residual disease (MRD): performed by MRD 4-color flow, allele-specific oligonucleotide PCR with sensitivity to 1 CLL cell per 10,000 leukocytes.

COMPLETE REMISSION with incomplete bone marrow recovery (CRi)

Otherwise CR, but who have persistent anemia, thrombocytopenia or neutropenia that appears to be related to persistent drug toxicity rather than to disease activity. The long-term outcome for these patients may be different from the noncytopenic CR.

PARTIAL REMISSION (PR)

At least 2 of the following:

- ≥ 50% decrease in peripheral blood lymphocyte count from the pretreatment baseline.
- ≥ 50% reduction in the noted pretreatment enlargement of the spleen or liver.
- 50% reduction in marrow infiltrate, or B-lymphoid nodules.
- ≥ 50% reduction in lymphadenopathy (preferably by CT) as defined by the following:
  - A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s), detected prior to therapy.
  - No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2 cm), an increase of less than 25% is not considered to be significant.
  - A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected

by CT scan (preferably).

At least one of the following:

- Polymorphonuclear leukocytes ≥ 1,500/μL or 50% improvement over baseline without need for exogenous growth factors.
- Platelets > 100,000/μL or 50% improvement over baseline.
- Hemoglobin > 11.0g.dL or 50% improvement over baseline without transfusions.

PROGRESSIVE DISEASE (PD)

At least one of the following:

- Appearance of any new lesion, such as enlarged lymph nodes (> 1.5 cm), de novo splenomegaly, de novo hepatomegaly or other organ infiltrates.
- An increase by ≥ 50% in greatest determined diameter of any previous site. A lymph node of 1 to 1.5 cm must increase by 50% or more to a size greater than 1.5 cm in the longest axis. A lymph node of more than 1.5 cm must increase to more than 2.0 cm in the longest axis.
- An increase of 50% or more in the sum of the product of diameters of multiple nodes.
- ≥ 50% increase in the size of the liver or spleen.
- ≥ 50% increase in the absolute number of circulating lymphocytes with ≥ 5,000 B lymphocytes per microliter.
- Transformation to a more aggressive histology (eg, Richter's syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.
- During therapy, cytopenias cannot be used to define disease progression. After treatment the progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by:
  - Decrease of Hb levels by > 20 g/L (2 g/dL) or to < 100 g/L (10 g/dL), or
  - Decrease of platelet counts by more than 50% or to less than 100 x 10^9/L (100,000/μL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

STABLE DISEASE (SD)

Subjects who have not achieved a CR or a PR, or who have not exhibited PD.

RELAPSE: defined as a patient who has previously achieved the above criteria ("Complete remission," "Partial remission") of a CR or PR, but after a period of 6 or more months, demonstrate evidence of disease progression (see preceding discussion of progressive disease).

[1] Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111(12):5446-56.

APPENDIX 3 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Anti-LAG-3 has not undergone the requisite preclinical testing for teratogenicity and therefore **requires two forms of contraception.** One method must be highly effective and the second method may also be highly effective or selected from the list of other contraceptive methods. Women and men who are not capable of reproduction or choose to be abstinent shall be exempt from following the pregnancy prevention requirements specified below.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oopherectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 135 days after the end of study treatment, plus 30 days, a total of 24 weeks.

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent **Failure rate of <1% per year when used consistently and correctly.**[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

• It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 3.3.1. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal(coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 33 weeks after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 33 weeks after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and for 33weeks after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 4 MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

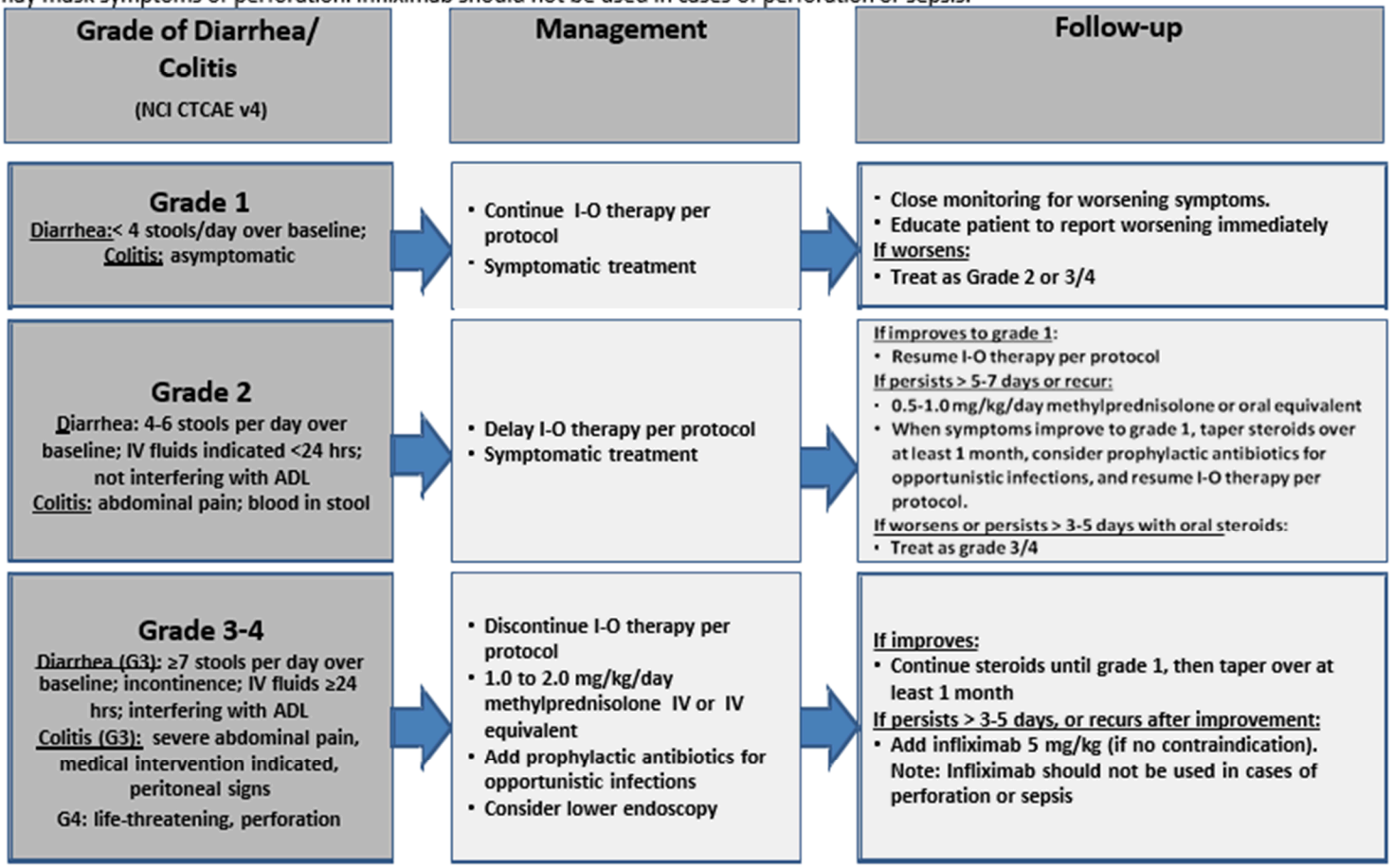
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

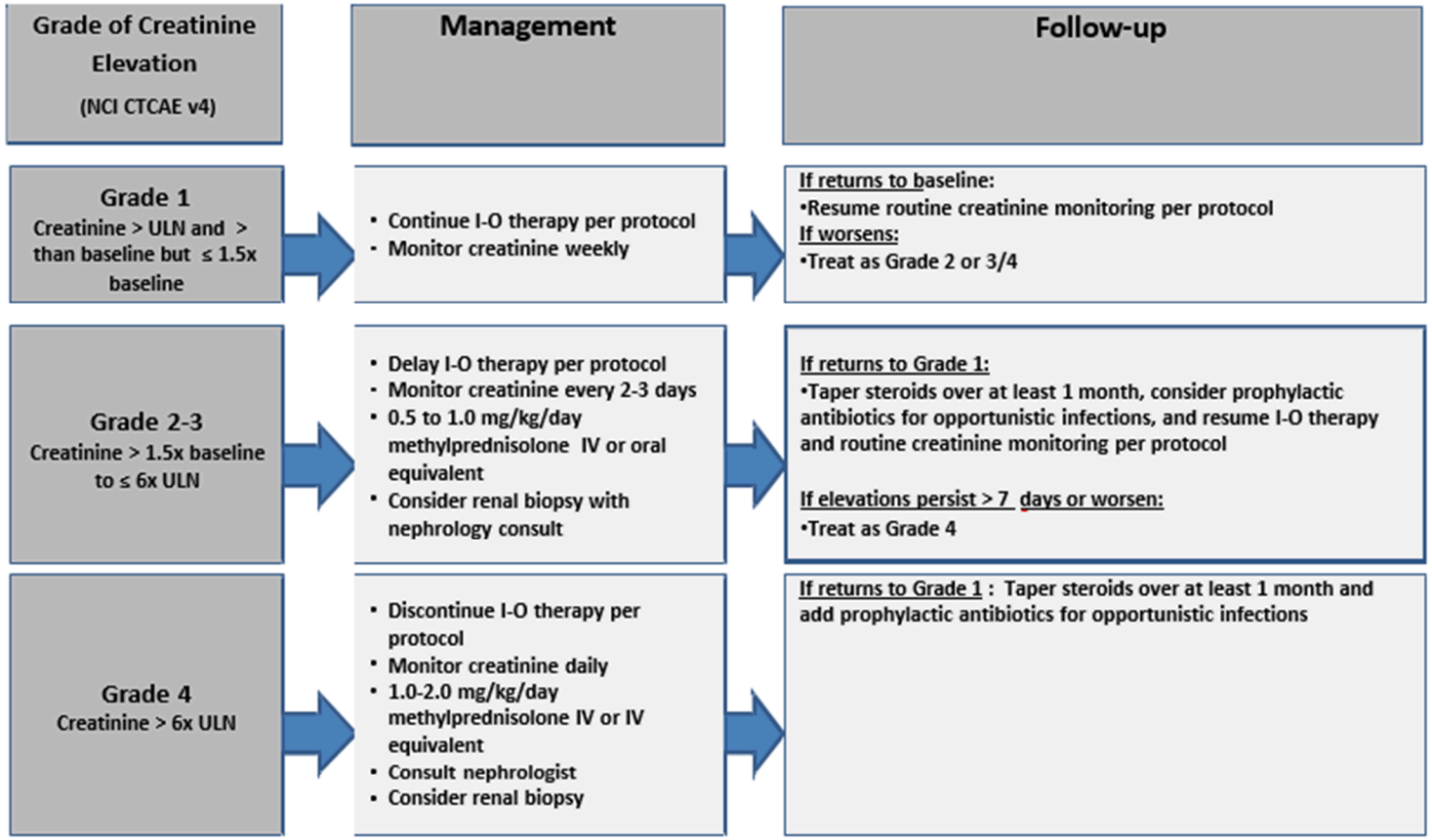


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

25-Jun-2019

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

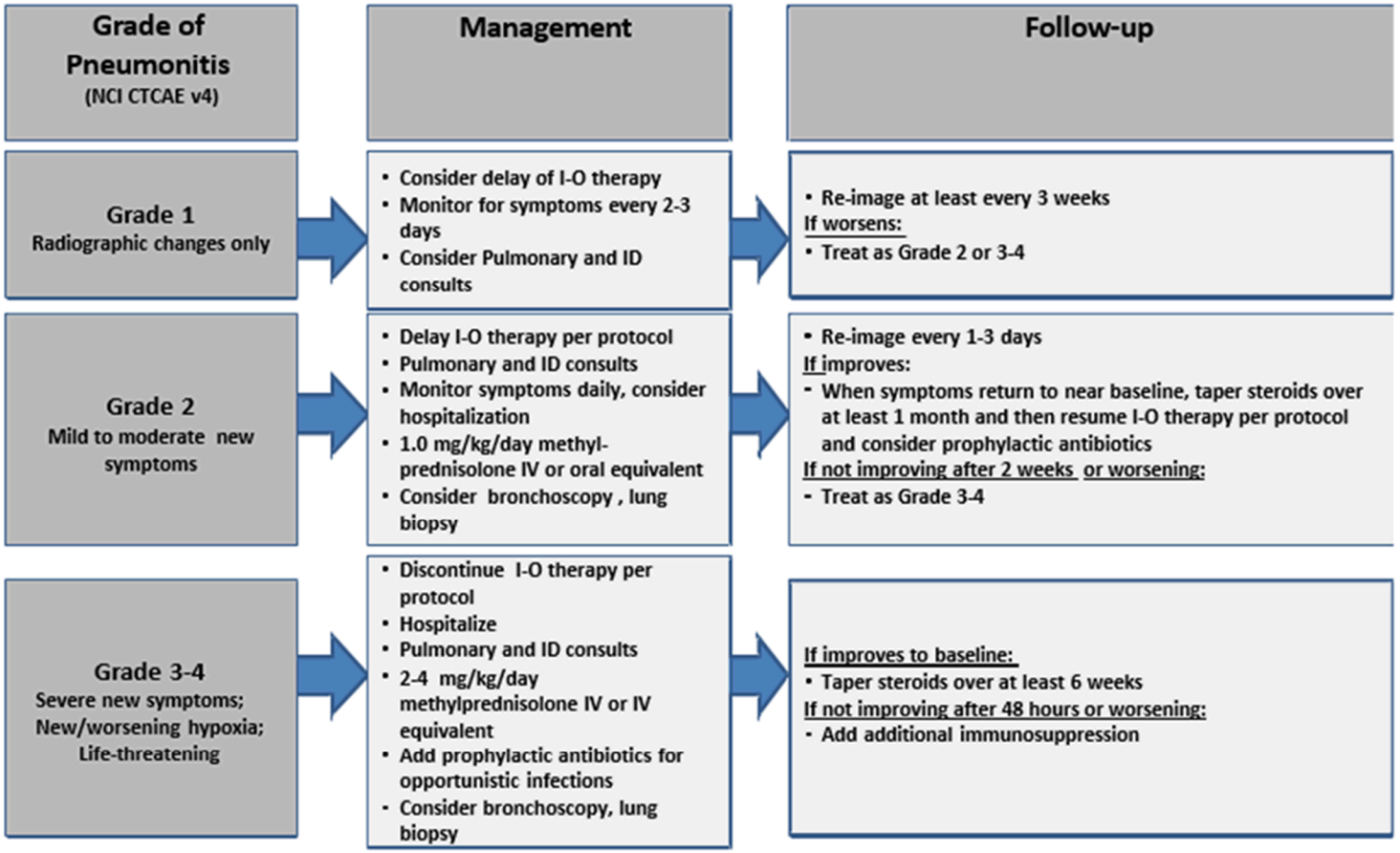


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

25-Jun-2019

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

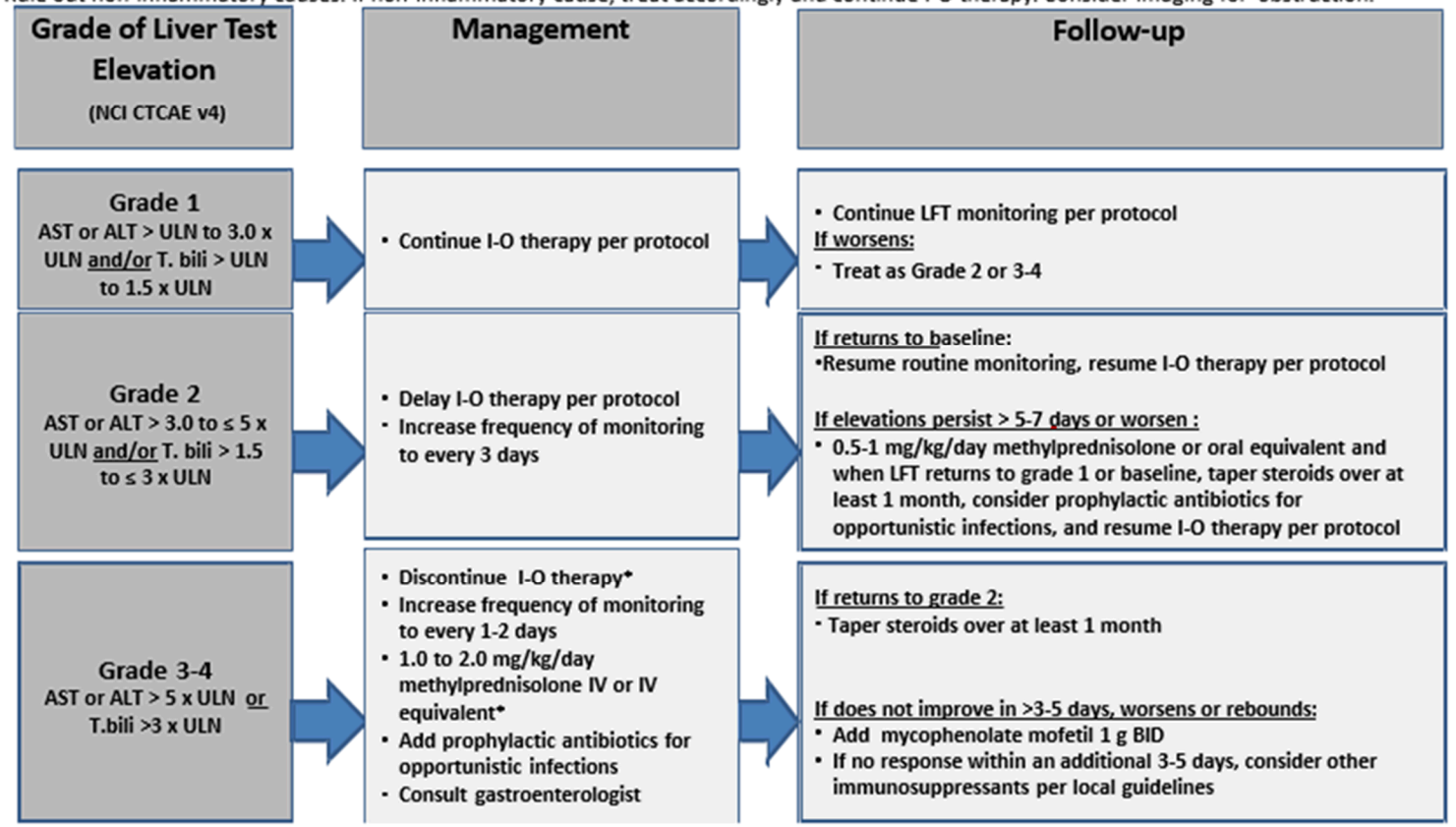


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

25-Jun-2019

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



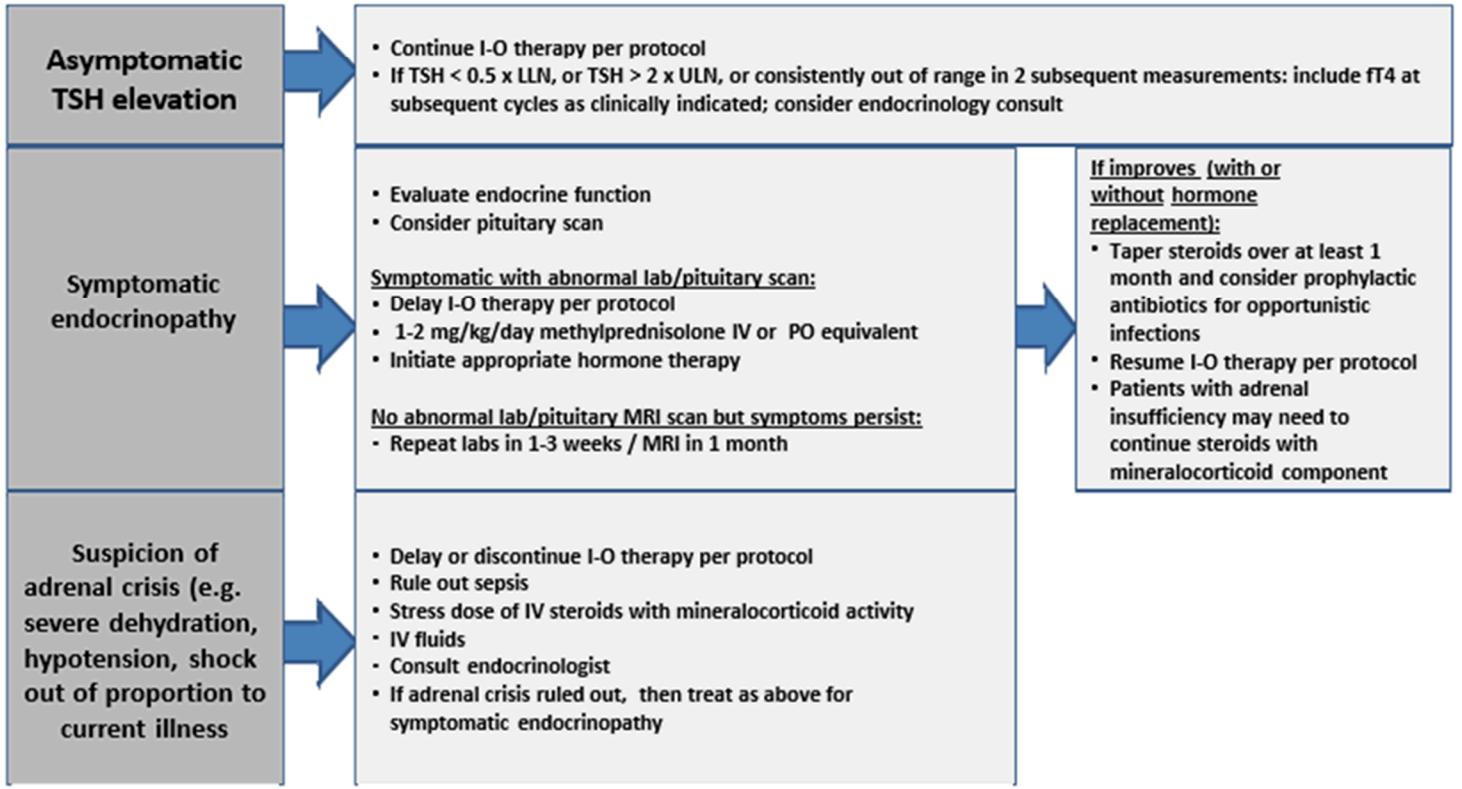
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

25-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

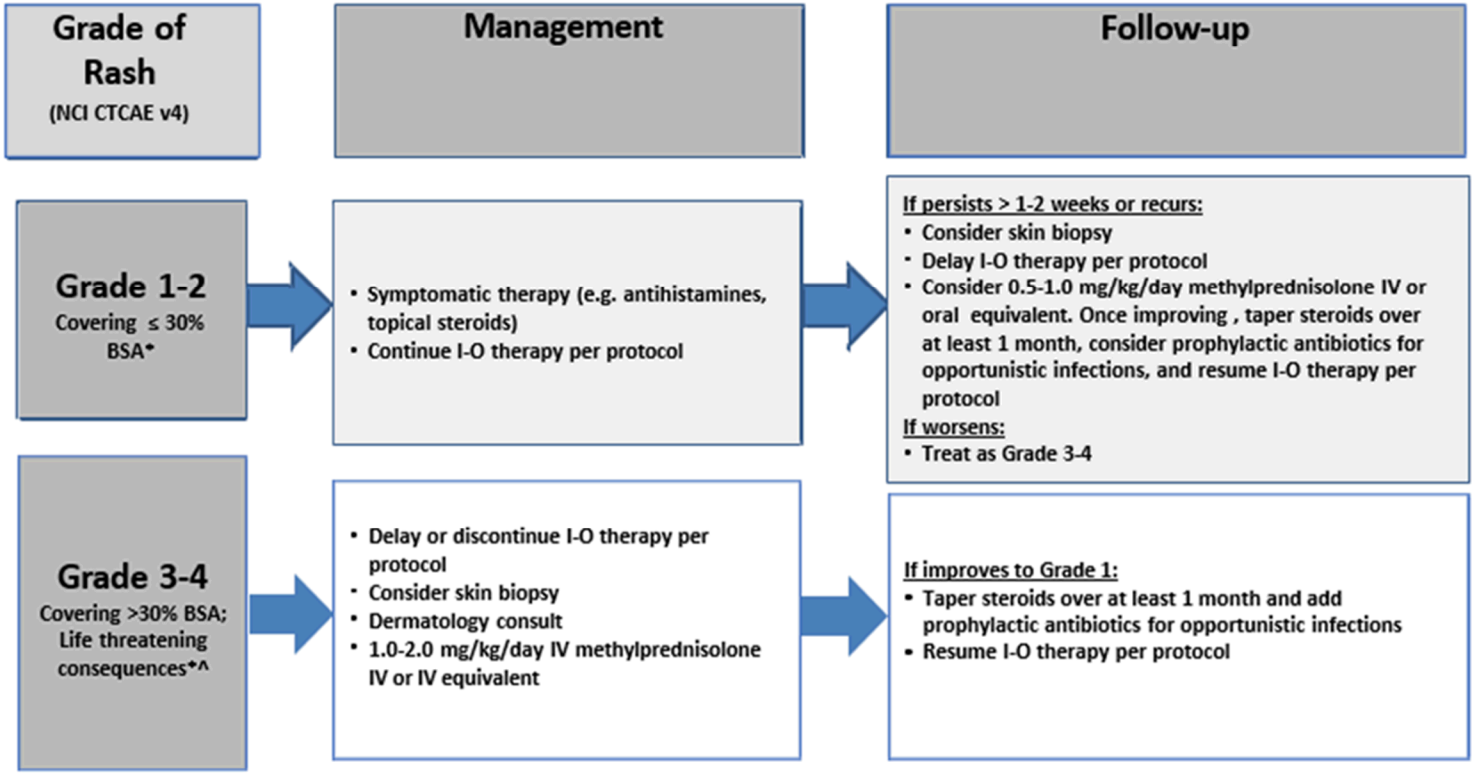


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

25-Jun-2019

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

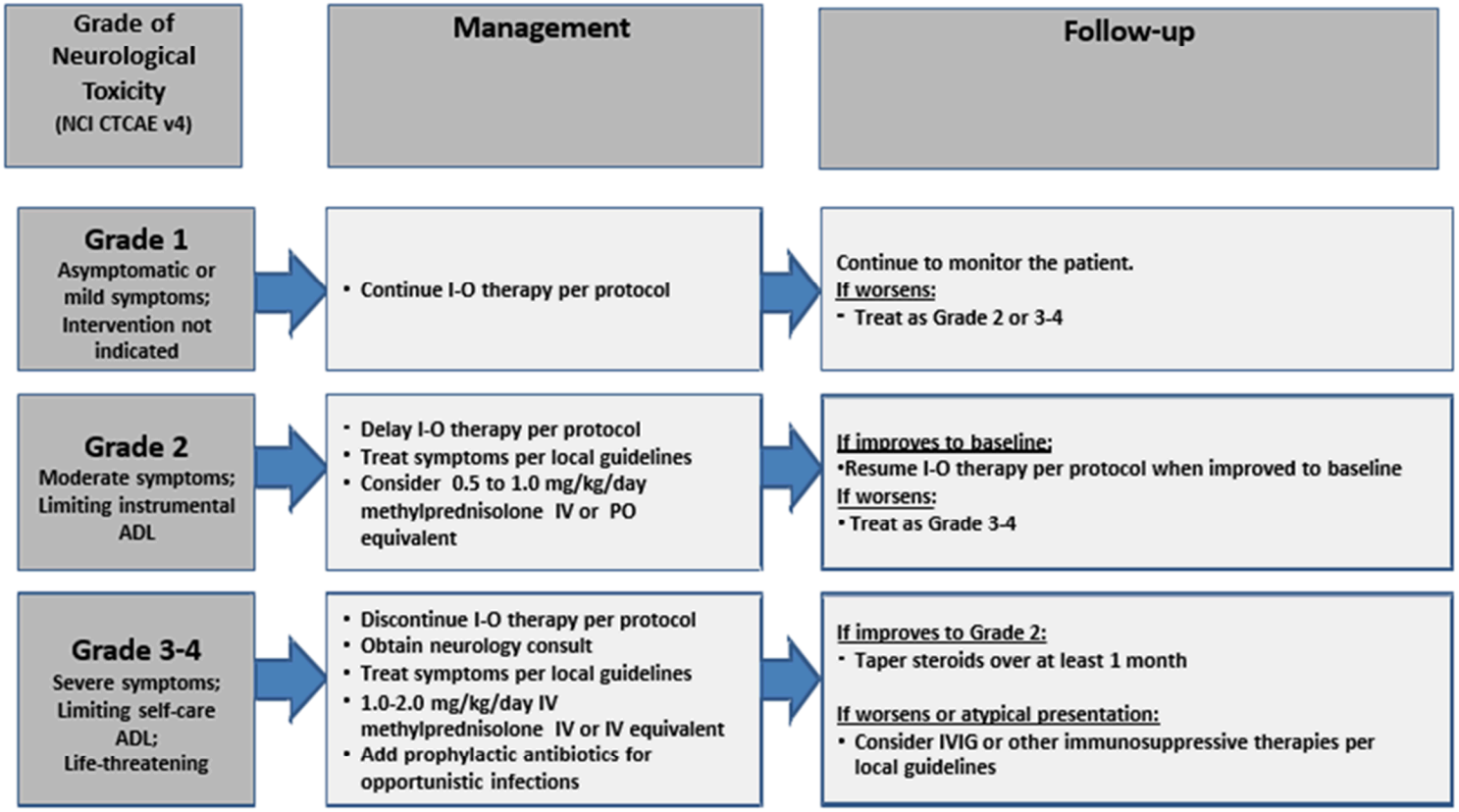
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

25-Jun-2019

Neurological Adverse Event Management Algorithm

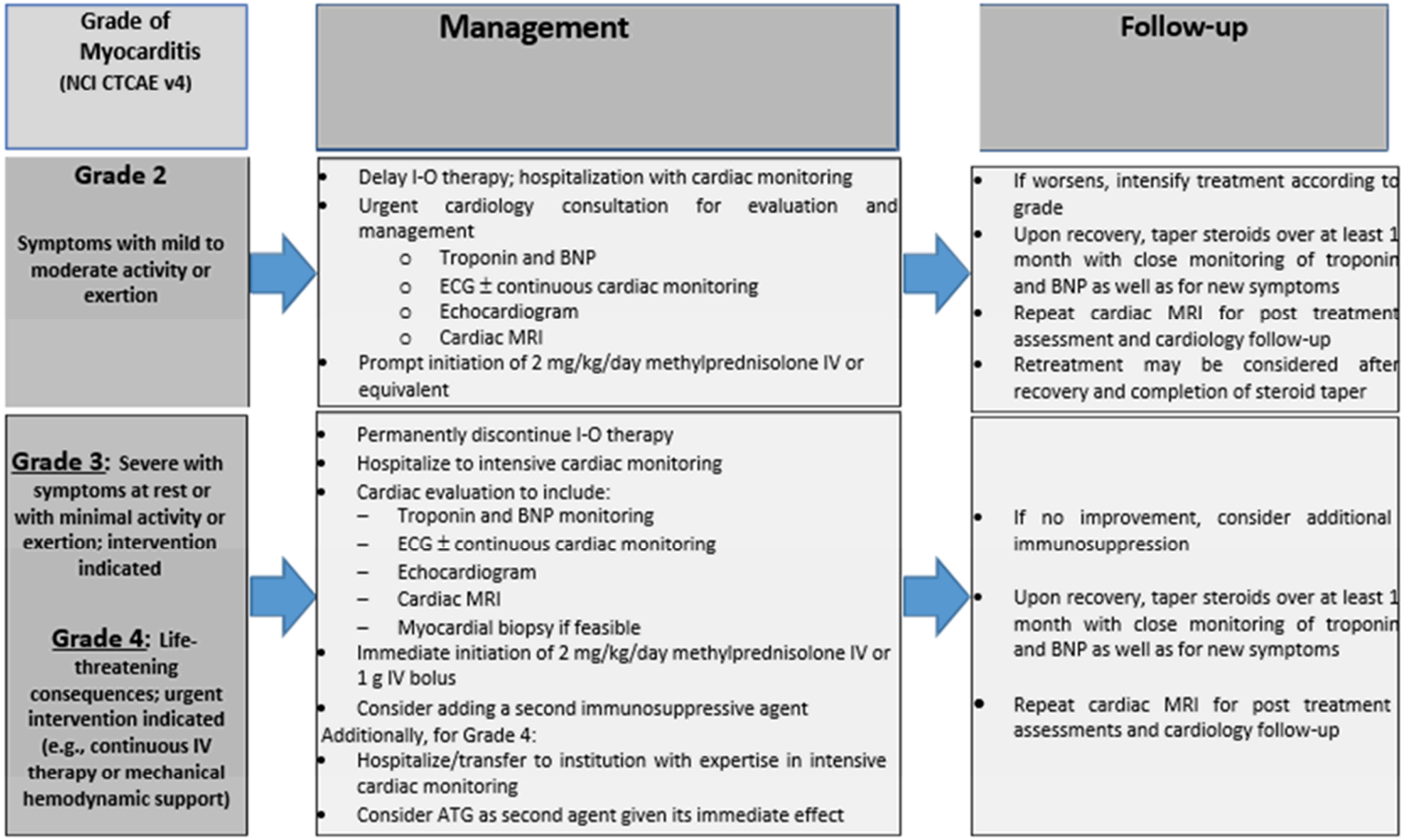
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

25-Jun-2019

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

25-Jun-2019

APPENDIX 5 ECOG, KARNOFSKY, AND LANSKY PERFORMANCE STATUS

PERFORMANCE STATUS CRITERIA: ECOG Score	
ECOG (Zubrod)	
Score	**Description**
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of alight or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair.

PERFORMANCE STATUS CRITERIA: Karnofsky and Lansky		
Score	**Karnofsky Description**	**Lansky Description**
100	Normal; no complaints; no evidence of disease	Fully active, normal
90	Able to carry on normal activity; minor signs or symptoms of disease.	Minor restrictions in physically strenuous activity
80	Normal activity with effort; some signs or symptoms of disease.	Active, but tires more quickly
70	Cares for self; unable to carry on normal activity or to do active work.	Substantial restriction of, and less time spent, in play activity
60	Requires occasional assistance, but is able to care for most of their personal needs.	Out of bed, but minimal active play; keeps busy with quiet activities
50	Requires considerable assistance and frequent medical care.	Gets dressed, but inactive much of day; no active play, able to participate in quiet play
40	Disabled; requires special care and assistance.	Mostly in bed; participates in some quiet activities
30	Severely disabled; hospital admission is indicated although death not imminent.	In bed; needs assistance even for quiet play
20	Very sick; hospital admission necessary; active supportive treatment necessary.	Often sleeping; play limited to passive activities
10	Moribund; fatal processes progressing rapidly.	No play; does not get out of bed
0	Dead	Unresponsive

APPENDIX 6 RESPONSE CRITERIA MODIFIED FROM IMWG FOR MULTIPLE MYELOMA

Response Subcategory	Response Criteria[1]
Stringent Complete Response (sCR)	CR, as defined below, plus the following: Normal FLC ratio and absence of clonal cells in bone marrow[2] by immunohistochemistry or immunofluorescence.[3]
Complete Response (CR)	• Negative immunofixation on the serum and urine. • ≤ 5% plasma cells in bone marrow.
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein level plus urine M-protein level < 100 mg per 24 hour.
Partial Response (PR)	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to < 200 mg per 24 hour.
Minor (Minimal) Response (MR)	Subjects who have reduction in M-protein but do not meet the criteria for PR are classified as MR if they meet all the following definition: • Between 25 - 49% reduction in serum M-protein. • Between 50 - 89% reduction in urinary light chain excretion which still exceeds 200 mg/24 hours. • If a skeletal survey is performed, no development of lytic lesions.
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, MR, or progression.
Progression Subcategory	**Progression Criteria**
Progressive disease'[4]	Requires an increase of ≥ 25% from lowest response level (nadir) in any one or more of the following: • Serum M-component (the absolute increase must be ≥ 0.5 g/dL).[5] • Urine M-component (the absolute increase must be ≥ 200 mg/24 hour). • Bone marrow plasma cell percentage: the absolute % must be ≥ 10%. • Definite development of new bone lesions or soft tissue plasmacytomas. • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.
Progression to Active Myeloma	Evidence of progression based on IMWG criteria for progressive disease in myeloma and any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder: • Development of new soft tissue plasmacytomas or bone lesions. • Hypercalcemia (> 11 mg/dL) • Decrease in hemoglobin of ≥ 2 g/dL • Rise in serum creatinine by 2 mg/dL or more

1 All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies

were performed. Radiographic studies are not required to satisfy these response requirements. The second of the 2 consecutive assessments should occur at the next planned tumor assessment.

2 Confirmation with repeat bone marrow biopsy not needed.

3 Presence or absence of clonal cells is based upon the κ/λ. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

4 To be used for calculation of time to progression and progression-free survival endpoints for all subjects, including those in CR (includes primary progressive disease and disease progression on or off therapy).

5 For progressive disease, serum M-component increase of ≥ 1 gm/dl is sufficient to define progression if starting M-component is ≥ 5 g/dL.

APPENDIX 7 LUGANO 2014 RESPONSE CRITERIA

For PET-based assessments, a clinical response of progressive metabolic disease (PMD), no metabolic response (NMR), partial metabolic response (PMR), or complete metabolic response (CMR) will be determined. PMD/PD includes radiological evidence of progression per Lugano Classification Revised Staging System for malignant lymphoma. The PET scan metabolic uptake will be graded using the Deauville 5-point scale, with a score of ≤ 3 considered to represent a CMR.

Deauville 5-point scale: 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.

Table 1: CMR / CR

Response/Site	FDG PET-CT-Based (Complete Metabolic Response)	CT-Based (CR)[a] All of the following:
Lymph nodes and extralymphatic sites	Score 1, 2 or 3 with or without a residual mass on 5-Point-Scale It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Non-measured 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

[a] CT-Based could also apply to MRI-Based

Note: Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059-68.

Table 2: PMR / PR

Response/Site	FDG PET-CT-Based (Partial Metabolic Response)	CT-Based (PR)[a] All of the following:
Lymph nodes and extralymphatic sites	Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings suggest residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value; when no longer visible, 0 X 0 mm; for a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesion	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

[a] CT-Based could also apply to MRI-Based

Note: Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059-68.

Table 3: NMR / SD

Response/Site	FDG PET-CT-Based (NMR)	CT-Based[a] (SD)
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 in SPD of up to 6 target measurable nodes and extranodal sites; no criteria for Progressive Disease met
Non-measured lesion	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

[a] CT-Based could also apply to MRI-Based

Note: Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059-68.

Table 4: PMD / PD

Response/Site	FDG PET-CT-Based (PMD)	CT-Based (PD)[a] At least one of the following:
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or 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 & Increase by ≥ 50% from PPD nadir & 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
Non-measured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., 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

[a] CT-Based could also apply to MRI-Based

Note: Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059-68.

APPENDIX 8 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for the Revised Protocol Revised Protocol 08, 11-Oct-2019

The revised protocol changes Study Director and Medical Monitor, adds the current packaging of relatlimab (BMS-986016) to the study formulary, and updates safety information based on the current relatlimab Investigator Brochure.

Additionally, the revised protocol adds exclusions and restrictions on participants receiving live / attenuated vaccines, requirements for reporting sexual activity in cases where study drug can be present in seminal fluid, and provides updates to Appendix 4.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Changed Study Director from: [redacted] Changed Medical Monitor from: [redacted]	Changed Study Director. Changed Medical Monitor as per Administrative Letter 07.
Title Page; Synopsis	Short Title added.	Short Title added for clarity and alignment with Short Title provided on ClinicalTrials.gov.
1.4.1.5: Clinical Safety-Monotherapy (Part A and Part B) and Combination Therapy (Part C and D) in CA224022; 1.4.1.6: Serious Adverse Events; 1.4.1.7: Infusion Reactions; 1.4.1.8: Adverse Events Leading to Discontinuation; 1.4.1.9: Deaths; 1.5: Clinical Safety - Monotherapy (Part A and A1) and Relatlimab in Combination with Nivolumab Therapy (Parts B, C, and D) in Solid Tumor Study CA224020; 1.5.1: Adverse Events; 1.5.2: Serious Adverse Events 1.5.3: Infusion Reactions; 1.5.4: Adverse Events Leading to Discontinuation; 1.5.5 Deaths;	Updated safety information based on current studies and current relatlimab Investigator Brochure.	To provide current clinical safety data.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
1.6: Clinical Efficacy - Studies CA224020 and CA224022; 1.8: Overall Risk/Benefit Assessment		
4.1: Study Treatments	Relatlimab Injection [redacted] mg/vial added to Table 4, Product Description and Dosage Form.	Study formulary updated to reflect current packaging of relatlimab.
5.1: Flow Chart/Time and Events Schedule	Removed the PK and immunogenicity assessments scheduled on follow-up visit 1 in Table 5.1-3, Follow-Up Procedural Outline (CA224022).	Table 5.1-3 updated as per Administrative Letter 06.
3.3.2: Exclusion Criteria, 4), a); 3.5: Discontinuation of Subjects from Treatment	Prisoners or subjects who are involuntarily incarcerated. (Note: under specific circumstances**, and only in countries where local regulations permit,** a person who has been imprisoned may be included as a participant. Strict conditions apply and BMS approval is required.)	The phrase in bold was added to align with BMS exclusion for prisoners.
3.3.2: Exclusion Criteria, 2), p), *ii*), (3); 3.4.1: Prohibited and/or Restricted Treatments	Participants who have received a live / **attenuated** vaccine **within 30 days of first treatment**. Any live / attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days post last dose.	The phrase in bold was added to align with Nivolumab Investigator Brochure. The text was added to align with Nivolumab Investigator Brochure.
4.3.2: Dose Delay Criteria	Myocarditis added to the list of toxicities for which management algorithms have been developed.	Added to reflect the current safety information for immuno-oncology agents.
6.4: Pregnancy	Added additional requirements for reporting sexual activity in cases where study drug can be present in seminal fluid.	To align with BMS policy on women of childbearing potential, exposure, and contraception.
6.5: Overdose	The following text was added, "Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify 'intentional overdose' as the verbatim term." Previous text was modified to now read: "All occurrences of **intentional** overdose	Text was added to clarify the need for the investigator to report the specific term of "intentional overdose" as an AE term. All other types of overdose should NOT be reported as an AE but should be recorded elsewhere on the CRF. There are no changes to the reporting of AEs associated with any type of overdose.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 08		
Section Number & Title	**Description of Change**	**Brief Rationale**
	must be reported as an SAE (see Section 6.1.1 for reporting details)."	Overdoses that meet the regulatory definition of SAE will be reported as an SAE.
10: Glossary of Terms	Serious Adverse Event: Section modified to read: "For reporting purposes only, BMS also considers the occurrence of pregnancy, **intentional** overdose, and cancer as important medical events."	Added the word "intentional" to align this section with clarifying updates made to overdose language.
Appendix 4: Management Algorithms	Hepatic Adverse Event Management Algorithm: Footnote stating I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN was removed. "Myocarditis Adverse Event Management Algorithm" table was added.	Language was modified to align protocol with current Nivolumab Investigator Brochure and nivolumab program safety parameters. Updating Management Algorithms to most recent version.
All	BMS-986016 has been replaced by its generic name, relatlimab, throughout the sections as appropriate. Minor formatting and typographical corrections.	Clarification. Minor, therefore have not been summarized.

Overall Rationale for the Revised Protocol Revised Protocol 07, 28-Mar-2018

The purpose of Revised Protocol 07 is to: 1) require pre-and on-treatment biopsies for all subjects in Part D 2) add Survival Follow-up and 3) clarify eligibility criteria; and 4) to update safety and clinical pharmacology information and criteria for dose delay and permanent discontinuation. See below for further details.

Biopsies required for [redacted] subjects in Part D [redacted], which will allow a more comprehensive investigation of markers associated to response and mechanisms of resistance. Survival Follow-up is defined and may continue for up to 5 years from the first dose in HL patients in Parts C and D. Subjects who were progressed on PD-1/PD-L1 inhibitors within 3 months of exposure are also allowed. Safety and clinical pharmacology information and criteria for dose delay and permanent discontinuation were updated based on the most recent IB [redacted] and emerging data.

Additionally, the revised protocol incorporates [redacted] change in Study Director and Medical Monitor, grammatical revisions and reference updates were also included.

Revisions apply to future participants enrolled in the study and where applicable to all participants currently enrolled.

Summary of key changes of Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Synopsis was updated	Synopsis was updated to reflect the changes made in the protocol
Section 1.3 Objectives, Synopsis	Aligned objectives with endpoints Removed two safety secondary objectives. Added an exploratory objective to assess the overall survival rates and PFS rates at various time points in selected patients in Part D	Alignment of objectives with endpoints. The two secondary objectives were repetitive with primary safety objective. The exploratory objective was added to assess the [redacted] in selected patient populations.
Section 1.4.1.4 Clinical Pharmacology	Clinical pharmacology information was updated based on current studies and updated Investigator Brochures (IB).	To provide current clinical pharmacology data.
Section 1.4.1.5 Clinical Safety Monotherapy (Part A and Part B) and Combination Therapy (Part C) in CA224022, Section 1.4.1.6 Serious Adverse Events, Section 1.4.1.7 Infusion Reactions, Section 1.4.1.8 Adverse Events Leading to Discontinuation, 1.5 Clinical Safety - Monotherapy (Part A) and BMS-986016 in combination with Nivolumab Therapy (Parts B and C) in Solid Tumor Study CA224020, 1.5.1 Adverse Events, 1.5.2 Serious Adverse Events, 1.5.3 Infusion Reactions, 1.5.4 Adverse Events Leading to Discontinuation, 1.5.5 Deaths, 1.6 Clinical Efficacy Monotherapy (Part A and Part B): CA224022 Study	Updated safety information based on current studies and updated IB.	To provide current clinical safety data.

Summary of key changes of Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
1.8 Overall Risk/Benefit Assessment	Updated safety information based on current studies.	To provide current risk/benefit assessment based on updated clinical safety data.
Section 3.1 Figure 3.1-1 Study Design Schematic, Figure 3.1-2 Study Schematic	Removed the dose combination of [redacted] nivolumab, and added the dose combination of [redacted] mg nivolumab in Part C Figure 3.1-1. Also clarified the figure notes. Added Survival Follow-up to Figure 3.1-2 schematic for Pats C and D of the study. Edited the text accordingly for Survival Follow Up.	The LAG-3 dose of [redacted] mg was removed and [redacted] mg was added due to the toxicity, safety and clinical pharmacology findings in Parts A and B. Survival Follow Up was added to allow selected participants to be followed for a longer time period to obtain additional data
	Treatment during the Re-challenge period was changed from 12 additional eight-week cycles to 6 additional eight-week cycles.	Decreasing re-challenge period ensures the study data can be concluded in a reasonable time period. Based on previous study experience, the re-challenge data is not expected to have significant impact on study conclusion.
Section 3.3.1 Part C Dose Escalation Combination Therapy, Section 3.3.1 Inclusion Criteria 2 e) ii	Allowed patients progressed within 3 months of previous anti-PD1 or anti-PD-L1 treatment.	Progression within 3 months of previous anti-PD1/PD-L1 is allowed according to the MOA.
Section 3.3.1: Inclusion Criteria 1 b) iv)	Changed the requirement for "the first 6 subjects" to "All subjects" in Part D must consent to allow on-treatment biopsy. Additionally if a fresh pre-treatment tumor biopsy was not medically feasible and enrollment was approved by the Medical Monitor with an archival tumor sample, the on-	The requirement for All subjects to consent for on-treatment biopsy was changed which will allow a more comprehensive investigation of markers associated to response and mechanisms of resistance. With the BMS Medical Monitor approval of

Summary of key changes of Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
	treatment tumor biopsy will not be required.	enrollment without a fresh pre-treatment biopsy, the on-treatment biopsy is also not required.
Section 3.3.2: Exclusion Criteria	Exclusion Criteria 2h) vii) details of Cardiac Troponin test results were clarified. 2J i), ii), iii) was revised to clarify hepatitis exclusion criteria.	The exclusion criterion text for Troponin and cardiac evaluation is revised to align with the most recent program requirements based on updated safety information. Exclusion criteria for hepatitis was updated to align with the standard program requirements
Section 3.4.2.2 Imaging Restrictions and Precautions	Added Imaging Restrictions and Precautions	Imaging restrictions and precautions were added to the study to provide guidance when using contrast.
Section 4.3.2 Dose Delay Criteria	Updated the dose delay criteria. Removed Grade 3 skin and added Grade 1 myocarditis and troponin elevations. Also added text defining delayed doses, maximum delays, and subsequent dosing.	To align with most recent program requirements based on updated safety information.
Section 4.3.3 Criteria to Resume Treatment after Dose Delay	Removed some of the exceptions to permanent discontinuation. See the revised document for the specific changes. Added troponin evaluations requiring cardiac evaluation and discussion with BMS Medical monitor.	To align with most recent program requirements based on updated safety information.
Section 4.3.5 Guidelines to Permanent Discontinuation	Added and removed criteria for permanent discontinuation of all study drugs. See revised document for details.	To align with most recent program requirements based on updated safety information.
Table 5.1-1 Screening Procedural Outline, Tumor	Updated to clarify tumor biopsy sample requirement for Part D and add footnote that re-	All subjects in Part D must consent to allow pre-treatment tumor biopsy or if

Summary of key changes of Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
tissue sample (eg, primary tumor, lymph node)	challenge subjects must be re-screened.	not clinically feasible, and approved by the Medical Monitor, must consent to allow the acquisition of an archived tumor sample.
Table 5.1-2 On-Treatment Procedural Outline, On-treatment tumor or lymph node biopsy	Updated Part D requirement for on-treatment tumor biopsy.	To allow a more comprehensive investigation of markers associated to response and mechanisms of resistance.
Table 5.1-3 Follow-Up Procedural Outline	Follow-Up Procedural Outline was updated to include Survival Follow-Up for HL participants in Parts C and D.	To align with study design.
Section 5.3.3: Laboratory Test Assessments	Removed requirement for Hepatitis A test.	Hepatitis A test was removed because to align with the standard nivolumab requirements.
Table 5.7-1 Biomarker Sampling Schedule & 5.7.7 Tumor-Based Biomarker Measures	Table titles were revised for re-challenge; updated table notes regarding biopsy and archival tissue requirements.	To align with study design and biomarker sampling requirements.
New Section 5.7.8 Additional Research Collection	Added the section which describes the retention of residual samples	To allow residual samples to be retained for possible future testing.
Section 8 Statistical Consideration	All applicable sections updated to include all revised parts of the study.	To align statistical language with study objectives.
Section 8.3.2.3 Receptor Occupancy	Receptor Occupancy was added.	Receptor Occupancy was added to provide additional data.
Section 8.3.2.3 ORR, DOR, CRR, PFS, and OS	Added definitions for each of the endpoints.	To provide robust definitions of the endpoints
Section 8.4.2 Efficacy Analysis	Individual ORR, CRR, DOR, and PFS will be determined.	To describe analyses and methodologies used.
Section 8.4.3 Safety Analyses	Description of how AEs will be listed and summarized was updated.	To provide more description of the analyses.

Summary of key changes of Revised Protocol 07		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix 3 Guidance on Contraception Women of Childbearing Potential and Methods of Contraception	Adds definition of Women of Childbearing Potential and revised methods of contraception.	To align with current BMS SOP.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.