Janssen Research & Development*

Clinical Protocol

A Phase 1/2a Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of the Combination of Ibrutinib with Nivolumab in Subjects with Hematologic Malignancies

Protocol PCI-32765LYM1002; Phase 1/2a
AMENDMENT 7

JNJ-54179060 (ibrutinib)

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This compound is being investigated in Phase 1, 2, and 3 clinical studies.
This compound is approved for marketing in 3 indications.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	15 Dec 2014
Amendment 1	29 Jan 2015
Amendment 2	19 Jun 2015
Amendment 3	23 Nov 2015
Amendment 4	02 Mar 2016
Amendment 5	18 Apr 2017
Amendment 6	12 Dec 2018
Amendment 7	12 Oct 2020

Amendments are listed beginning with the most recent amendment.

Amendment 7 (12 Oct 2020)

The overall reasons for the amendment: To further reduce all assessments after the clinical cutoff date and provide treatment for subjects until the end of study endpoint is reached. Since primary and secondary objectives have been analyzed and published, reduction of assessments for subjects who are currently on treatment or in (survival) follow up until the End of Study assessment are performed.

Applicable Section(s)	
Rationale: To further reduce data collection for ongoing subjects	
Table 1: Time and event schedule	Based on the established safety profile of the study drugs, safety data collection limited to: SAEs and Grade ≥3 AEs that are at least possibly related to treatment, AEs leading to discontinuation or modification, efficacy assessments, and study treatment administration. Footnote 'a' added to allow subjects who discontinued treatment during follow up to terminate survival follow up and complete end of study assessments.
Rationale: To terminate PK and pharmacodynamic assessments	
Table 2: Time and Events Schedule for Pharmacokinetic and Pharmacodynamic Assessments	Footnote 'p' added to confirm no PK, pharmacodynamic assessments, or biomarker samples will be obtained
Rationale: To permit ibrutinib single agent treatment if subjects meet CAN3001 rollover criteria	
6.4 Dose modifications	Added text to cease single agent ibrutinib therapy unless subjects are rolling over to the long-term extension study CAN3001.
Rationale: To terminate study treatment following disease progression	
10.2 Treatment after initial evidence of disease progression	Added text to prohibit continuation on study treatment following disease progression.
Rationale: To terminate collection of PD and PK samples	
10.3.1	Added text to terminate collection of PD and PK samples.

Rationale: To terminate collection of biomarker samples	
10.5 Biomarkers	Added text to terminate collection of biomarker samples.
Rationale: To reference updates to Table 1 regarding collection of adverse event data	
13.3.1 All Adverse events	Added reference to Table 1

Amendment 6 (12 Dec 2018)

The overall reason for the amendment: To reduce the pharmacokinetic (PK) and biomarker assessments after the clinical cutoff date; this will not have any impact on safety of primary endpoint of the trial.

Applicable Section(s)	Description of Change(s)
Rationale: To render consistency within the hypothesis statement in the synopsis and report body.	
Synopsis – Objectives and Hypothesis	Cohort B4 was added during Protocol Amendment 4 prepared in March 2016. Although this new cohort was reflected in Section 2.2. Hypothesis, it was not reflected within the hypothesis statement included in the Synopsis of Protocol Amendment 4. This also was not reflected in Protocol Amendment 5. This oversight is now being corrected in Protocol Amendment 6.
Rationale: To reduce the intensity of data collection as the primary endpoint for this study has already been met.	
Table 2: Time and Events Schedule for Pharmacokinetic and Pharmacodynamic Assessments	Added footnote 'o' indicating that assessments at Q8 cycles, at Q16 cycles, and at complete response are no longer required post clinical cutoff. Additionally, tumor biopsy and bone marrow (BM) aspirate/biopsy at progression; ibrutinib PK, nivolumab PK, and nivolumab anti-drug antibody (ADA) at end of treatment (EOT); and nivolumab PK, and nivolumab ADA at follow-up 1 (FU1, 100 days after last dose of nivolumab) will no longer be required post clinical cutoff. Also, ibrutinib pharmacodynamic (PD) and biomarker assessment at FU will no longer be required post clinical cutoff.
Rationale: To reduce the intensity of data collected after the clinical cutoff date as the primary endpoint for this study has already been met.	
Synopsis – Overview of Study Design; Table 1: Time and Events Schedule; 3.1. Overview of Study Design;	Added a statement that after the clinical cutoff only the following data will be collected on eCRF: serious adverse events (SAEs) and adverse events (AEs) Grade ≥3, laboratory assessments (Grade ≥3 or clinically significant), efficacy, survival status, and treatment administration.
13.3.1 All adverse events	Added the following statement: After the clinical cutoff, only SAEs and Grade ≥3 AEs will be collected.

Applicable Section(s)	Description of Change(s)
Table 1: Time and Events Schedule	In addition to the note above, the following changes were made to the Time and Events Schedule: 1. Deleted a note within the Time and Events Schedule emphasizing that after EOT (within 30 days after the last dose of ibrutinib or nivolumab, whichever treatment occurred last) only SAEs and Grade 3 or higher AEs that are at least possibly related to the study treatment will be reported. 2. Added a note within the Time and Events Schedule emphasizing that post clinical cutoff, disease assessments, using CT imaging with oral and IV contrast, will be performed Q12 cycles or per local standards (but at a minimum of Q26 weeks).
Rationale: To only conduct limited biomarker assessments post the clinical cutoff date as the primary endpoint for this study has already been met.	
Synopsis – Biomarker Evaluations; Table 1: Time and Events Schedule; Table 2: Time and Events Schedule for Pharmacokinetic and Pharmacodynamic Assessments; 10.5 Biomarkers	Removed the requirement of biomarker assessments (bone marrow aspirate/biopsy) post clinical cutoff.
Rationale: To remove the requirement of conducting PK assessments post the clinical cutoff date as the primary endpoint for this study has already been met.	
Synopsis – Pharmacokinetic Evaluations; Table 2: Time and Events Schedule for Pharmacokinetic and Pharmacodynamic Assessments; 10.3.1 Sample Collection	Removed the requirement of PK assessments post clinical cutoff.
Rationale: To incorporate appropriate changes specified within the Janssen protocol templates released after Protocol Amendment 5 was issued.	
Title Page;	Added "Janssen Pharmaceutica NV" to the Sponsorship Statement.

Applicable Section(s)	Description of Change(s)
11.3 Withdrawal from the Study;	Added the following text: If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented. When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. If a subject discontinues study treatment and withdraws from the study before the onset of disease progression, end-of-treatment and post- treatment assessments should be obtained. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.
18.11 Use of Information and Publication	Changed the time for submitting combined study results for publication from within 12 months to 18 months.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 5 (18 April 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is for clarification of protocol wording related to the primary analysis, to ensure wording is consistent and clear throughout the protocol

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of scheduled adverse event, concomitant medication, and efficacy assessments after the end of treatment.	
Synopsis Overview of Study Design, Table 1 Time and Events Schedule; 3.1. Overview of Study Design; Objectives; 10.1. Efficacy (Assessment of Disease Response and Progressive Disease); 12.7 Study Evaluation Team	Reworded Study Evaluation Team (SET) review to state that subjects may be evaluated by SET for Part B. Defined end of study as the last subject who completed the End of Treatment (EOT) assessment. Clarified minimum data collection during the period between primary analysis and the end of study to include: SAEs, AE Grade ≥3, laboratory assessments, efficacy, survival status, and treatment administration. Also clarified that concomitant medication collected after EOT assessment will include only subsequent anti-lymphoma treatment. Clarified that during the Follow-up period efficacy assessments will be conducted at least every 6 months up to disease progression or start of subsequent therapy.
Rationale: Update reference to CYP3A inhibits and inducers	
9.4. Concomitant Medications to be Avoided, or to be Used with Caution (Table 20); Attachment 7; Attachment 8	Replaced 'http://www.pharmacologyweekly.com/content/pages/online-drug-therapy-tables (Pharmacology Weekly)' with 'http://medicine.iupui.edu/clinpharm/ddis/main-table/'
Rationale: Update with standard of care consideration for prophylactic treatment of opportunistic infection.	
1.2.2 Clinical Safety of Ibrutinib; 8.10 Infection; References	New text and reference added for consideration of antimicrobial prophylaxis in accordance with standard practice in subjects who are at increased risk for opportunistic infections.
Rationale: Update with Adverse Events of Special Interest / Major Hemorrhage sections to align with other ongoing ibrutinib protocols.	
13.3.3 Adverse Events of Special Interest (AESI)	Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities by the Sponsor. These events will be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious adverse events) following the procedure described above for serious adverse events and will require enhanced data collection.

13.3.3.1 Major Hemorrhage	Major hemorrhage is defined as: Treatment-emergent hemorrhagic adverse events of Grade 3 or higher. • Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher. All hemorrhagic events requiring a transfusion of red blood cells should be reported as Grade 3 or higher AE per CTCAE. • Any treatment-emergent serious adverse event of bleeding of any grade. • Any treatment-emergent central nervous system hemorrhage/hematoma of any grade.
Rationale: Update to storage recommendations for ibrutinib	
15.4 Preparation, Handling, and Storage	The recommended storage condition for ibrutinib capsules is controlled room temperature (15ºC to 25ºC) **with excursions permitted to 30°C (86°F)**.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 4 (02 Mar 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to add a Richter syndrome cohort (B4). There is some evidence that ibrutinib has potential as a novel therapeutic approach for patients with Richter syndrome. In an investigator-initiated study (Tsang 2015)[56] one subject achieved a CR while 2 subjects experienced PR. All 3 subjects reported an improvement of constitutional symptoms. In addition, in a Phase 1b/2 study 3 subjects with Richter syndrome received a combination regimen of ibrutinib and the anti-CD20 antibody ofatumumab (Jaglowski 2015)[28] Of these, 2 subjects experienced disease stabilization for 471 and 137 days respectively, while 1 subject achieved a PR which lasted for 4.6 months (Jaglowski 2015)[28].

Applicable Section(s)	Description of Change(s)
Rationale: A Richter syndrome cohort (B4) is added and the overall number of subjects has been revised.	
Synopsis, Time & Events Schedule Table 2 (footnotes d and l), 1.1 Background, 1.2.4 Richter syndrome (new paragraph), 2.1 Objectives, Primary (Part B), 2.2 Hypothesis, 3.1 Overview of Study Design, 3.2 Study Design Rationale, 4.1.2 Additional Inclusion Criteria for Part B: Expansion Cohorts, 4.2 Exclusion Criteria, 6.1.2 Dosing Schedule, Table 5; 10.1 Efficacy (Assessment of Disease Response and Progressive Disease), Table 21; 12.3 Sample Size Determination, 12.4 Efficacy Analyses, References	The new Richter syndrome cohort (B4) is described throughout the protocol and new inclusion criteria specific for Richter syndrome are added. The exclusion of Richter syndrome is removed. The overall number of subjects is increased to 158 and to 140 in Part B.
Rationale: The response criteria used for SLL and Richter syndrome is clarified.	
Synopsis, Efficacy Evaluations/Endpoints; 10.1 Efficacy (Assessment of Disease Response and Progressive Disease), Table 21	It is clarified that the Response Assessment of Non-Hodgkin Lymphoma is to be used for SLL and Richter syndrome subjects.
Rationale: The collection of concomitant medications is clarified.	
Time & Events Schedule (Table 1), 9 Concomitant Therapy	Concomitant medications will be collected for 30 days after the last dose of ibrutinib, 100 days after the last dose of nivolumab, or, afterwards, during the follow-up of a related SAE (if applicable).
Rationale: The end of study definition is clarified to allow for subjects who are still on study after the End of Treatment visit and 100 days of follow-up after the nivolumab infusion.	
3.1 Overview of Study Design	End of study is defined as the last assessment for the last subject in the study (eg, the last follow-up visit or death).
Rationale: Updates have been made based on Janssen protocol template changes. These are of an instructional nature and do not affect study design.	

Title page,	Template changes include:
13 Adverse Event Reporting,	New text on the method of detecting adverse events and serious adverse events is added.
13.2.2 Other,	~~Inadvertent or~~ Accidental **or occupational** exposure to a sponsor study drug
13.3.1 All Adverse Events,	The sponsor will also report to the investigator (and the head of the investigational institute where required) all **suspected unexpected** serious adverse events that are unlisted (unexpected) and associated with the use of the study drug.
13.3.3 Pregnancy,	All initial reports of pregnancy **in female subjects or partners of male subjects** must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, **fetal death**, stillbirth, and congenital anomalies, **ectopic pregnancy**) are considered serious adverse events and must be reported using the Serious Adverse Event Form.
15.5 Drug Accountability,	Unused study drug, **and study drug returned by the subject**, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. **Returned study drug must not be dispensed again, even to the same subject.** Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor. **The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug.**
17.2.5 Country Selection,	This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, **if the need for the product persists,** unless explicitly addressed as a specific ethical consideration in Section 17.1, Study-Specific Design Considerations.

18.4 Source Documentation,	At a minimum, source ~~documentation~~ **documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care** must be available for the following ~~to confirm data collected in the eCRF~~: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; **drug receipt/dispensing/return records**; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. ~~In addition,~~ The author of an entry in the source documents should be identifiable. ~~At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care.~~ Specific details required as source data for the study **and source data collection methods** will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document). **An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If and electronic source is utilized, references made to the CRF in the protocol include the electronic source system but information collected through electronic source may not be limited to that found in the CRF.**
18.5 Case Report Form Completion,	Case report forms are **prepared and** provided **by the sponsor** for each subject in electronic format. Electronic data capture (eDC) will be used for this study. **All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.** The study data will be transcribed by study-site personnel from the source documents onto an eCRF, **if applicable. Study-specific data will be** ~~and~~ transmitted in a secure manner to the sponsor. ~~within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.~~ Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source **documents** ~~documentation~~. ~~All data relating to the study must be recorded in the eCRFs prepared by the sponsor.~~ Data must be entered into eCRFs in English. ~~Study site personnel must complete the eCRF~~ **The CRF must be completed** as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit. All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. ~~The investigator~~

	~~must verify that all data entries in the eCRFs are accurate and correct.~~
	~~All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study site personnel must adjust the eCRF (if applicable) and complete the query.~~ If **necessary, queries will be generated in the eDC tool**. If **corrections** to a CRF are needed after the initial entry into the CRF, this can be done in ~~3 different~~ **either of the following** ways: • **Investigator and study** site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool). • **Sponsor or sponsor delegate** ~~Study site manager~~ can generate a query for resolution by the study-site personnel. • ~~Clinical data manager can generate a query for resolution by the study site personnel.~~
18.8 Monitoring	The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the ~~eCRFs with the hospital or clinic records (source documents).~~ **CRF with the source documents (eg, hospital/clinic/physician's office medical records).** Direct access to source **documents** ~~documentation~~ (medical records) must be allowed for the purpose of verifying that the ~~data~~ recorded data ~~in the eCRF~~ are consistent with the original source data. Findings from this review ~~of eCRFs and source documents~~ will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source ~~documentation~~ **documents** will be accessible, and a suitable environment will be provided for review of study-related documents.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 3 (23 November 2015)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to clarify that baseline assessments should occur prior to study treatment initiation regardless of whether a subject is enrolled in run-in phase or not.

Applicable Section(s)	Description of Change(s)
Rationale: Baseline assessments should occur prior to study treatment initiation regardless of whether a subject is enrolled in run-in phase or not.	
Table 1: Time and Events Schedule	The column header for Cycle 1 Day 1 treatment period was renamed "Baseline Assessment" and additional revisions were made to clarify that assessments are to be collected prior to study drug administration regardless of whether a subject is enrolled in run-in phase or not: The column header for the Screening Period was revised to indicate that assessments are to be collected up to 28 days before the start of any study treatment Text was added to "Notes" for pregnancy, hematology and serum chemistry assessments for clarification.
Rationale: Clarification regarding collection of 12-lead ECG assessment was added.	
Table 1: Time and Events Schedule	Text was revised in the "Notes" for 12-lead electrocardiogram (ECG) to indicate that the baseline predose ECG is to be collected prior to any study treatment, and the Cycle 2 Day 1 predose ECG is to be collected within 1 hour prior to nivolumab dosing Text was added to clarify that the baseline postdose ECGs are to be collected on Cycle 1 Day 1, immediately after nivolumab infusion and 2 hours after ibrutinib dosing.
Rationale: Timing of biomarker sample collection was clarified.	
Table 2: Time and Events Schedule for Pharmacokinetic and Pharmacodynamic Assessments	Footnote "f" revised to specify that biomarker assessment can be collected within 48 hours after last intake of ibrutinib.
Rationale: Samples collected for pharmacokinetic assessment may be used to document the presence of circulating metabolites.	
10.3.3 Analytical Procedure	Text was added to allow that if required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method.
Rationale: Clarification regarding availability of screening laboratory results.	
10.6 Safety Evaluations	Text was revised to clarify that screening laboratory results must be available to the investigator for evaluation before the first dose of any study drug.
Rationale: Clarification regarding period during which blood is collected, and correction to remove redundant text.	
17.1 Study-Specific Design Considerations	Text was revised to clarify that the total blood volume to be collected is estimated to be approximately 25 mL at screening and approximately 60 mL at baseline.

Applicable Section(s)	Description of Change(s)
Rationale: Trephine biopsies are not required; therefore immunohistochemistry (IHC) analysis is not required.	
Table 1: Time and Events Schedule Laboratory Assessments	Text regarding IHC analysis deleted.
Attachment 5 Efficacy Procedures Bone Marrow Assessment	If bone marrow involvement can be confirmed with morphology, IHC **or flow cytometry** need not be done.
Rationale: Alignment with Company Core Data Sheet (CCDS).	
Attachment 7 Instruction for Concomitant Medications to be Used With Precaution	Text regarding concomitant use of CYP inhibitors was revised to align with CCDS.
Rationale: The clinical study protocol template has been updated.	
4 Subject Population	Text was revised to specify that the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.
13.3.3 Pregnancy	Text regarding reporting of pregnancies in partners of male subjects included in the study was revised for clarity.
17.2.2 Independent Ethics Committee or Institutional Review Board.	Text regarding IEC/IRB review and approval of the final protocol and amendments was revised to allow for local requirements.
18.10 On-site Audits	Text regarding audits of source documents was revised.
18.11 Use of Information and Publication	Text was regarding direct transmission of central laboratory results was deleted:
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (19 June 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The primary reasons for the amendment are to remove the interim analysis and to revise the dose modification criteria for hematologic toxicities and rash.

The interim analysis in study Part B has been removed for the following reasons: (1) rapid accrual is expected, (2) the potential for delayed clinical response due to the specific mode of action of the immunotherapeutic agent nivolumab, and (3) to increase the number of subjects to ensure the required number of response-evaluable subjects are enrolled.

The hematologic dose modifications are revised to align with IMBRUVICA® prescribing information in which treatment emergent Grade 3 or 4 cytopenias are described. These Grade 3 and 4 cytopenias are readily manageable as outlined in the prescribing information. The study is conducted in subjects with advanced hematologic malignancies and it can be anticipated that Grade 3 or 4 hematologic toxicities observed with the combination regimen would be primarily caused by ibrutinib rather than nivolumab. The addition of nivolumab, which does not seem to affect the hematopoietic system, may not alter the recovery or outcome of hematologic toxicities in subjects receiving the combination regimen. By applying the dose modifications outlined in the nivolumab (OPDIVO®) prescribing information to hematologic toxicities, the opportunity to establish the safety profile and explore the preliminary efficacy of the ibrutinib and nivolumab combination regimen is severely restricted. Therefore, the dose modifications for hematologic toxicities should follow the ibrutinib (IMBRUVICA®), rather than the nivolumab (OPDIVO®), prescribing information. At the time of this amendment, 6 subjects have been treated with ibrutinib 420 mg/day plus nivolumab 3mg/kg every two weeks. One subject experienced a DLT (Grade 3 increased bilirubin); one subject experienced grade 4 neutropenia which recovered within 4 days. Based on this amendment and following the IMBRUVICA® prescribing information, grade 4 neutropenia that is manageable (eg, recovered within 7 days; see Table 8) would no longer result in discontinuation of study therapy and thus no longer constitute a DLT.

The dose modifications criteria for rash are updated to reflect the label for nivolumab (OPDIVO®).

Applicable Section(s)	Description of Change(s)
Rationale: Remove the interim analysis and increase the number of subjects enrolled in Part B, as described above.	
Synopsis (Overview of Study Design, Statistical Methods), 3.1 Overview of Study Design, 12.3 Sample Size Determination, 12.4 Interim Analysis (removed)	The interim analysis is removed. The statistical power in Part B will be increased to 80%. By maintaining the same statistical assumptions (Overall Response Rate [ORR] under null hypothesis: 20%; ORR under alternative hypothesis: at least 38%; one-sided α of 0.1), the number of subjects in each treatment arm of Part B will increase from 30 to 35 to accrue at least 32 evaluable subjects. The overall number of subjects is increased to 123 and to 105 in Part B. Enrollment in each Cohort in Part B is increased to 35 subjects each. The probability to correctly reject the null hypothesis when alternative hypothesis is true was changed from 0.7 to 0.8.
Rationale: Changes are made to account for other efficacy response (eg, PFS) along with ORR and safety concerns when the SET undertakes the review of Part B data.	

Synopsis (Overview of Study Design, Statistical Methods), 3.1 Overview of Study Design, 12 Statistical Methods, 12.4 Interim Analysis (removed), 12.8 Study Evaluation Team	Removed the following text for consistency: All analyses will be descriptive. No formal statistical inference will be made. Removed text for Part B regarding determining early stopping criteria or continuation of each cohort and specified that the SET will review efficacy endpoints including but not limited to ORR, and that the SET can review safety concerns on an ad hoc basis.
Rationale: Table 8, which provides dose adjustments for related non-hematologic and related hematologic toxicities and Table 9, which provides dose adjustments for rash, have been revised taking into consideration the ibrutinib and nivolumab prescribing information, respectively.	
6.4.3 Guidelines for Dose Modification, Table 8, Table 9	• Under hematologic toxicity, removed the section "General" and revised the guidelines for neutropenia and thrombocytopenia. Added febrile neutropenia. • Revised the guidelines for rash. • Changed to <12 weeks to ≤12 weeks throughout the tables. • The reason to qualify a DLT is indirectly updated by revision to the dose modification tables; however, the DLT definition remains the same, per Section 3.3.1. Under the category of other lab values, for the first event of a Grade 3 toxicity, clarification that resolution not just to Grade ≤1 but also to the baseline value.
Rationale: Modified assessments for hematology, serum chemistry, coagulation panel, thyroid function, β2 microglobulin and serum Ig, and bone marrow aspirate/biopsy. Overall volume of blood to be drawn in the first year has increased.	
Table 1: Time and Events Schedule, 17.1 Study-Specific Design Considerations	• Hematology: to be repeated every week during the first 4 weeks; thereafter, on Day 1, prior to start of each cycle. • Serum chemistry: to be performed on Day 1 of every cycle. Previously this was every 2 cycles starting at Cycle 3. • β2 microglobulin and serum Ig: clarified only for FL and CLL/SLL. • Bone marrow aspirate/biopsy: at least 1 assessment is required. The extent of bone marrow involvement must be documented at screening. • Coagulation panel, thyroid function, and β2 microglobulin/serum Ig should be performed within 48 hrs. prior to the start of applicable cycle.
Rationale: Revised the wording regarding diarrhea in the Introduction to better align with the Investigator's Brochure for ibrutinib.	
1.2.2 Clinical Safety of Ibrutinib	Updated text regarding the clinical experience of ibrutinib regarding diarrhea.
Rationale: To update general information for biomarker analyses, per current protocol template wording.	
10.5 Biomarkers	Added text regarding biomarker analyses, per the current protocol template.
Rationale: Clarified that Grade ≥ 3 events of clinical interest related to nivolumab will have same reporting timelines as for serious adverse events.	
13.2.1 Nivolumab	Clarified that the reporting of events of clinical interest related to nivolumab applies to Grade ≥3.

Rationale: Subjects with small lymphocytic lymphoma (SLL) will be included in the study population. Criteria for inclusion have been added and references to CLL throughout have been updated to CLL/SLL where appropriate.	
Synopsis, 1 Introduction, Table 1, 1.1 Background, 2.1 Objectives, 2.2 Hypothesis, 3.1 Overview of Study Design, Figure 1, 3.2 Study Design Rationale, 4.1.1 Additional Inclusion Criteria for Part A: Dose Optimization, 4.1.2 Additional Inclusion Criteria for Part B: Expansion Cohorts, 12.3 Sample Size Determination	Criteria number 14, 15, and 16 have been modified accordingly to allow inclusion of subjects with SLL into the study. The criteria describing disease requirements for CLL were combined into one criterion, #13, and the new criteria for SLL added to criterion #14.
Synopsis, 2.2 Hypothesis	The hypothesis will evaluate and describe as opposed to test the overall response rate.
Table 23 Footnote #1 and #12	For consistency with Table 1 and 2, bone marrow must be evaluated within 90 days prior to enrollment, not the start of study therapy.
Synopsis, Abbreviations, 1.2.4 Clinical Efficacy of Ibrutinib, 12.3 Sample Size Determination, 12.4 Efficacy Analyses	Where appropriate, objective response rate was changed to overall response rate.
Rationale: Previously, the ibrutinib pharmacodynamic/biomarkers collected at Cycle 1 predose were to be taken from Cohorts A1, A2, and B3 that did not have an ibrutinib run-in. These samples will now be collected from all subjects. Clarification that the fine needle aspirate (FNA) at the C3D1 timepoint may be collected from C2D1 onwards. Blood volume for pharmacokinetic and biomarker assessments collected from subjects in the run-in visit has been added.	
Table 2, 17.1 Study-Specific Design Considerations	Footnote “d” deleted from C1D1 predose pharmacodynamic/biomarker sample. Footnote “l” revised to add that the C3D1 timepoint for the FNA can be taken from C2D1 onwards. Subjects in Cohorts B1and B2 will have an additional 43 mL of blood collected for ibrutinib pharmacodynamics and biomarkers during the run-in visit.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (29 Jan 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall primary reasons for the amendment are to align with the approved nivolumab United States (US) prescribing information and to incorporate feedback from US Food and Drug Administration (FDA) into the protocol.

Applicable Section(s)	Description of Change(s)
Rationale: Align with approved nivolumab US prescribing information.	
6.4.3 Guidelines for Dose Modification	Tables 8 and 9 were revised to align with the approved nivolumab US prescribing information.
Rationale: To incorporate feedback from the FDA into the protocol.	
4.2 Exclusion Criteria	Text added to exclusion criterion #6 to specify that subjects who have congenital long QT syndrome or QTcF >470 ms at Screening will be excluded from this study.
Time and Events Schedule (Table 1); 10.6 Safety Evaluations (Electrocardiogram)	Text added to specify timings and methods for ECG assessment of QT interval.
9.2 Permitted Medications	Text added: "The use of glucocorticoids is allowed for clinical management of AEs. However, inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks is a reason for discontinuation of study therapy."
Synopsis- Statistical Methods; 3.3.2 Dose Optimization – Part A; 12.3 Sample Size Determination	Text was revised to specify that a minimum of 6 subjects, instead of a minimum of 3 subjects, may be treated in each cohort in Part A.
List of References	One new reference (to Fridericia publication) was added.
Rationale: Correction.	
Time and Events Schedule for Pharmacokinetic and Pharmacodynamic Assessments (Table 2)	The following text was deleted from Footnote a: "Assessment only for expansion part of the study (Part B): mandatory for Cohort B2 only, other cohorts per SET decision."
Rationale: To maintain consistency within protocol and for alignment with changes made to Section 6.4.3.	
3.3.1 Evaluation of Dose-limiting Toxicity	Text regarding non-hematologic and hematologic adverse events was deleted. Text regarding central nervous system hemorrhage of any grade was retained and grouped with other listed adverse events.

Applicable Section(s)	Description of Change(s)
Rationale: Alignment of information between Sections 3.1 and 6.	
6.4.1 Ibrutinib Dose Modification	Text regarding ibrutinib intra-patient dose escalation was added: "In Part A, intra-patient dose escalation may be requested by the investigator and discussed with the medical monitor once a subsequent higher combination dose has been declared acceptable by the SET for subjects who (1) have received at least 4 cycles of combination treatment at the assigned dose level, and (2) have not experienced a DLT or therapy-related SAE. Subjects whose dose has been escalated will not be considered for the safety evaluation in the subsequent dose level and the determination of the RP2D."
Rationale: Correction.	
8.2 Hepatic Adverse Events	In Table 11, "I-O therapy" revised to "study treatment".
Rationale: Clarification.	
9.3 Prohibited Medications	Footnote #3 to Table 19 revised and was split into 2 footnotes for clarity.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Phase 1/2a Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of the Combination of Ibrutinib with Nivolumab in Subjects with Hematologic Malignancies

Ibrutinib, (IMBRUVICA®; PCI-32765; JNJ-54179060), is a first-in-class, potent, orally-administered, covalently-binding small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently being co-developed by Janssen Research & Development, LLC (JRD) and Pharmacyclics LLC. for the treatment of B-cell malignancies.

Nivolumab (BMS-936558) is a fully human, IgG4 (κ) isotype, monoclonal antibody (mAb) that binds the programmed-cell death 1 (PD-1) receptor and is being developed by Bristol Myers Squibb for the treatment of hematological cancers and solid tumors.

OBJECTIVES AND HYPOTHESIS

Primary Objective

Part A (Dose Optimization Cohorts): The primary objective of Part A is to determine whether ibrutinib and nivolumab can be safely combined and to establish the recommended Phase 2 dose (RP2D) for this combination in subjects with hematological disorders.

Part B (Expansion Cohorts): The primary objective of Part B is to determine the preliminary activity of the ibrutinib/nivolumab combination regimen in subjects with relapsed/refractory CLL/SLL and poor prognosis (deletion 17p or deletion 11q), relapsed/refractory FL, relapsed/refractory DLBCL, and in subjects with Richter syndrome in comparison to historical results.

Secondary Objectives

The secondary objectives are:

- To evaluate the safety profile of the ibrutinib and nivolumab combination regimen
- To assess overall response rate, duration of response, duration of stable disease, progression-free survival rate at 1 year, and overall survival at 1 year of the ibrutinib and nivolumab combination regimen
- To characterize and explore the pharmacokinetic profile of ibrutinib and nivolumab compared with existing single-agent treatment data; and the potential relationships between ibrutinib and nivolumab metrics of exposure with relevant clinical or biomarker information (Part A and B)

Exploratory Objectives

- To characterize the molecular effects of the ibrutinib and nivolumab combination regimen on tumor cells and the immune response; and identify biomarkers of response or resistance to the combination
- To evaluate the immunogenicity of nivolumab

Hypothesis

In Part A (Dose Optimizations), the study will evaluate and describe whether ibrutinib, administered at daily oral doses between 420 mg and up to 560 mg, can be safely combined with nivolumab 3 mg/kg administered IV every 2 weeks such that ≤30% of subjects with CLL/SLL or NHL experience a DLT.

In Part B (Dose Expansion; Cohorts B1, B2, B3, and B4), the study will evaluate and describe whether ibrutinib combined with nivolumab can result in an overall response rate of more than 20%.

OVERVIEW OF STUDY DESIGN

This is an open-label Phase 1/2a study, which consists of Part A (Dose Optimization Cohorts) and Part B (Expansion Cohorts). In the context of this study, a treatment 'cycle' is defined as a course of treatment of 14 days starting with the intravenous administration of nivolumab on Day 1 of each cycle along with once daily oral intake of ibrutinib on all days.

It is anticipated that approximately 158 subjects will be enrolled throughout the study; up to 18 subjects in the dose optimization period (Part A) and approximately 140 subjects during the expansion period (Part B).

Part A (Dose Optimization Cohorts) is designed to determine the RP2D for the combination based on safety, pharmacokinetic, and pharmacodynamic assessments. Two dose optimization cohorts will be explored, applying the Modified Toxicity Probability Interval (mTPI) design to evaluate subjects with relapsed/refractory CLL/SLL or B-NHL.

Part B (Dose Expansion Cohorts) will be open for enrollment after the RP2D is determined in Part A. In Part B, further assessment of the RP2D will be explored in 4 subject populations to further evaluate the safety and clinical activity of ibrutinib in combination with nivolumab. During the expansion period, subjects with CLL/SLL with del 17p or 11q (Cohort B1), FL (Cohort B2), DLBCL (Cohort B3), and Richter syndrome (Cohort B4) will be enrolled. Approximately 35 subjects will be enrolled in each of the expansion cohorts. The subjects will be treated at the RP2D level selected to further assess the safety, pharmacokinetics, pharmacodynamics, pharmacogenomics, and activity of the combination.

The average duration of study therapy is expected to be approximately 6 months.

In Part A of the study, a Study Evaluation Team (SET), consisting of the principal investigators, sponsor medical monitors, and the sponsor's clinical pharmacologist, or their designees, and the sponsor statistician will review all available data upon completion of the first 2 treatment cycles (ie, 4 weeks of study therapy) for all subjects at each dose cohort to determine DLTs, if dose escalation is acceptable, and ultimately to determine the recommended Phase 2 dose.

In Part B of the study, all subjects in each cohort may be evaluated for response by the SET and additional functional representatives from Janssen, as applicable. The SET along with optional other internal members may review safety data on an ad hoc basis, and efficacy endpoints (including but not limited to ORR).

The End-of-Treatment Visit will occur within 30 days after the last dose of ibrutinib or nivolumab, whichever treatment occurred last.

During the Follow-up Period, long-term safety, survival status, disease progression, subsequent aniticancer therapy, and occurrence of other primary malignancy data will be collected as well as ADA sampling if applicable. During the Follow-up Period, subjects should be followed for safety up to 30 days after the last dose of ibrutinib or 100 days after the last nivolumab infusion, whichever is later. The safety includes adverse event reporting and laboratory assessments (at the first follow up). Thereafter, follow-up visits will be completed approximately every 3 months until death or the end of study. Subjects who have developed treatment-related Grade 3 or higher toxicity at the end of treatment will be assessed until recovery to Grade ≤1 or baseline, deemed irreversible, or until end of study. Adverse events leading to discontinuation will be followed up until resolution or return to baseline, or end of study, whichever occur first.

The primary analysis of the study will be performed 6 months after the last subject has received the first dose of study medication, or earlier if that subject discontinues study therapy. After the cutoff for primary analysis, subjects who are receiving study treatment can continue treatment per protocol until progression, unacceptable toxicity, withdrawal of consent, or other reason as listed in Section 11.2. End of study is defined as the last subject who completed the End of Treatment assessment. After the clinical cutoff at a minimum following data will be collected on eCRF: SAEs and AEs Grade ≥3, laboratory assessments (Grade ≥3 or clinically significant), efficacy, survival status, and treatment administration. Data collected from the primary analysis until end of study will be summarized in a clinical study report addendum.

SUBJECT POPULATION

Subjects in the study must be 18 years of age or older, with Eastern Cooperative Oncology Group (ECOG) performance status grade 0, 1, or 2 and adequate bone marrow, liver, and renal function. Subjects in Part A will have measurable, relapsed or refractory B-NHL or CLL/SLL (deletion 17p or deletion 11q). In Part B, subjects in cohort B1 will have CLL/SLL (deletion 17p or deletion 11q) and active disease meeting at least 1 of the criteria outlined by the IWCLL. In Cohort B2, subjects with FL will have histologically confirmed initial diagnosis of FL of Grade 1, 2, or 3a according to World Health Organization (WHO) criteria without pathological evidence of transformation and relapsed or refractory disease with at least 1 measurable site. In Cohort B3, subjects with DLBCL will have histologically confirmed disease with at least 1 measurable site and received standard systemic therapy/stem cell transplantation or not eligible for stem cell transplantation. In Cohort B4, subjects will have histologically confirmed Richter syndrome with at least 1site of measurable disease and will have received at least one line of standard systemic therapy.

DOSAGE AND ADMINISTRATION

Ibrutinib capsules will be self-administered once daily. Ibrutinib should be taken around the same time each day with approximately 240 mL of water (ie, 8 ounces). The capsules should be swallowed whole and should not be opened, broken, or chewed.

Eligible subjects will receive treatment with nivolumab at a dose of 3 mg/kg given as a 60-minute IV infusion on Day 1 of every 14-day cycle. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.

EFFICACY EVALUATIONS/ENDPOINTS

The investigator will perform tests that will allow evaluation of response to therapy according to corresponding disease criteria:

Response Criteria

Criteria	PART A	PART B	Attachment
IWCLL[a]	Subjects with CLL	Cohort B1 (CLL)	6.1
Response Assessment of Non-Hodgkin Lymphoma[b]	Subjects with B-cell NHL, including SLL	Cohorts B1 (SLL), B2, B3, B4	6.2

[a] International Workshop on Chronic Lymphocytic Leukemia (Hallek 2008)
[b] Recommendations for Initial Evaluation, staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson 2014)

The efficacy endpoints are defined as follows, based on the IWCLL or the Lugano Classification by Cheson (2014), as appropriate for the disease:

- Overall response rate (ORR), which is defined as the proportion of evaluable subjects who achieve CR or PR, as assessed by the investigators.
- Duration of response (DOR) will be calculated from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death. Subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment.
- Progression-free survival (PFS) is defined as the duration from the date of first dose of study drug until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death, whichever comes first. Subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment.
- Overall survival (OS) is measured from the date of first dose of study drug to the date of the subject's death. If the subject is alive or the vital status is unknown, the subject will be censored at the date the subject was last known to be alive.

PHARMACOKINETIC EVALUATIONS

Blood samples will be collected from all subjects for determination of plasma concentrations of ibrutinib and the PCI-45227 metabolite (if possible and judged relevant), as well as serum concentrations of nivolumab. Pharmacokinetic assessments will not be conducted post clinical cutoff.

IMMUNOGENICITY EVALUATIONS

Subjects will be monitored for anti-nivolumab antibodies throughout the study. Blood for serum anti-nivolumab antibody testing should be collected.

BIOMARKER EVALUATIONS

Biomarkers will be assessed in all subjects to further characterize the pharmacodynamic profile and to investigate the molecular efficacy of the ibrutinib and nivolumab combination regimen.

Biomarkers will be analyzed in:

- Tumor tissue
- Blood samples (collected serially)
- Fine-needle aspirates (from affected lymph nodes)
- Bone marrow aspirates or biopsies

After clinical cutoff, some biomarker assessments (bone marrow aspirate/biopsy) will no longer be conducted.

SAFETY EVALUATIONS

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, electrocardiograms, physical examinations, clinical laboratory tests and ECOG performance status.

STATISTICAL METHODS

This is a Phase 1/2a dose optimization and expansion study. For Part A, a statistical design based on the approach described in Ji, et al. (2010) and Ji and Wang (2013) will be used. This method requires a definition of an equivalence interval (EI), [*0.25; 0.30*], in which any dose is considered as a potential candidate for the true MTD, where *0.30* is the targeted DLT rate. Defining an EI results in the partition of the unit interval (0, 1) into 3 subintervals; (*0; 0.25*), [*0.25, 0.30*], and (*0.30; 1*). Doses in these 3 intervals are deemed lower, close to, and higher than the MTD, respectively. At least 6 and up to 9 subjects may be treated in each cohort in Part A. Approximately 18 subjects may be enrolled in Part A.

Part B, Cohorts B1 (CLL/SLL), B2 (FL), B3 (DLBCL), and B4 (Richter syndrome) are designed to evaluate the feasibility and safety of treating subjects with ibrutinib in combination with nivolumab and to evaluate preliminary activity. The sample size is calculated based on the following assumptions (denoting the true response rate of ibrutinib in combination with nivolumab as *p*):

- The overall response rate under null hypothesis is 20%
- The overall response rate under alternative hypothesis is at least 38%
- The probability to mistakenly rejecting the null hypothesis when it is actually true is 0.1 (one-sided).
- The probability to correctly rejecting null hypothesis when alternative hypothesis is true is at least 0.8

Under the above assumptions, the study will enroll approximately 35 subjects to get at least 32 response-evaluable subjects in each cohort of Part B (dose expansion, Cohorts B1, B2, B3, and B4).

Approximately 158 subjects (with up to 18 subjects in Part A and approximately 140 subjects in the Part B, dose expansion) will be enrolled in this study.

Part A: Individual best tumor responses and duration of response (defined as the time from first response to progression) will be listed for each dose cohort.

Part B: The following efficacy analyses will be performed to explore the clinical activity of ibrutinib in combination with nivolumab in each cohort in the treated population unless otherwise stated:

- Overall response rate (CR or PR) will be calculated with 95% CI for each disease-specific cohort (B1, B2, B3, and B4) on the response-evaluable population.
- Progression-free survival and overall survival at 1 year will be evaluated using Kaplan-Meier method.
- Duration of response and duration of stable disease will be evaluated if there are sufficient data for responders within each cohort.

Table 1: Time and Events Schedule

	Notes	Screening Period	Treatment Period (14 day cycles)			Follow-up Period [a]
		up to 28 days before start of any study treatment	BASELINE ASSESSMENT C1D1 (without run-in phase) C1D-7 (with run-in phase)	Day 1, subsequent cycles	EOT	Q3m
Treatment Period begins with the first administration of study therapy. EOT visit is required for all subjects and should take place within 30 days after last dose of study therapy with a window of ±7 days. If the subject requires subsequent anti-lymphoma/neoplastic therapy in the interim period between last dose of study drug and the EOT visit, then this visit should be completed just prior to initiation of subsequent therapy. Follow-up visits in all subjects will be completed every 3 months with a window of ±7 days until death or end of study. Note that the first FU visit should be approximately 100 days after end of nivolumab therapy; during this first FU visit, additional sampling will be done. After the clinical cutoff, subjects who are ongoing on treatment continue all assessment per protocol, however data collected on eCRF will be limited to at least: SAEs and AEs Grade ≥3, laboratory assessments (Grade ≥3 or clinically significant), efficacy assessments, survival status, and study treatment administration. Per Amendment 7, subjects who are receiving study treatment will continue all assessments per protocol. Data collected in the eCRF will be further limited to: SAEs and Grade ≥3 AEs that are at least possibly related to treatment, AEs leading to discontinuation or modification, efficacy assessments, and study treatment administration.						
Screening/Administrative						
Informed consent	ICF must be signed before any study-related procedures are performed.	X				
Eligibility criteria		X				
Demography/ Medical History		X				
Study Drug Administration						
Ibrutinib			Refer to Section 6			
Nivolumab			Refer to Section 6			
Diary Review				X	X	
Safety Assessments						
Physical exam	Including lymphoma symptoms if applicable. In Treatment Period, directed physical exam of organ systems previously abnormal/involved with disease and of clinically relevant abnormalities in any organ. In the Follow-up Period, collect only physical exam findings for disease assessment.	X	X	X	X	X
ECOG		X	X	X	X	
Vital signs	Heart rate, blood pressure (monitor with same method and position (sitting or supine) throughout study), pulse oximetry, and temperature, prior to infusion of nivolumab in Treatment Period (after C1D1, obtain within 72 hrs prior to each infusion) and within 1 hr after infusion of nivolumab	X	X	X	X	

	Notes	Screening Period	Treatment Period (14 day cycles)			Follow-up Period [a]
		up to 28 days before start of any study treatment	BASELINE ASSESSMENT C1D1 (without run-in phase) C1D-7 (with run-in phase)	Day 1, subsequent cycles	EOT	Q3m
Treatment Period begins with the first administration of study therapy. EOT visit is required for all subjects and should take place within 30 days after last dose of study therapy with a window of ±7 days. If the subject requires subsequent anti-lymphoma/neoplastic therapy in the interim period between last dose of study drug and the EOT visit, then this visit should be completed just prior to initiation of subsequent therapy. Follow-up visits in all subjects will be completed every 3 months with a window of ±7 days until death or end of study. Note that the first FU visit should be approximately 100 days after end of nivolumab therapy; during this first FU visit, additional sampling will be done. After the clinical cutoff, subjects who are ongoing on treatment continue all assessment per protocol, however data collected on eCRF will be limited to at least: SAEs and AEs Grade ≥3, laboratory assessments (Grade ≥3 or clinically significant), efficacy assessments, survival status, and study treatment administration. Per Amendment 7, subjects who are receiving study treatment will continue all assessments per protocol. Data collected in the eCRF will be further limited to: SAEs and Grade ≥3 AEs that are at least possibly related to treatment, AEs leading to discontinuation or modification, efficacy assessments, and study treatment administration.						
Weight/Height	Height at Screening only.	X	X	X	X	
12-lead ECG	Assessment of triplicate ECG to determine QTcF; repeat ECG 3 times approximately 1-2 minutes apart. Predose Baseline= prior to any study treatment Predose C2D1=within 1 hour prior to nivolumab dosing	X	•Predose •Immediately after nivolumab infusion on C1D1 •2 hours after ibrutinib dosing on C1D1	•Cycle 2 Day1: predose •Cycle 5 Day 1: after end of nivolumab infusion •To be repeated as clinically indicated	X	
Concomitant Medications	Collect up to EOT (within 30 days after the last dose of ibrutinib or whichever treatment occurred last). Thereafter, collect only subsequent anti-lymphoma/neoplastic therapy.	<----------X---------->				
Adverse Events	Record all AEs from signing of ICF to EOT (within 30 days after the last dose of ibrutinib or nivolumab, whichever treatment occurred last).	<----------X---------->				
Laboratory Assessments						
Pregnancy test	For women of childbearing potential only. Not repeated at baseline (C1D1 or C1D-7) if obtained within 24 hours, unless clinically indicated.	X	X	as clinically indicated		
Hematology	Hemoglobin, platelet count, WBC, ANC, and ALC. Not repeated on C1D1 or C1D-7 if obtained within 48 hours. Perform within 24 hrs prior to weekly scheduled assessment. Perform within 48 hrs prior to the start of each subsequent cycle (≥Cycle 3); results must be reviewed prior to each nivolumab infusion. Perform once every week during the first 4 weeks, prior to treatment; thereafter prior to start of each cycle.	X	X	X	X	

	Notes	Screening Period	Treatment Period (14 day cycles)			Follow-up Period [a]
		up to 28 days before start of any study treatment	BASELINE ASSESSMENT C1D1 (without run-in phase) C1D-7 (with run-in phase)	Day 1, subsequent cycles	EOT	Q3m
Treatment Period begins with the first administration of study therapy. EOT visit is required for all subjects and should take place within 30 days after last dose of study therapy with a window of ±7 days. If the subject requires subsequent anti-lymphoma/neoplastic therapy in the interim period between last dose of study drug and the EOT visit, then this visit should be completed just prior to initiation of subsequent therapy. Follow-up visits in all subjects will be completed every 3 months with a window of ±7 days until death or end of study. Note that the first FU visit should be approximately 100 days after end of nivolumab therapy; during this first FU visit, additional sampling will be done. After the clinical cutoff, subjects who are ongoing on treatment continue all assessment per protocol, however data collected on eCRF will be limited to at least: SAEs and AEs Grade ≥3, laboratory assessments (Grade ≥3 or clinically significant), efficacy assessments, survival status, and study treatment administration. Per Amendment 7, subjects who are receiving study treatment will continue all assessments per protocol. Data collected in the eCRF will be further limited to: SAEs and Grade ≥3 AEs that are at least possibly related to treatment, AEs leading to discontinuation or modification, efficacy assessments, and study treatment administration.						
Serum chemistry	Sodium, potassium, magnesium, creatinine, total bilirubin, glucose (only at Screening), albumin, AST, ALT, alkaline phosphatase, LDH, amylase and lipase. Not repeated on C1D1 or C1D-7 if obtained within 48 hours. Perform within 48 hrs prior to the start of each cycle; results must be reviewed prior to each nivolumab infusion.	X	X	X	X	X (only at first FU<100 days after last dose of nivolumab)
Coagulation panel	PT, APTT, INR Perform within 48 hrs. prior to the start of applicable cycle; results must be reviewed prior to the nivolumab infusion.		X	as clinically indicated	X	
Thyroid function	T3, free T4, TSH Perform within 48 hrs. prior to the start of applicable cycle; results must be reviewed prior to the nivolumab infusion.	X	Q4cycles (starting cycle 5)			
β2 microglobulin and serum Ig	Only for FL and CLL/SLL Perform within 48 hrs. prior to the start of applicable cycle; results must be reviewed prior to the nivolumab infusion.		X	Q8cycles (starting cycle 9) during the first year, thereafter Q16cycles		

	Notes	Screening Period	Treatment Period (14 day cycles)			Follow-up Period [a]
		up to 28 days before start of any study treatment	BASELINE ASSESSMENT C1D1 (without run-in phase) C1D-7 (with run-in phase)	Day 1, subsequent cycles	EOT	Q3m
Treatment Period begins with the first administration of study therapy. EOT visit is required for all subjects and should take place within 30 days after last dose of study therapy with a window of ±7 days. If the subject requires subsequent anti-lymphoma/neoplastic therapy in the interim period between last dose of study drug and the EOT visit, then this visit should be completed just prior to initiation of subsequent therapy. Follow-up visits in all subjects will be completed every 3 months with a window of ±7 days until death or end of study. Note that the first FU visit should be approximately 100 days after end of nivolumab therapy; during this first FU visit, additional sampling will be done. After the clinical cutoff, subjects who are ongoing on treatment continue all assessment per protocol, however data collected on eCRF will be limited to at least: SAEs and AEs Grade ≥3, laboratory assessments (Grade ≥3 or clinically significant), efficacy assessments, survival status, and study treatment administration. Per Amendment 7, subjects who are receiving study treatment will continue all assessments per protocol. Data collected in the eCRF will be further limited to: SAEs and Grade ≥3 AEs that are at least possibly related to treatment, AEs leading to discontinuation or modification, efficacy assessments, and study treatment administration.						
HBV surface antigen and hepatitis C (antibodies)	If positive, further testing of quantitative levels to rule out positivity.	X				
Efficacy Assessments						
CT imaging (neck, chest, abdomen, and pelvis) with oral and IV contrast	CT scan with IV contrast (oral if IV is contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites present at Screening. MRI only for disease sites that cannot be adequately imaged using CT. Brain MRI required only if clinically indicated.	X (imaging part of standard assessments; within 6 weeks prior to dosing is acceptable		Q5cycles (starting cycle 5) for first 15 months, thereafter Q12 cycles until PD. After clinical cutoff, disease assessments to be performed Q12 cycles or per local standards (but at a minimum of Q26 weeks). To be performed at the time of atypical responses 'tumor flare'. The same imaging technique used at Screening should be used throughout the study. Results are preferably available before start of treatment in the following cycle. During Follow-up, to be performed at PD and at least Q6 months up to PD or start of subsequent therapy	
Whole body FDG-PET scan	For NHL assessments, PET scan at baseline is recommended but not mandatory. Maximal tumor reduction: eg CR or 2 consecutive CT scans showing no further tumor reduction.	X		at the time of maximal tumor reduction, relapse from CR		
Evaluation of other sites of disease	May be performed by radiological imaging, physical examination, or other procedures as necessary	as clinically indicated		as clinically indicated, using the same method of assessment as used at Screening		

	Notes	Screening Period	Treatment Period (14 day cycles)			Follow-up Period [a]
		up to 28 days before start of any study treatment	BASELINE ASSESSMENT C1D1 (without run-in phase) C1D-7 (with run-in phase)	Day 1, subsequent cycles	EOT	Q3m
Treatment Period begins with the first administration of study therapy. EOT visit is required for all subjects and should take place within 30 days after last dose of study therapy with a window of ±7 days. If the subject requires subsequent anti-lymphoma/neoplastic therapy in the interim period between last dose of study drug and the EOT visit, then this visit should be completed just prior to initiation of subsequent therapy. Follow-up visits in all subjects will be completed every 3 months with a window of ±7 days until death or end of study. Note that the first FU visit should be approximately 100 days after end of nivolumab therapy; during this first FU visit, additional sampling will be done. After the clinical cutoff, subjects who are ongoing on treatment continue all assessment per protocol, however data collected on eCRF will be limited to at least: SAEs and AEs Grade ≥3, laboratory assessments (Grade ≥3 or clinically significant), efficacy assessments, survival status, and study treatment administration. Per Amendment 7, subjects who are receiving study treatment will continue all assessments per protocol. Data collected in the eCRF will be further limited to: SAEs and Grade ≥3 AEs that are at least possibly related to treatment, AEs leading to discontinuation or modification, efficacy assessments, and study treatment administration.						
Bone marrow aspirate; biopsy	Morphological examination of the bone marrow is required; bone marrow aspirate/ bone marrow biopsy: at least 1 assessment is mandatory. Extent of disease involvement in the bone marrow must be documented at screening based on the results of a bone marrow biopsy/aspirate performed within 90 days prior to enrollment or a bone marrow biopsy/aspirate performed during the screening period. If bone marrow biopsy/aspirate is performed during screening (after obtaining informed consent), submission of bone marrow aspirate is encouraged. In subjects with bone marrow involvement prior to treatment, bone marrow aspirate or biopsy must be repeated once during the study for confirmation of CR (preferably within 30 days of initial documentation of CR). Assessment will not be conducted post clinical cutoff.	X		to confirm CR		
Survival [a]						X
Pharmacokinetic and Pharmacodynamic Assessments						
Please refer to Table 2.						
Biomarker Assessments						
Please refer to Table 2.						

	Notes	Screening Period	Treatment Period (14 day cycles)			Follow-up Period [a]
		up to 28 days before start of any study treatment	BASELINE ASSESSMENT C1D1 (without run-in phase) C1D-7 (with run-in phase)	Day 1, subsequent cycles	EOT	Q3m
Treatment Period begins with the first administration of study therapy. EOT visit is required for all subjects and should take place within 30 days after last dose of study therapy with a window of ±7 days. If the subject requires subsequent anti-lymphoma/neoplastic therapy in the interim period between last dose of study drug and the EOT visit, then this visit should be completed just prior to initiation of subsequent therapy. Follow-up visits in all subjects will be completed every 3 months with a window of ±7 days until death or end of study. Note that the first FU visit should be approximately 100 days after end of nivolumab therapy; during this first FU visit, additional sampling will be done. After the clinical cutoff, subjects who are ongoing on treatment continue all assessment per protocol, however data collected on eCRF will be limited to at least: SAEs and AEs Grade ≥3, laboratory assessments (Grade ≥3 or clinically significant), efficacy assessments, survival status, and study treatment administration. Per Amendment 7, subjects who are receiving study treatment will continue all assessments per protocol. Data collected in the eCRF will be further limited to: SAEs and Grade ≥3 AEs that are at least possibly related to treatment, AEs leading to discontinuation or modification, efficacy assessments, and study treatment administration.						

Abbreviations: AE=adverse event; ALC=absolute lymphocyte count; ALT=alanine aminotransferase; ANC=absolute neutrophil count; APTT=activated partial thromboplastin time; ALT=alanine aminotransferase; AST=aspartate aminotransferase; b-hCG=beta-human chorionic gonadotropin; C1D1=Cycle 1 Day 1; C1D-7=Cycle 1 Day -7; CLL=chronic lymphocytic leukemia; CR=complete response; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end-of-treatment; FDG= fluorodeoxyglucose; FL=follicular cell lymphoma; FNA=fine needle aspirate; FU=follow-up; HBV=hepatitis B virus; ICF=informed consent form; Ig=immunoglobulins; INR=international normalized ratio; IV=intravenous; LDH=lactate dehydrogenase; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; NHL= non-Hodgkin lymphoma; PD=progressive disease; PE=physical examination; PET=positron emission tomography; PT=prothrombin time; Q3m=every 3 months; QTcF=QT interval corrected for heart rate, using Fridericia formula; SAE=serious adverse event; SLL=small lymphocytic lymphoma; TSH=thyroid stimulating hormone; WBC=white blood count

a. Per amendment 7: Survival follow up is no longer required, patients who discontinued treatment and are in follow up may complete end of study assessments.

Table 2: Time and Events Schedule for Pharmacokinetic and Pharmacodynamic Assessments [p]

			Ibrutinib PK	Ibrutinib PD + Biomarkers	Nivolumab PD + Biomarkers	Nivolumab PK	Nivolumab ADA	Tumor biopsy	BM aspirate/ biopsy	FNA [l]
Screening								X[g]	X[h]	X
Cycle 1	**Day -7 [c]**	**predose [a]**	X	X						
		1hr post dose	X							
		2hr post dose	X	X						
		4hr post dose	X	X						
	Day 1	**predose [a,b]**	X[d]	X	X	X	X			
		1hr post dose	X[d]							
		2hr post dose	X[d]							
		4hr post dose	X[d]	X						
Cycle 3	**Day 1**	**predose [a,b]**	X	X	X	X	X			X
Cycle 5	**Day 1**	**predose [a,b]**		X	X	X	X			
Cycle 13[e]	**Day 1**	**predose [a,b]**	X[e]	X	X	X	X	X[j,o] any time after C13		
		1hr post dose	X[e]							
		2hr post dose	X[e]							
		4hr post dose	X[e]	X						
Cycle 25	**Day 1**	**predose [a,b]**		X	X	X	X			
Q8 cycles°	**Day 1**	**predose [a,b]**				X	X			
Q16 cycles°	**Day 1**	**predose [a,b]**		X	X					
At CR°					X				X[i]	
At progression [k]				X	X			X°	X°	
EOT			X[f,o]	X[f]		X[m,o]	X[m,o]			
FU 1 (100 days after last dose of nivolumab)						X°	X°			
FU				X (to be repeated Q6m starting at FU3) [n,o]						

ADA=anti-drug antibodies; CR=complete response; EOT=End of Treatment; FNA=fine needle aspirate; FU=Followup; PD=pharmacodynamic; PK=pharmacokinetic

a. Predose samples should be taken just prior to the administration (preferably within 30 minutes, however predose collection up to 4 hours before study drug administration would be acceptable). If the infusion is delayed and a predose sample was already collected, there is no need to collect an additional predose sample.

b. When both study drugs are given, predose samples should be obtained prior to administration of any study drug.

c. Required for Cohort B1 and B2 only.

d. Cohorts A1, A2, B3, and B4 that did not have an ibrutinib run-in.

e. If not done in Cycle 13, postdose samples for ibrutinib PK can be collected at a subsequent cycle.

f. If possible, the EOT sample should be obtained within 48 hours after last intake of ibrutinib.

g. Submission of tumor tissue from a biopsy performed during screening is mandatory (diagnostic block or slides), archival tissue is acceptable if fresh biopsy is not available.

h. Extent of disease involvement in the bone marrow must be documented at screening based on the results of a bone marrow biopsy/aspirate performed within 90 days prior to enrollment or a bone marrow biopsy/aspirate performed during the screening period. If bone marrow biopsy/aspirate is performed during screening (after obtaining informed consent), submission of bone marrow aspirate is encouraged.

i. If the bone marrow was involved by lymphoma at baseline, a bone marrow biopsy and/or aspirate will be required to confirm a CR. Submission of bone marrow aspirate to the central lab is required if clinically feasible.

j. Subjects are required to undergo tumor and/or bone marrow biopsies from C13 onwards if clinically indicated. When tumor biopsy is performed, submission of tumor biopsy to the central lab is required if clinically feasible.

k. Samples, including fresh biopsy upon progression, are to be taken ± 7 days at the discretion of the investigator.

l. Applicable to Part B : Only required for subjects (as clinically indicated) in Cohort B1 (mandatory), B2 (mandatory), and optional for B3 and B4. C3D1 timepoint can be taken from C2D1 onwards.

m. Sampling at clinical visit End-of-treatment per T&E Table 1 (approx. 30 days post Ibrutinib dose).

n. During FU to be repeated until progressive disease.

o. After clinical cutoff: Assessment is no longer required.

p. Pharmacokinetic, pharmacodynamic or biomarker samples will not be obtained at any visit, including follow up, after implementation of protocol amendment 7.

ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AESI	adverse events of special interest
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BCR	B-cell receptor
BM	bone marrow
B-NHL	B-cell non-Hodgkin lymphoma
BTK	Bruton's tyrosine kinase
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
Cmax	maximum observed plasma concentration
CMV	cytomegalovirus
CT	computed tomography
CV	coefficient of variation
DILI	drug-induced-liver-injuries
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EI	equivalence interval
EOT	end of treatment
ERK	extracellular signal-regulated kinase
FISH	fluorescence in situ hybridization
FL	follicular cell lymphoma
FU1	follow up 1
GCB	germinal-center –B-cell like
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFNγ	interferon gamma
IHC	immunohistochemistry
IL-2	interleukin 2
irAE	immune-related adverse event
INR	international normalized ratio
IRB	Institutional Review Board
ITK	interleukin-2-inducible T-cell kinase
ITSM	distal immunoreceptor tyrosine-based switch motif
IV	intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWRS	interactive web response system
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LDT	lymphocyte doubling time
LFT	liver function test
mAb	monoclonal antibody

MCL	mantle cell lymphoma
MDRD	Modified Diet in Renal Disease (formula)
MedDRA	Medical Dictionary for Regulatory Activities
MLR	mixed lymphocyte reaction
MM	multiple myeloma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI	Modified Toxicity Probability Interval
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	non-small-cell lung cancer
ORR	overall response rate
PD	pharmacodynamic
PD-1	programmed-cell death 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PQC	Product Quality Complaint
PR	partial response
PRL	partial response with lymphocytosis
QTcF	QT interval corrected for heart rate, using Fridericia formula
RCC	renal-cell cancer
RP2D	recommended phase 2 dose
SET	Study Evaluation Team
SIPPM	Site Investigational Product Procedures Manual
SJS	Stevens-Johnson Syndrome
SLL	small lymphocytic lymphoma
TCR	T-cell receptor
Th2	T-helper type 2
ULN	upper limit of normal
WHO	World Health Organization
WM	Waldenström's macroglobulinemia
WOCBP	women of childbearing potential

1. INTRODUCTION

Ibrutinib, (IMBRUVICA®; PCI-32765; JNJ-54179060), is a first-in-class, orally administered, potent inhibitor of Bruton's tyrosine kinase (BTK), a mediator of critical B-cell signaling pathways implicated in the pathogenesis of B-cell cancers. Ibrutinib is currently being co-developed by Janssen Research & Development, LLC (JRD) and Pharmacyclics LLC. It has demonstrated single-agent activity and an acceptable safety profile in several B-cell lymphomas, including relapsed/refractory mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). Ibrutinib and PCI-32765 refer to the same molecule; hereafter, ibrutinib will be used.

Ibrutinib is currently being evaluated in over 26 ongoing and 9 completed company-sponsored clinical studies in healthy volunteers and in subjects with recurrent B-cell lymphomas, including CLL/small lymphocytic lymphoma (SLL), MCL, follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), multiple myeloma (MM), Waldenström's macroglobulinemia (WM), and marginal zone lymphoma (MZL).

Nivolumab (BMS-936558) is a fully human, IgG4 (κ) isotype, monoclonal antibody (mAb) that binds PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-γ release in the MLR. The effect of nivolumab on antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA. These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-γ secretion from CMV-specific memory T-cells in a dose-dependent manner. PD-1 blockade by nivolumab is therefore considered a promising immunotherapeutic option.

Relevant clinical and nonclinical information are discussed within this section. For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of ibrutinib and nivolumab, refer to the latest version of the ibrutinib and nivolumab Investigator's Brochures, Addenda, and Supplements. The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

Conventional treatment regimens of cytotoxic chemotherapy and/or agents targeting oncogenic signal-transduction pathways can lead to substantial remission rates in patients with hematologic malignancies and solid tumors by eliminating actively dividing tumor cells. Ibrutinib is a potent small-molecule inhibitor of BTK-mediated B-cell receptor signaling and has demonstrated encouraging clinical efficacy in B-cell malignancies. However, the therapeutic efficacy of standard anti-proliferative treatments including ibrutinib is often limited by the emergence of molecular resistance leading to the occurrence of clinical disease relapse. It is widely believed that the expansion of sub-populations of initially quiescent tumor stem cells are responsible for the disease relapse due to inherited or acquired resistance to anti-proliferative therapies. In order to better target the specific tumor stem cell populations, therapeutic strategies activating the immune system have been successfully explored (Brody 2011).[7] The addition of passive immunotherapies with antibodies directed against relevant antigens and receptors expressed on proliferating tumor cells

and stem cells have already transformed the standard-of-care in selected hematologic malignancies and solid tumors. More recently, major clinical progress has been observed with active immunotherapies addressing molecular mechanisms of evasion of immune-mediated tumor destruction. Multiple therapeutic approaches are currently being pursued to overcome the immune-tolerance of tumors (Drake 2014).[15] Of these the blockade of immune-checkpoint receptor-ligand interactions between tumor cells and tumor-specific T-lymphocytes (Drake 2014)[15] has emerged as the most promising novel therapy. Among the immunotherapies targeting immune-checkpoints, antibodies directed against the PD-1 receptor expressed on tumor-specific T-lymphocytes such as nivolumab, have demonstrated astonishing single-agent efficacy in patients with advanced melanoma, renal cell cancer (RCC), non-small-cell lung cancer (NSCLC) and other solid tumor indications (Robert 2013; Dranoff 2013; Sznol 2013).[47,16,52] Limited clinical data also indicate activity of anti-PD 1 antibody therapy in patients with hematologic malignancies (Brody 2011; Shi 2013)[7,50] suggesting a very broad clinical potential for specific immune check point inhibitors (Robert 2013; Sznol 2013).[47,52] Clinical studies are underway to further investigate the efficacy of PD-1 immune check-point inhibition in hematologic malignancies (Armand 2013).[3]

Pre-clinical data obtained in relevant tumor models as well as early clinical data indicate that due to the different mode-of-action, anti-proliferative therapies targeting oncogenic signal-transduction pathways can be safely combined with antibody-mediated PD-1 immune-checkpoint blockade (Sznol 2013).[52] More importantly, based on the different onset of clinical activity, which is often early with signal-transduction inhibitors and frequently delayed with immune-checkpoint inhibitors, these treatments may ultimately complement one another, leading to a more pronounced anti-tumor activity in sensitive tumor indications (Sznol 2013).[52]

The current study is designed to explore the safety, pharmacokinetic, and pharmacodynamic profile of a novel treatment regimen combining ibrutinib administered on a daily oral schedule with nivolumab administered intravenously every 2 weeks. The aim of the Phase 1 portion of the study (Part A) is to establish the recommended phase 2 dose (RP2D) for the combination in subjects with relapsed or refractory B-cell NHL. In the Phase 2a portion of the study (Part B), subjects with hematologic malignancies, for which ibrutinib or nivolumab may be considered to have single-agent activity, will be enrolled into 3 expansion cohorts. The purpose of the Phase 2a portion is to generate additional safety data and to explore the efficacy of this novel combination regimen. The expansion cohorts will include subjects with either advanced CLL/SLL harboring a deletion 17p or 11q deletion (Cohort B1), FL (Cohort B2), DLBCL (Cohort B3), or Richter syndrome (Cohort B4).

1.2. Ibrutinib

Ibrutinib or 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl) -1H-pyrazolo[3,4 d] pyrimidin-1-yl]-1-piperidin-1-yl]prop-2-en-1-one, is a small molecule tyrosine kinase inhibitor with a molecular weight of 440.50 g/mole (anhydrous basis).

1.2.1. Non-clinical Ibrutinib Data

Ibrutinib binds covalently to a cysteine residue (Cys-481) in the active kinase domain of BTK, thus potently inhibiting its enzymatic activity. BTK is a critical part of the B-cell receptor (BCR) signaling pathway, which is implicated in the pathogenesis of B-cell malignancies. In cellular signal transduction assays, ibrutinib inhibited the autophosphorylation of BTK, the phosphorylation of the physiological downstream substrate, phospholipase-Cγ (PLCγ), and the phosphorylation of the further downstream extracellular signal-regulated kinase (ERK). In addition, ibrutinib has in vitro activity against other selected members of the closely related Tec and Src/Ab1 family kinases. The 50% growth inhibition (GI_{50}) values for BTK and other selected kinases are listed in Table 3. Of note, while covalent binding of ibrutinib to BTK and the structurally related interleukin-2-inducible T-cell kinase (ITK) has been demonstrated, it can be hypothesized that based on the specific molecular interaction (ie binding to a Cys-481 residue), ibrutinib binds covalently to a majority of its target kinases.

Table 3: Median IC_{50} Values of Ibrutinib Toward Selected Tec and Src/Ab1 Family Kinases

Kinase[a]	Median IC_{50} (nM)	N[b]	Selectivity for BTK[c]
Btk*	0.39	7	1.0
ErbB4/HER4*	0.64	2	1.6
Blk*	0.94	2	2.4
Bmx/Etk*	1.10	2	2.8
Fgr	2.86	2	7.3
Txk*	2.87	1	7.4
Lck	3.49	4	9.0
Yes/YES1	3.94	2	10
Tec*	5.49	2	14
Csk	6.17	2	16
EGFR*	7.8	6	20
Brk	10.10	2	26
Itk*	11.70	3	30
Hck	16.98	2	44
ErbB2/HER2*	21.57	2	55
JAK3*	21.90	3	56

[a] Kinases labeled with an asterisk (*) have a cysteine in the active site representing a possible target for covalent binding with ibrutinib.
[b] Number of independent assays from which median IC_{50} values were calculated.
[c] Selectivity ratios were calculated using non-rounded values.

Ibrutinib inhibits the growth of a subset of B-cell lymphoma-derived cell lines in vitro, with GI_{50} values ranging from 0.1 to 5.5 µM. In addition, in vitro efficacy was also observed in proliferation assays conducted with selected cell lines derived from breast, head and neck, islet cell, and NSCLC (unpublished data). Moreover, ibrutinib inhibits the growth of B-cell-lymphoma tumor in mouse xenograft models and reduces naturally occurring non-Hodgkin's lymphoma (NHL) tumors in dogs. In vivo efficacy has also been observed in ErbB2/HER-2 overexpressing breast and gastric cancer xenograft models as well as NSCLC models expressing epidermal growth factor receptor (EGFR)-activating mutations (unpublished data).

1.2.2. Clinical Safety of Ibrutinib

As outlined in detail in the Investigator's Brochure, safety data are available for subjects who have received ibrutinib either as monotherapy or in combination therapy regimens. Discontinuation of ibrutinib treatment due to AEs has been infrequent and was most commonly associated with complications of disease progression or infectious events.

General safety - Monotherapy

Among subjects receiving ibrutinib as monotherapy in nonrandomized studies (N=1061), the most frequently reported treatment-emergent adverse events (>10%) were:

- diarrhea
- fatigue
- nausea
- cough
- anemia

The most frequently reported nonhematologic Grade 3 or 4 adverse events (>2%) were pneumonia, fatigue, hypertension, and atrial fibrillation.

The most commonly reported hematologic Grade 3 or 4 adverse events (>5%) were neutropenia, thrombocytopenia, and anemia.

The most frequently reported SAEs (any grade) that were considered related to ibrutinib were pneumonia, atrial fibrillation, and febrile neutropenia.

General safety – Combination Therapy

In subjects (n=136) treated with ibrutinib in combination with standard chemo/immunotherapy, the most frequently reported treatment-emergent adverse events (>20%) were:

- diarrhea
- nausea
- neutropenia
- fatigue
- peripheral sensory neuropathy
- upper respiratory tract infection
- vomiting
- anemia
- thrombocytopenia

The most frequently reported nonhematologic Grade 3 or 4 adverse events (>4%) were pneumonia, diarrhea, cellulitis, and urinary tract infection.

The most commonly reported hematologic Grade 3 or 4 adverse events (>4%) were neutropenia, febrile neutropenia, thrombocytopenia, and anemia.

The most frequently reported serious adverse events that were considered related to ibrutinib (note: some of these events were also reported as related to other study drug) were febrile neutropenia, pneumonia, cellulitis, and hypotension.

Adverse events of clinical concern

Bleeding-related events: There have been reports of hemorrhagic events in patients treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events including gastrointestinal bleeding, intracranial hemorrhage, and hematuria.

Lymphocytosis and Leukostasis: Reversible increase of lymphocyte counts (≥ 50% from baseline and absolute count > 5,000/µl) often associated with reduction of lymphadenopathy have been observed during the first weeks of ibrutinib therapy (median onset: 1.1 weeks; median resolution: 8 weeks). There were isolated cases of leukostasis reported in patients treated with ibrutinib. A high number of circulating lymphocytes (> 400000/mcL) may confer increased risk.

Infections: Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Isolated cases of JC virus reactivation resulting in progressive multifocal encephalopathy (PML) have been observed and resulted in death. Two cases in subjects with relapsed CLL have been reported. One case occurred after multiple prior rituximab regimens and less than one year after the last dose of rituximab and high dose steroid administration. The second case occurred during concomitant administration of rituximab, bendamustine and ibrutinib. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (reference Section 8.10).

Diarrhea: Diarrhea is the most frequently reported nonhematologic adverse event with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe, and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal adverse events and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged, ibrutinib treatment should be modified as directed in the protocol.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anemia) were reported in patients treated with ibrutinib.

Cardiac events: Atrial fibrillation and atrial flutter have been reported in patients treated with ibrutinib, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. There is no evidence of QT prolongation with increasing doses of ibrutinib.

Other malignancies: Other malignancies, most frequently skin cancers (18/357 subjects or 5%), have occurred in patients treated with ibrutinib.

Rash: Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Rash occurred at a higher rate in the ibrutinib arm than in the ofatumumab arm in a randomized, comparator-controlled study, Study 1112. Most rashes were mild to moderate in severity. One case of Stevens-Johnson Syndrome (SJS), with a fatal outcome, was reported in a subject with CLL. The subject received ibrutinib (420 mg/day) and was also receiving various antibiotics and antigout medication (allopurinol) known to be associated with SJS.

Tumor lysis syndrome: TLS has been reported with ibrutinib therapy.

1.2.3. Clinical Pharmacology Data

In vitro preclinical data show that ibrutinib is metabolized primarily by CYP3A. Its absolute bioavailability was 2.9% and highly variable, as determined in a study in 8 healthy subjects (PCI-32765CLL1011). The interaction with a strong CYP3A inhibitor was determined in Study PCI-32765CLL1002, an open-label drug-drug interaction study in 18 healthy men, in which ibrutinib was administered alone at a 120 mg dose or in combination with ketoconazole at a 40 mg dose. Results demonstrated that ketoconazole, a strong CYP3A4 inhibitor, increased ibrutinib exposure (maximum observed plasma concentration [C_{max}] and area under the plasma concentration versus time curve from time zero to the time corresponding to the last quantifiable concentration [$AUC_{0\text{-}last}$]) by 29- and 24-fold, respectively. The maximal observed ibrutinib exposure (AUC) was ≤ 2-fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Guidance on concomitant use of ibrutinib with CYP3A inhibitors or inducers is provided in Attachment 8.

1.2.4. Clinical Efficacy of Ibrutinib

The clinical benefit of ibrutinib was first demonstrated in a Phase 1 dose-escalation study of ibrutinib in subjects with recurrent B-cell lymphomas with ORRs ranging from 85.7% in subjects with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL) to 33.3% in subjects with diffuse large B-cell lymphoma (DLBCL). These findings were further demonstrated in subsequent Phase 2 studies in subjects with previously treated MCL or CLL/SLL, and a randomized, comparator-controlled Phase 3 pivotal study in subjects with previously treated CLL/SLL. Activity was also demonstrated in other histologies (follicular lymphoma, Waldenström's macroglobulinemia, marginal zone lymphoma, multiple myeloma) and with combination therapy (fludarabine, cyclophosphamide, rituximab; bendamustine + rituximab; and ofatumumab).

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

In the Phase 2 study PCYC-1102-CA, subjects with relapsed or refractory or treatment-naïve CLL/SLL were treated with 420 mg or 840 mg daily continuously until disease progression or until the subject could no longer tolerate the treatment. Ibrutinib produced an overall response rate of 78.4% in 51 subjects with relapsed/refractory disease. Responses were rapid (median of 1.8 months) and durable. Objective responses appeared independent of poor-risk factors including cytogenetics such as deletion of the short arm of chromosome 17 ie, del(17p13.1) or deletion of the long arm of chromosome 11 ie, del(11q21-q23). At Month 24, the proportion of subjects treated with the 420 mg/day dose who were alive and progression-free was 82.3%, and the overall survival rate was 89.6%. The 840 mg dose level did not appear to improve efficacy. Therefore, 420 mg daily dose was chosen as the recommended dose for further development in CLL/SLL.

An analysis of long-term follow-up in subjects with CLL/SLL from the Phase 2 Study 1102 and the 1103 extension study showed that efficacy was sustained over time. Overall response rate (ORR) (per IRC assessment) was 83.9% in treatment-naïve subjects and 76.2% in previously treated subjects. The ORR when including PR-L (per IRC assessment) was 90.3% and 79.2%, respectively. At 30 months, the PFS rate was 96.3% for treatment-naïve subjects and 68.4% for previously treated subjects.

In a Phase 3 randomized, comparator-controlled, pivotal study in subjects with CLL/SLL (Study 1112), ibrutinib improved efficacy outcomes in subjects with previously treated CLL/SLL compared to that ofatumumab. Analysis of PFS (per the Independent Review Committee [IRC]) demonstrated a statistically significant reduction in the risk of disease progression or death in the ibrutinib arm compared to the ofatumumab arm (HR=0.215, $p<0.0001$). Analysis of OS showed that subjects in the ibrutinib arm had a statistically significant reduction in the risk of death (HR=0.434, $p=0.0049$). The ORR (IRC assessment) was significantly higher ($p<0.0001$) for subjects in the ibrutinib arm (42.6%) than those in the ofatumumab arm (4.1%). The ORR, when including partial response with lymphocytosis (PR-L) (per IRC assessment), was 62.6% for the ibrutinib arm and 4.1% for the ofatumumab arm ($p<0.0001$).

Follicular Lymphoma (FL)

In the Phase I study PCYC-04573, sixteen subjects enrolled to the dose-escalation phase had a diagnosis of FL (Fowler 2012).[18] Eleven subjects received ibrutinib at doses that achieved full BTK occupancy (ie, 2.5 mg/kg or higher). Median time on ibrutinib was 7 months (0 to 29 months) and time to response was 4.6 months. Overall response rate was 54.5% (3 CRs, 2 PRs). Responses were durable (median response duration: 12.3 months). Three patients had chemorefractory disease; 2 of these patients responded (1 CR, 1 PR). On the basis of these very encouraging early efficacy data the single-arm, multicenter Phase 2 study PCI-32765FLR2002 was initiated.

Diffuse Large B-cell Lymphoma (DLBCL)

In a Phase 2 study of ibrutinib in subjects with DLBCL (Study 1106), an interim analysis of response in DLBCL showed an ORR of 25% (CR 9% and PR 16%) with a median time on study of 3.9 months. An analysis of response by molecular subtype demonstrated that subjects with molecular subtype activated B-cell-like (ABC) (non-germinal-cell B-cell-like [GCB]) had an ORR of 41% (CR 17% and PR 24%) and among subjects with the GCB subtype, ORR was 5% (CR 0% and PR 5%).

Richter syndrome

Only limited data are currently available on the clinical efficacy of ibrutinib in subjects with Richter syndrome defined as the transformation of CLL into an aggressive lymphoma, most commonly DLBCL (Parikh 2014)[45]. In an investigator-initiated study, 4 subjects with Richter syndrome, all heavily pretreated, received ibrutinib as single-agent therapy (Tsang 2015)[56] of which 3 subjects were evaluable for disease response. The median duration of ibrutinib therapy was 6.1 months (range of 2.8 to 10.8 months). One subject achieved a CR while 2 subjects experienced PR. All 3 subjects reported an improvement of constitutional symptoms. The authors concluded that ibrutinib has potential as a novel therapeutic approach for patients with Richter syndrome (Tsang 2015)[56]. In a Phase 1b/2 study, 3 subjects with Richter syndrome received a combination regimen of ibrutinib and the anti-CD20 antibody ofatumumab (Jaglowski 2015)[28]. Of these, 2 subjects experienced disease stabilization for 471 and 137 days respectively, while 1 subject achieved a PR which lasted for 4.6 months (Jaglowski 2015)[28].

1.3. Nivolumab

Nivolumab (BMS-936558) is a fully human, IgG4 (κ) isotype, mAb that binds PD-1.

1.3.1. Non-clinical Nivolumab Data

Preclinical animal models of tumors have shown that blockade by PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1-positive tumors as well as in tumors that are negative for the expression of PD-L1(Blank 2004, Dong 2002, Hirano 2005, Iwai 2002, Iwai 2005, Strome 2003).[5,14,25,26,27,51] This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative

tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies, including NHL (Azuma 2008, Konishi 2004, Ohigashi 2005, Thompson 2005a, Thompson 2004, Thompson 2005b, Tsushima 2006).[4,31,41,54,53,55,57] PD-L1 expressed by tumor cells, including FL and DLBCL, has been shown to enhance apoptosis of activated tumors. Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells (Andorsky 2011, Chen 2013, Nishimura and Honjo 2001).[1,11,36] Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by immunohistochemistry (IHC)) of PD-L1 may permit immune evasion by tumors.

Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell costimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA (Freeman 2000).[20] PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems (Carter 2002, Latchman 2001).[9,32] PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region (Chemnitz 2004, Sheppard 2004).[10,49] PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells. Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus (Nishimura 1999, Nishimura 2001, Okazaki 2003).[37,38,42] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes (Blazar 2003, Salama 2003).[6,48] Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Preclinical animal models of tumors have shown that blockade by PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1-positive tumors as well as in tumors that are negative for the expression of PD-L1 (Blank 2004, Dong 2002, Hirano 2005, Iwai 2002, Iwai 2005, Strome 2003).[5,14,25,26,27,51]

Interestingly, recent clinical studies have also demonstrated influence of PD-L1/PD1 interaction as a major mechanism for immune evasion in CLL in preclinical models. Aberrant PD-L1 expression in myeloid cells was shown to be a major culprit for immune deregulation in a murine CLL model (Hanna 2014).[24] Furthermore, it is also demonstrated that T cell and myeloid cell immune defects can be generated in the wild type mice by the adoptive transfer (AT) of murine CLL cells. The group also demonstrated in vivo that early PD-L1 blockade in CLL results in restoration of effector function of the myeloid and T cells translating to effective anti-tumor response. These findings are highly suggestive that targeting PD-L1/PD1 can be a novel strategy in CLL, especially with novel drugs in the high risk group of CLL where the efficacy of novel drugs have been demonstrated to be inferior.

1.3.2. Clinical Safety of Nivolumab

A total of 39 and 306 subjects with selected recurrent or treatment-refractory malignancies have been treated in a completed Phase 1 single-dose study (MDX1106-01) and a completed Phase 1 multidose study (CA209003 or MDX1106-03), respectively. As the safety profile from MDX1106-03 to date is consistent with that observed for MDX1106-01, only data from the larger and more recent study (MDX1106-03 or CA209003) is presented here.

A review of the safety data by tumor type (RCC, NSCLC, metastatic castration-resistant prostate cancer, colorectal cancer, and melanoma) did not show any clinically meaningful differences in the proportion of subjects with AEs noted across tumor types.

Overall, the safety profile of nivolumab monotherapy was generally manageable and was consistent with the mechanism of action of nivolumab. No MTD was reached at doses tested up to 10 mg/kg Q2W. The nature, frequency, and severity of any causality and treatment-related safety events were similar across tumor types.

The following were the key safety findings for the subjects in MDX1106-03 or CA209003

- Drug-related AEs (any grade) were reported in 75.2%, and drug-related Grade 3-4 AEs were reported in 17.0% of subjects.
- The most frequently reported drug-related AE was fatigue (28.1%). Other drug-related AEs Grade 3-4 reported in more than 2 subjects were pneumonitis (1.3%), lymphopenia (1.3%), diarrhea (1.0%), abdominal pain (1.0%), CD4 lymphocytes decreased (1.0%), and hypophosphatemia (1.0%).
- The most frequently reported drug-related SAE was pneumonitis (7 subjects, 2.3%). Drug-related Grade 3-4 pneumonitis was reported in 4 (1.3%).
- The most frequently reported drug-related select AE categories (any grade) were skin (24.5%), GI (14.1%), and endocrine (9.5%).
- AEs belonging to the pulmonary and renal select AE categories were unexpected, drug-related toxicities associated with the use of nivolumab.
- AEs belonging to select AE categories were generally manageable and reversible with the use of immunosuppressants.

Deaths

The majority of the deaths were due to disease progression. Three subjects (1.0%) died due to study drug toxicity at the time of database lock; 2 out of 3 subjects died within 100 days of last dose of nivolumab, and 1 died > 100 days after the last dose of nivolumab. The reported causes of death for these 3 subjects were:

- Non-drug-related cardiopulmonary arrest due to complications from Grade 5 sepsis (drug-related)
- Drug-related sepsis
- Drug-related respiratory failure secondary to pneumonitis and progressive disease

After database lock for the final CSR, 2 subjects were reported to have died; both were subjects with NSCLC treated with 3-mg/kg nivolumab. The reported causes of death for these 2 subjects were:

- Drug-related pneumonitis
- Non-drug-related infection after experiencing drug-related Grade 3 pneumonitis

Although not considered to be the primary cause of death in all 5 subjects described above, pneumonitis was considered a contributory factor in each case.

Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported. 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.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the BMS-936558 (nivolumab) Investigator Brochure (IB).

Adverse Event Management Algorithms

Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, gastrointestinal, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and nephrotoxicity.

The algorithms recommended for utilization are contained in Section 8 of the protocol.

1.3.3. Clinical Efficacy of Nivolumab

In CA209003 (MDX1106-03), the clinical activity of nivolumab was demonstrated in various tumor types and across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg).

For monotherapy in NSCLC, the overall objective response rate was 17%; the most active doses were 3 mg/kg and 10 mg/kg. Only a single response was reported at 1 mg/kg. Responses were observed in subjects with NSCLC (both squamous and nonsquamous subtypes) with a median duration of response of 17 months. A summary of ORR, progression-free survival rate (PFSR), and overall survival (OS) rate for NSCLC subjects by histology is provided in the Investigator's Brochure.

For melanoma subjects who were administered nivolumab monotherapy Q2W at doses ranging from 0.1 mg/kg to 10 mg/kg, the ORR was 31% (N = 107). The majority of responses were durable and exceeded 6 months. A summary of ORR, PFSR, and OS rate for subjects with melanoma is provided in the Investigator's Brochure.

The ORR was 21% (N = 34) for RCC subjects who were administered nivolumab monotherapy Q2W at doses of 1 mg/kg or 10 mg/kg. The majority of responses were durable and exceeded 6 months. A summary of ORR, PFSR, and OS rate for subjects with RCC is provided in IB.

Results from a Phase I study including 29 patients with B-NHL showed activity of nivolumab in patients with relapsed DLBCL and FL (Lesokhin 2014).[33] The patients were heavily pretreated including prior autologous transplant and > 3 lines of prior chemotherapy. The total number of patients with DLBCL was 11, CR is reported in 1 (9%), PR in 3 (27%), and SD in 3 (27%) of patients with PFS of 24% at 24 weeks. The total number of patients with FL in the study was 11; CR was reported in 1 (10%), PR in 3 (30%), SD in 6 (60%) of patients with PFS of 24% at 24 weeks.

1.4. Overall Rationale for the Study

Unpublished data obtained in a model of A20 murine B-cell lymphoma tumors xenografted onto immune-competent BALB/C mice indicate a potent and synergistic anti-tumor efficacy of a combination treatment of ibrutinib and an antibody against the murine PD-1 ligand PD-L1. It is of importance that the enhanced anti-tumor efficacy of the ibrutinib and anti-PD-L1 antibody combination treatment was observed in a lymphoma model resistant to ibrutinib monotherapy.

These experimental data give rise to separate scientific hypotheses:

a. The PD-1/PD-L1 axis is a mechanism of intrinsic or acquired resistance to ibrutinib in tumors otherwise sensitive to its inhibitory activity and/or
b. Ibrutinib has immune-modulatory activity potentiating the anti-tumor activity of PD-1/PD-L1 immune checkpoint inhibition.

Recent data have shown that the tumor microenvironment plays an important role in the clinical course of the disease and the outcome of patients with NHL. Lymph nodes in patients with NHL contain not just malignant B cells but normal immune cells including T cells, intratumoral macrophages, monocytes, dendritic cells, and natural-killer cells (Ansell 2013).[2] Although this tumor microenvironment supports the growth and survival of malignant B cells, the malignant B cells also define the constitution of the tumor microenvironment. The composition of this microenvironment and the presence of specific immune cells have prognostic significance for patients with FL (Dave 2004; Richendollar 2011).[13,46] In addition, expression data obtained from biopsies of NHL patients indicate that malignant B cells modulate immune surveillance by driving the differentiation and function of intratumoral T cells (Ansell 2013).[2] Malignant B cells have been found to express multiple ligands responsible for inducing regulatory T cells (Treg cells) and suppressing intratumoral effector T cells.

Of particular interest is the interaction between the PD-L1, a member of the B7 family (B7-H1) of co-stimulatory molecules which is frequently over-expressed on malignant B-cells (Richendollar 2011)[46] and its cognate receptor PD-1, a member of the CD28 receptor family, expressed on activated, effector T-cells. In CLL, overexpression of both PD-1 and PD-L1 has been detected (Grzywnowicz 2012)[22] while PD-1 expression appears to be of importance in FL (Carreras 2009).[8] The PD-1/PD-L1 interaction between malignant B-cells and effector T-cells results in a suppression of the cellular immune response directed against the malignant B-cells. This suppression occurs through decreased induction of various cytokines, decreased expression of T-cell survival proteins, impaired cytotoxic capabilities and most through a direct inhibition of the proliferation of activated T-cells (Gzywnowicz 2012).[22] PD-1/PD-L1 thereby attenuates the T-cell response, leading to “T-cell exhaustion” and the maintenance of peripheral immune tolerance in lymphoma (Chen 2013; McClanahan 2012).[11,34]

Ibrutinib has Immunomodulatory Activity in Lymphoma

Bruton’s tyrosine kinase, the molecular target of ibrutinib, is a member of the non-receptor TEC-kinase family, which also includes the structurally homologous tyrosine-protein kinase (TEC), the IL2-inducible T cell kinase (ITK) and the endothelial/epithelial tyrosine kinase BMX/ETK.

Intracellular tyrosine kinase is active in T-cell malignancies and has been linked to tumor immune evasion and survival through its critical role in T-helper type 2 (Th2) cell differentiation (Dubovsky 2013).[17] Recent experimental data demonstrate that ibrutinib, in addition to blocking BTK, also irreversibly binds to ITK. In relevant in vitro and in vivo models, ibrutinib inhibited ITK-mediated downstream activation of T-cell receptor (TCR) stimulation in Th2 polarized CD4-T helper cells. Th1 cells were not affected possibly because they express a kinase that can compensate for loss of ITK signaling. Consistent with these findings, a blocking of Th2 cell activation and dominance of a Th1-profile was induced upon ibrutinib exposure of CD4 T-cell populations isolated from CLL patients in vitro (Dubovsky 2013).[17] Similarly, a Th-1 skewed cytokine pattern was detected in clinical samples obtained from ibrutinib treated CLL patients (Dubovsky 2013; Niemann 2013).[17,35] It has been proposed that the stimulation and expansion of

Th2 polarized CD4 T-cells constitutes a specific molecular mechanism of immune evasion observed in solid tumors and leukemias (Dubovsky 2013).[17]

This identification of ibrutinib as an inhibitor of ITK-mediated TCR signaling in Th2-polarized CD4-T-cells may address and reverse this specific molecular mechanism. In consequence, the therapeutic activity of ibrutinib as a single-agent immunomodulator or in combination with T-cell based cancer immunotherapies (Dubovsky 2013)[17] including antibodies targeting the PD-1/PD-L1 axis should be explored.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

Part A (Dose Optimization Cohorts): The primary objective of Part A is to determine whether ibrutinib and nivolumab can be safely combined and to establish the recommended Phase 2 dose (RP2D) for this combination in subjects with hematological disorders.

Part B (Expansion Cohorts): The primary objective of Part B is to determine the preliminary activity of the ibrutinib/nivolumab combination regimen in subjects with relapsed/refractory CLL/SLL and poor prognosis (deletion 17p or deletion 11q), relapsed/refractory FL, relapsed/refractory DLBCL, or Richter syndrome in comparison to historical results.

Secondary Objectives

The secondary objectives are:

- To evaluate the safety profile of the ibrutinib and nivolumab combination regimen
- To assess overall response rate (ORR), duration of response, duration of stable disease, progression-free survival rate at 1 year, and overall survival at 1 year of the ibrutinib and nivolumab combination regimen
- To characterize and explore the pharmacokinetic profile of ibrutinib and nivolumab compared with existing single-agent treatment data; and the potential relationships between ibrutinib and nivolumab metrics of exposure with relevant clinical or biomarker information (Part A and B)

Exploratory Objectives

- To characterize the molecular effects of the ibrutinib and nivolumab combination regimen on tumor cells and the immune response; and identify biomarkers of response or resistance to the combination
- To evaluate the immunogenicity of nivolumab

2.2. Hypothesis

In Part A (Dose Optimizations), the study will evaluate and describe whether ibrutinib, administered at daily oral doses between 420 mg and up to 560 mg, can be safely combined with

nivolumab 3 mg/kg administered IV every 2 weeks such that ≤30% of subjects with CLL/SLL or NHL experience a DLT.

In Part B (Dose Expansion; Cohorts B1, B2, B3, and B4), the study will evaluate and describe whether ibrutinib combined with nivolumab can result in an overall response rate of more than 20%.

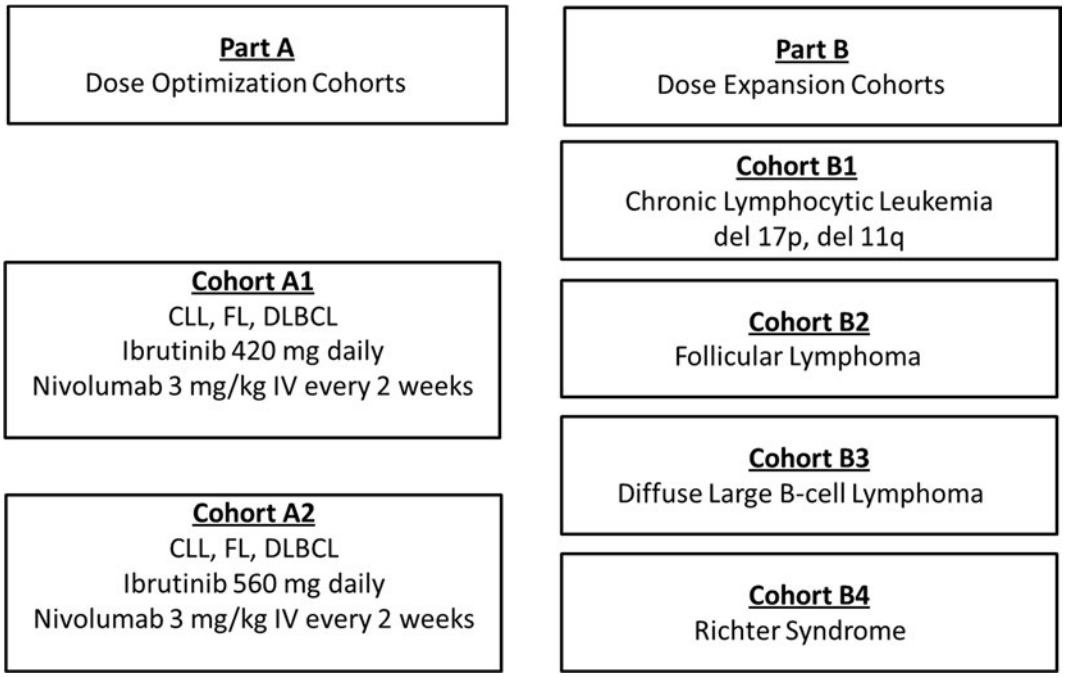
3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is an open-label Phase 1/2a study, which consists of Part A (Dose Optimization Cohorts) and Part B (Expansion Cohorts). In the context of this study, a treatment 'cycle' is defined as a course of treatment of 14 days starting with the intravenous administration of nivolumab on Day 1 of each cycle along with once daily oral intake of ibrutinib on all days.

It is anticipated that approximately 158 subjects will be enrolled throughout the study; up to 18 subjects in the dose optimization period (Part A) and approximately 140 subjects during the expansion period (Part B).

Figure 1: Study Design Overview



Part A (Dose Optimization Cohorts) is designed to determine the RP2D for the combination based on safety, pharmacokinetic, and pharmacodynamic assessments. Two dose optimization cohorts will be explored, applying the Modified Toxicity Probability Interval (mTPI) design to evaluate subjects with relapsed/refractory CLL/SLL or B-NHL.

Part B (Dose Expansion Cohorts) will be open for enrollment after the RP2D is determined in Part A. In Part B, further assessment of the RP2D will be explored in 3 subject populations to further evaluate the safety and clinical activity of ibrutinib in combination with nivolumab. During the expansion period, subjects with CLL/SLL with del 17p or 11q (Cohort B1), FL (Cohort B2), DLBCL (Cohort B3), and Richter syndrome (Cohort B4) will be enrolled. Approximately 35 subjects will be enrolled in each of the expansion cohorts. The subjects will be treated at the RP2D level selected to further assess the safety, pharmacokinetics, pharmacodynamics, pharmacogenomics, and activity of the combination.

Part A and Part B of the study will be divided into 3 periods:

- Screening Period: pretreatment screening period of up to 28 days before enrollment
- Treatment Period: open-label treatment period ending at the End-of-Treatment Visit
- Follow-up Period: posttreatment follow-up period until the end of study (when all subjects have completed the End-of-Treatment Visit). Refer to Table 1 for a complete list of procedures to be performed during the study.

During the Treatment Period, all subjects will be closely monitored for safety. Toxicities (AEs and laboratory abnormalities) will be evaluated and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4).

Preliminary activity and clinical response will be evaluated every 5 cycles for the first 15 months, thereafter every 12 cycles until progression, at the end of treatment, and every 6 months in follow-up, in the event the subject has not progressed while on therapy and did not start subsequent therapy. Lymphoma including Richter syndrome will be evaluated for response according to the Lugano Classification (Cheson 2014);[12] CLL will be evaluated according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) (Hallek 2008), see Section 10.1.[23] Identical methodology should be used for disease assessment at baseline and throughout the course of the study.

Subjects will be assigned to receive oral daily doses of ibrutinib (self-administered) in combination with intravenous nivolumab on Day 1 of each cycle starting from Dose Level 1 (Table 4). In Cohort B1 and B2, to assess pharmacokinetic and pharmacodynamic characteristics of ibrutinib monotherapy, ibrutinib will be given at the recommended Phase 2 dose over an initial period of seven days prior to the first dose of nivolumab (Day -7 to -1). Refer to the Dosage and Administration schedule (Section 6) for further detail. Protocol specified treatment modifications for ibrutinib and nivolumab will be implemented as necessary (Section 6.4). Additional dosing or schedule changes for ibrutinib or nivolumab can be requested by the Study Evaluation Team (SET) based on preliminary clinical data during dose optimization. Doses may be held or reduced based on the severity of and the recovery from previous toxicity. Dose re-escalation may be allowed after

recovery from toxicity following consultation with the Sponsor. In Part A intra-patient dose escalation may be requested by the investigator and discussed with the medical monitor once a subsequent higher combination dose has been declared acceptable by the SET for subjects who (1) have received at least 4 cycles of combination treatment at the assigned dose level, and (2) have not experienced a DLT or therapy-related SAE. Subjects whose dose has been escalated will not be considered for the safety evaluation in the subsequent dose level and the determination of the RP2D.

The study treatment will be continued until:

- documented confirmed disease progression (except in cases of clinical improvement/stability; see Section 11.2)
- unacceptable toxicity
- intercurrent illness that prevents further administration of treatment
- subject refuses further therapy
- investigator's decision to withdraw the subject
- pregnancy of the subject
- noncompliance with study treatment or procedure requirements

The average duration of study therapy is expected to be approximately 6 months.

In Part A of the study, a SET, consisting of the principal investigators, sponsor medical monitors, and the sponsor's clinical pharmacologist, or their designees, and the sponsor statistician will review all available data upon completion of the first 2 treatment cycles (ie, 4 weeks of study therapy) for all subjects at each dose cohort to determine DLTs, if dose escalation is acceptable, and ultimately to determine the recommended Phase 2 dose.

In Part B of the study, all subjects in each cohort may be evaluated for response by the SET and additional functional representatives from Janssen, as applicable. The SET along with optional other internal members may review safety on an ad hoc basis, and efficacy endpoints (including but not limited to ORR).

The End-of-Treatment Visit will occur within 30 days after the last dose of ibrutinib or nivolumab, whichever treatment occurred last.

During the Follow-up Period, long-term safety, survival status, disease progression, subsequent anticancer therapy, and occurrence of other primary malignancy data will be collected as well as anti-drug antibody (ADA) sampling if applicable. During the Follow-up Period, subjects should be followed for safety up to 30 days after the last dose of ibrutinib or 100 days after the last nivolumab infusion, whichever is later. The safety follow-up includes adverse event reporting and laboratory assessments (at the first follow-up). Thereafter, follow-up visits will be completed approximately every 3 months until death or the end of study. Subjects who have developed treatment-related Grade 3 or higher toxicity at the end of treatment will be assessed until recovery to Grade ≤1 or baseline, deemed irreversible, or until end of study. Adverse events leading to

discontinuation will be followed up until resolution or return to baseline, or end of study, whichever occur first.

The primary analysis of the study will be performed 6 months after the last subject has received the first dose of study medication, or earlier if that subject discontinues study therapy. After the cutoff for primary analysis, subjects who are receiving study treatment can continue treatment per protocol until progression, unacceptable toxicity, withdrawal of consent, or other reason as listed in Section 11.2. End of study is defined as the last subject who completed the EOT Treatment assessment.

After the clinical cutoff at a minimum the following data will be collected on eCRF: SAEs and AEs Grade ≥3, laboratory assessments (Grade ≥3 or clinically significant), efficacy, survival status, and treatment administration. Data collected from the primary analysis until end of study will be summarized in a clinical study report addendum.

3.2. Study Design Rationale

Rationale for Ibrutinib Dose and Regimen Selection

The recommended monotherapy dose and schedule for ibrutinib is:

- CLL/SLL: 420 mg given orally per day
- B-cell malignancies including follicular lymphoma and Richter syndrome: 560 mg given orally per day

The starting dose of ibrutinib will be the recommended monotherapy dose for CLL (420 mg). Given that the mechanism of action of ibrutinib and nivolumab are distinct, as well as the fact that both compounds have very favorable safety profiles, combination treatment with both compounds together is not expected to result in additive toxicity.

In Part A, cohorts of 420 mg/day and 560 mg/day of ibrutinib will be explored as outlined in Section 6. Upon recommendation of the SET and in agreement with the study sponsor, additional dose cohorts and alternative dosing schedules may be explored. However, the starting dose of ibrutinib will not be increased above 560 mg/day or decreased below 420 mg/day.

Rationale for Nivolumab Dose and Regimen Selection

Single-dose pharmacokinetics (PK) of nivolumab were evaluated in 39 subjects with multiple tumor types in study MDX1106-01 in the dose range of 0.3 to 10 mg/kg. The median T_{max} across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab is linear in the range of 0.3 to 10 mg/kg with dose proportional increase in C_{max} and $AUC_{(inf)}$ with low to moderate inter-subject variability observed at each dose level (ie, coefficient of variation (CV) ranging from 7 to 45%). Geometric mean clearance (CL) after a single intravenous (IV) dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution (Vz) varied between 83 to 113 mL/kg across doses. The mean terminal t_{half} of nivolumab is 17 to 25 days, which is consistent with the half-life of endogenous IgG4, indicating that the elimination

mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied.

A preliminary population PK model was developed by nonlinear mixed effect modeling using data from 350 subjects from MDX1106-01, MDX1106-02 and CA209003. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weight, and hence is appropriate for future clinical trials of nivolumab. Clearance of nivolumab is similar in all tumor types studied and is independent of dose range studied (0.1 to 10 mg/kg).

The dose and schedule selected for evaluation in this study, 3 mg/kg every 2 weeks, has been evaluated in solid tumors in the ongoing CA209003 study. Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no MTD was identified. Anti-tumor activity was observed at dose levels ranging from 1 to 10 mg/kg in melanoma, NSCLC, and RCC, as well as at dose levels of 0.1 and 0.3 mg/kg in melanoma. The antitumor activity of nivolumab tended to increase with dose, as did the incidence of SAEs. The anti-tumor activity of nivolumab in RCC was investigated at dose levels of 1 and 10 mg/kg, with the higher activity observed at 10 mg/kg. The observed anti-tumor activity in melanoma, and NSCLC was highest at 3 mg/kg, suggesting that anti-tumor activity approaches a plateau at dose levels of 3 mg/kg and above. The ongoing CA209039 study in hematologic malignancies includes 2 dose levels: 1 mg/kg and 3 mg/kg every 2 weeks. The 3 mg/kg dose level has been shown to be adequately tolerable and this dose has been expanded in select tumor types for further evaluation. Objective responses have been observed at both dose levels in study CA209039. Based upon the totality of available data across the program, a dose of 3 mg/kg every 2 weeks is selected as the dose anticipated to maximize the benefit-risk ratio.

Refer to the current BMS-936558 (nivolumab) Investigator Brochure for additional information.

Rationale for Subject Population

In this study patients will be enrolled (1) whose tumor is amenable to therapy with either ibrutinib and/or nivolumab based on efficacy data generated in previous studies but (2) who are in need of effective therapies. This includes patients with CLL/SLL whose disease presents with the recurrent chromosomal abnormalities del 17p or del 11q which are associated with rapid progression, poor response to chemotherapy, and shorter survival. Similarly, the particular populations of patients with relapsed and/or refractory FL, DLBCL or Richter syndrome selected for this study are in need of additional effective therapeutic options.

Rationale for Pharmacokinetic Analysis

Pharmacokinetics of ibrutinib and nivolumab when administered in combination will be evaluated in this study as specified in Table 2.

Rationale for Anti-Nivolumab Antibodies

The emergence of antibodies against nivolumab has been low, but as this is a new combination treatment regimen the development of anti-drug antibodies will be monitored. Anti-nivolumab antibodies will be evaluated in the study as specified in Table 2.

Rationale for Pharmacodynamic and Biomarker Analysis

This study is based on the hypothesis that the combination of these 2 drugs will potentiate each other, and therefore the biomarker and pharmacodynamics evaluations are important in understanding the mechanism of action of the combination. Biomarker sampling during the course of the study will help to examine changes in the immune system and in the tumor. Fine needle aspirates from lymph nodes will be collected at baseline and at C3D1 in selected cohorts, in order to examine the possible changes in the T-cell subtypes within the tumor microenvironment, as these may differ from the peripheral blood compartment. Tumor biopsies obtained at screening and post-progression may contribute to understanding the mechanism of resistance to drug treatment and may aid in the development of biomarkers to identify subjects in need of additional or modified therapy.

Peripheral blood and tumor tissue will be collected prior to therapy and at selected timepoints on treatment as outlined in Table 1 and Table 2 unless restricted by local requirements.

3.3. Safety Monitoring

The function and composition of the SET is described in Section 12.7. Upon completion of the first 2 cycles for all subjects in each dose cohort, there will be a review of all available safety data (at the time of decision-making) by the SET.

Decisions on DLT determination, dose escalations or de-escalations, changes in the timing of pharmacokinetic/ADA or pharmacodynamic sampling, exploration of alternative schedule(s), cycle duration, or other study conduct recommendations, will be made by the SET and documented in a SET decision document and distributed to investigators. The Institutional Review Board (IRB) will be notified before implementation of any SET decision, if required. This document will be provided in the sponsor's instruction manual and retained in the study master file and in the study center's files.

3.3.1. Evaluation of Dose-limiting Toxicity

Dose-limiting toxicities will be assessed during the first and second treatment cycle (ie, first 28 days of study therapy) starting with the first day of combination therapy (ibrutinib and nivolumab). Only AEs that occur during this time period, and after a subject has received at least one dose of nivolumab and one dose of ibrutinib, will be considered for DLT. Adverse events fulfilling the criteria of DLT need to be reviewed and confirmed by the SET. In addition, all AEs occurring while a subject is participating in the study will be reviewed by the SET as part of the continued safety evaluation (Section 12.7). All subjects in Part A will be evaluated for DLTs. Subjects who are not evaluable for DLT may be replaced; the safety profile of subjects who were replaced will be included in the SET review.

The following AEs considered to have at least a possible relationship to study therapy by the investigators and confirmed by the SET will qualify as DLTs:

- Any AE that requires discontinuation of study drug (see also Section 6.4.3, Table 8, and Table 9)
- Any AE that results in a delay of dosing for more than 2 weeks within the DLT period
- Central nervous system hemorrhage of any grade.

3.3.2. Dose Optimization – Part A

During the dose optimization stage, subjects will be entered in each dose level based on a modified Toxicity Probability Interval (mTPI) method (Ji and Wang 2013).[30] The size of the group can be changed as indicated by safety. A minimum of 6 and up to 9 subjects may be treated in each dose cohort.

After the last subject in each group has completed treatment in the DLT observation period, the SET will evaluate all safety and pharmacokinetic data and make the decision whether to escalate, stay at the current dose or de-escalate the dose cohort with the second group of subjects treated, based on the guidelines outlined in Attachment 1.

3.3.3. Dose Expansion - Part B (Recommended Phase 2 Dose)

The dose for the expansion part of this study (Part B) will be determined based on either:

- The highest planned dose (ibrutinib 560 mg daily + nivolumab 3 mg/kg every 2 weeks) in the dose optimization schedule
- A lower dose determined by the SET following a review of all available safety and efficacy data from the dose optimization part of the study (Part A)

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days before administration of the study drug. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 12.3, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study. In addition, subjects enrolled to each cohort must satisfy cohort-specific criteria as listed below.

1. Subject must be 18 years of age or older.

2. Eastern Cooperative Oncology Group (ECOG) performance status grade 0, 1, or 2 (Attachment 4)

3. Adequate bone marrow, liver, and renal function defined as:
   - Absolute neutrophil count (ANC) ≥1.5 x 10^9cells/L (ie, ≥1500/ µL).
   - Platelets ≥75 x 10^9cells/L (ie, ≥75,000/µL) without transfusion support within 7 days prior to test.
   - Hemoglobin ≥8g/dL without transfusion support within 7 days prior to test
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN)
   - Total bilirubin <2mg/dL (unless due to Gilbert's syndrome).
   - Creatinine determined by serum creatinine levels ≤1.5 x ULN or a calculated creatinine clearance of ≥50 mL/min/1.73 m^2 (see Attachment 2 for Modified Diet in Renal Disease [MDRD] formula)

4. Women of childbearing potential (WOCBP) and men who are sexually active with a woman of childbearing potential must be practicing a highly effective method of birth control during and after the study, consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies. These restrictions apply for the duration of treatment with study drug plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post nivolumab treatment or 3 months post ibrutinib completion (whichever occurs last).

5. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug plus 90 days (duration of sperm turnover) for a total of 31 weeks post nivolumab treatment or 12 weeks post ibrutinib completion (whichever occurs last).

6. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

7. Men must agree to not donate sperm during or for a total of 31 weeks post nivolumab treatment or 3 months post ibrutinib completion (whichever occurs last) and a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during or for a total of 23 weeks post nivolumab treatment or 3 months post ibrutinib completion (whichever occurs last).

8. Must sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study.

9. Subject is able to swallow capsules and is able to take or tolerate oral medications on a continuous basis.

4.1.1. Additional Inclusion Criteria for Part A: Dose Optimization Cohorts

10. Histologically confirmed and documented B-NHL (FL and DLBCL) or CLL/SLL (deletion 17p or deletion 11q as determined by FISH analysis) as conducted by the local lab.

11. Relapsed or refractory disease after at least 1 but not more than 4 lines of prior, systemic therapy.

12. Measurable disease defined as:

- **B-NHL**: At least 1 measurable site of disease according to the Lugano Classification (see Attachment 6.2). The site of disease must be greater than 1.5 cm in the long axis regardless of short axis measurement or greater than 1.0 cm in the short axis regardless of long axis measurement, and clearly measurable in 2 perpendicular dimensions

- **CLL**: ≥5,000 leukemia cells/µL

4.1.2. Additional Inclusion Criteria for Part B: Expansion Cohorts

Cohort B1: Chronic Lymphocytic Leukemia/or Small Lymphocytic Lymphoma

13. Criterion modified per amendment

13.1 Diagnosis of CLL requires the following:

- Lymphocytosis with ≥5,000 B-lymphocytes/µL.
- Prolymphocytes ≤55% of total blood lymphocytes.

14. Criterion modified per amendment

14.1 Diagnosis of SLL requires measurable disease

15. Criterion modified per amendment

15.1 CLL/SLL with deletion of short arm of chromosome 17 ie, del(17p13.1) or deletion of the long arm of chromosome 11 ie, del(11q21-q23) as defined by del (17p) or del (11q) in ≥20% of cells based on interphase FISH and documented in subject's record prior to start of study therapy.

16. Criterion modified per amendment

16.1 Relapsed or refractory CLL/SLL following at least 1 prior line of systemic therapy (consisting of at least 2 cycles of a chemotherapy containing regimen)

17. Active disease meeting at least 1 of the criteria outlined by the IWCLL (Attachment 6.1):

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia or thrombocytopenia
- Massive (ie, at least 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
- Massive nodes (ie, at least 10 cm in longest diameter), progressive, or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time (LDT) of less than 6 months (which may be extrapolated). Lymphocyte doubling time can be obtained by linear regression extrapolation of absolute lymphocyte count (ALC) obtained at intervals of 2 weeks over an observation period of 2 to 3 months. For patients with initial ALC of less than 30 x 10^9/L (30,000/μL), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded
- Constitutional symptoms, defined as 1 or more of the following disease-related symptoms or signs:
  - Unintentional weight loss of >10% within the previous 6 months prior to screening
  - Significant fatigue (inability to work or perform usual activities)
  - Fevers higher than 100.5°F or 38.0°C for 2 or more weeks without evidence of infection; or
  - Night sweats for more than 1 month without evidence of infection

Cohort B2: Follicular Lymphoma

18. Histologically confirmed initial diagnosis of FL of Grade 1, 2, or 3a according to World Health Organization (WHO) criteria without pathological evidence of transformation.

19. Relapsed or refractory disease defined as:

    - Previously treated with at least 2 prior lines of therapy using different treatment regimens and separated by disease progression or relapse
    - Received or not eligible for prior treatment with a CD20 antibody combination chemotherapy regimen

20. At least 1 measurable site of disease according to the Lugano Classification (Attachment 6.2).

Cohort B3: Diffuse Large B-cell Lymphoma

21. Histologically-confirmed DLBCL.

22. Previously treated with a standard, rituximab and anthracycline-containing systemic chemotherapy regimen (such as R-CHOP), or

    Received or not eligible for high-dose chemotherapy and autologous stem cell transplantation (HD-ASCT)

    Of Note: Additional, prior salvage chemotherapy regimens are allowed

23. At least 1 measurable site of disease based on the Revised Response Criteria for Malignant Lymphoma (Attachment 6.2).

Cohort B4: Richter Syndrome

24. Histologically-confirmed Richter syndrome defined as transformation of CLL or SLL into an aggressive lymphoma

25. Previously treated with at least one line of standard, systemic chemotherapy or not eligible for standard therapy

26. At least 1 measurable site of disease based on the Revised Response Criteria for Malignant Lymphoma (Attachment 6.2).

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

1. Major surgery within 4 weeks of the first dose of ibrutinib.

2. Diagnosed or treated for malignancy other than the indication under study except for:

   - Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of ibrutinib or nivolumab
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   - Adequately treated cervical carcinoma in situ without evidence of disease

3. History of stroke or intracranial hemorrhage within 6 months prior to the first dose of ibrutinib.

4. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon).

5. Requires treatment with strong CYP3A inhibitors (Attachment 8).

6 Criterion modified per amendment 1

   6.1 Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification (Attachment 3), or congenital long QT syndrome, or QT interval corrected for heart rate, using Fridericia formula[21] (QTcF) at Screening >470 ms.

7.
   - Subjects with a history of Human Immunodeficiency Virus (HIV)
   - Subjects who have active infection or are chronic carriers of Hepatitis B or Hepatitis C.

8. History of disallowed therapies:

   - Prior treatment/exposure with ibrutinib or other BTK inhibitor
   - Prior exposure to anti-PD1, anti-PDL1, anti-PD-L2, anti-CD137 or anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) antibody
   - Concurrent enrollment in another therapeutic investigational clinical study

9. Prior anti-tumor therapy including (all times measured prior to start of study therapy)
   - nitrosoureas within 6 weeks
   - chemotherapy within 3 weeks
   - therapeutic antibodies within 4 weeks
   - radio- or toxin-immunoconjugates within 10 weeks
   - radiation therapy within 3 weeks
   - investigational agents within 3 weeks
   - carmustine (BCNU) ≥ 1000 mg received as part of pre-transplant conditioning regimen
   - chest radiation ≤ 24 weeks prior to first dose of the study drug
10. Criterion revised per Amendment 4

    10.1 Known central nervous system (CNS) lymphoma.

11. Received an allogeneic hematopoietic SCT.

12. Any uncontrolled active systemic infection, active non-infectious pneumonitis, evidence or history of interstitial lung disease, or any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.

13. Any active autoimmune disease or a documented history of autoimmune disease (excluded/exception to the rule: subjects with vitiligo or resolved childhood asthma/atopy, type I diabetes mellitus, subjects with hypothyroidisms stable on hormone replacement, Sjorgen's syndrome, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger).

14. Any syndrome that requires systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Of note: Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents, are permitted in the absence of active autoimmune disease.

15. A woman who is pregnant or breast feeding.

16. Subject is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records)

after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, the subject may be re-evaluated at a later timepoint to assess eligibility.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Requires surgery or invasive procedures:

    - For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib and nivolumab should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes
    - For minor procedures (such as a central line placement, tissue or needle biopsy, thoracentesis, or paracentesis) ibrutinib and nivolumab should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures
    - For emergency procedures, ibrutinib and nivolumab should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure
2. Foods or beverages containing grapefruit or Seville oranges should be avoided, as these contain certain ingredients that inhibit CYP3A.

3. Prohibited medications and precautions with concomitant medications as detailed in Section 9.

5. TREATMENT ALLOCATION AND BLINDING

Randomization will not be used in this study. Subjects will be sequentially assigned to treatment. No blinding is required as this is an open-label study. All subjects enrolled will receive open-label treatment with ibrutinib capsules and nivolumab infusions.

6. DOSAGE AND ADMINISTRATION

6.1. Study Treatment Administration

For the purposes of this study, ‘study drug’ or ‘study therapy’ refers to both ibrutinib and/or nivolumab. All dosing information must be recorded in the Dosage Administration page of the eCRF. A treatment and study design scheme is provided in Figure 1.

The duration of each treatment cycle is 14 days. Day 1 or start day of a new cycle is triggered by the infusion of nivolumab. The cycle duration may be changed based on decision by the SET (Section 3.3). Study drugs will be administered until disease progression or unacceptable toxicity,

whichever occurs first. On days when both drugs will be administered, the sequence of administration will be nivolumab IV followed by oral ibrutinib.

6.1.1. Dose Optimization Cohorts

Two pre-defined, escalating dose combinations will be tested in subjects with hematologic malignancies in Part A. Additional cohorts may be added in order to explore alternative dose combinations (Section 3.3). The decision to add additional cohorts will be made upon recommendation of the SET and in agreement with the study sponsor.

Dose escalation above 560 mg for ibrutinib is not permitted. Administration of each study drug in Part A is described in Table 4.

Table 4: Ibrutinib and Nivolumab Dose Levels: Part A (Dose Optimization Cohorts)

Dosing Cohort[a]	Ibrutinib (daily oral administration)[b]	Nivolumab (IV infusion Day 1 every cycle)[b]
A1	420 mg	3 mg/kg
A2	560 mg[c]	3 mg/kg

[a] Additional dosing schedules may be explored if recommended by SET and agreed upon by sponsor.
[b] On days that both drugs will be administered, the sequence of administration will be nivolumab IV followed by oral ibrutinib
[c] The maximum dose of ibrutinib will not exceed 560 mg. The dose of nivolumab will be 3 mg/kg.

6.1.2. Dosing Schedule

Study drugs will be administered as described below in Table 5.

Table 5: Ibrutinib and Nivolumab Dosing Schedule

	Ibrutinib Run-in, Day -7 to Day 1	Cycle 1 Day 1	Cycle 2 Day 1	Day 1 of every cycle, Cycle 3 and all subsequent cycles
		DLT Determinative Period		
Part A, Cohort A1 and A2				
Ibrutinib		<----------continuous dosing---------->		
Nivolumab[a]		3 mg/kg	3 mg/kg	3 mg/kg
Part B, Cohort B1 and B2				
Ibrutinib	<----------continuous dosing---------->			
Nivolumab[a]		3 mg/kg	3 mg/kg	3 mg/kg
Part B, Cohort B3 and B4				
Ibrutinib		<----------continuous dosing---------->		
Nivolumab[a]		3 mg/kg	3 mg/kg	3 mg/kg

[a] Nivolumab administered first followed by ibrutinib.

Ibrutinib Run-in Period: In Cohort B1 and B2, to assess pharmacokinetic and pharmacodynamic characteristics of ibrutinib monotherapy, ibrutinib will be given at the recommended Phase 2 dose over an initial period of seven days prior to the first dose of nivolumab (Day -7 to -1).

Nivolumab will be administered on Day 1 of each 14-day treatment cycle.

DLT Period: DLT will be documented over the first 2 cycles beginning with the first concomitant administration of ibrutinib and nivolumab on Day 1 of Cycle 1.

6.2. Ibrutinib Administration

Ibrutinib capsules will be self-administered once daily. Ibrutinib should be taken around the same time each day with approximately 240 mL of water (ie, 8 ounces). The capsules should be swallowed whole and should not be opened, broken, or chewed.

Ibrutinib dosing is outlined in Table 6. On the study days scheduled for serial pharmacokinetic sampling of ibrutinib, the investigator or designee will supervise administration of ibrutinib and the exact time of administration will be recorded in the eCRF or in the laboratory requisition form. On other days, ibrutinib will be self-administered, and a subject diary card will be used to record administration and aid compliance with ibrutinib administration compliance.

Table 6: Ibrutinib Dosing

Ibrutinib (prescribed dose)	Number of Capsules (of 140mg)
280 mg	2 x 1
420 mg	3 x 1
560 mg	4 x 1

If a dose of study drug is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose. The missed dose will be recorded on the eCRF and must be returned to the site at the next scheduled visit

Subjects should avoid consuming food and beverages containing grapefruit or Seville oranges for the duration of the study due to cytochrome (CYP) 3A inhibition.

Sufficient study drug required for treatment until the next visit will be dispensed. Unused ibrutinib dispensed during previous visits must be returned and drug accountability records will be updated. Returned capsules must be discarded and may not be re-used in this study or outside the study. Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol. Storage instructions are provided in the Site Investigational Product Procedures Manual (SIPPM).

There is limited data on the effects of ibrutinib overdose. No Maximum Tolerated Dose was reached in the Phase 1 study in which patients received up to 12.5 mg/kg/day (1,400 mg). There is no specific antidote for ibrutinib. Subjects who ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

6.3. Nivolumab Administration

Eligible subjects will receive treatment with nivolumab at a dose of 3 mg/kg given as a 60-minute IV infusion on Day 1 of every 14-day cycle. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.

There are no premedications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to guidelines provided in Section 8.11.

Subjects may receive nivolumab infusions with no less than 12 days between doses and no more than 3 days after the scheduled dosing date. A dose given after the 3-day window is considered a dose delay. A maximum delay of 42 days between doses is allowed.

6.3.1. Interactive Web Response System

Drug supply for nivolumab will be managed through IWRS at least for Part B.

For IWRS, the requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject. Details on the use of IWRS will be provided in the IWRS manual.

The subject should receive their dose of study medication within 1 day of vial assignment following call to IWRS.

6.4. Dose Modifications

Treatment modifications may be made to both ibrutinib and nivolumab. Changes in dose apply only to ibrutinib. Nivolumab will be given at fixed dose, treatment modifications are primarily dose delays.

Adjustments of study drug dose should be overseen by the principal- or sub-investigator(s) unless an immediate safety risk is apparent. The dose adjustments are applicable to all subsequent treatment cycles.

Note: The recommendation to discontinue study therapy applies to both study drugs. If appropriate and after consultation with the Sponsor, subjects may receive ibrutinib alone. Following implementation of amendment 7, treatment with single agent ibrutinib will be discontinued and an End of Trial visit will be performed for patients not scheduled to rollover into long-term extension study CAN3001. Patients scheduled to roll over into Study CAN3001 will continue treatment.

6.4.1. Ibrutinib Dose Modifications

Dose reduction levels for ibrutinib, if required in Section 6.4.3, are listed in Table 7.

Table 7: Dose Reduction for Ibrutinib

Ibrutinib Dose	420 mg	560 mg
Dose Level -1	280 mg	420 mg
Dose Level -2	NA	280 mg

Ibrutinib dose reductions below 280 mg per day are not permitted and may require discontinuation of study therapy after consultation with the Sponsor. Dose escalations of ibrutinib to the previous higher dose may be considered after consultation with the Sponsor.

In Part A, intra-patient dose escalation may be requested by the investigator and discussed with the medical monitor once a subsequent higher combination dose has been declared acceptable by the SET for subjects who (1) have received at least 4 cycles of combination treatment at the assigned dose level, and (2) have not experienced a DLT or therapy-related SAE. Subjects whose dose has been escalated will not be considered for the safety evaluation in the subsequent dose level and the determination of the RP2D.

6.4.2. Nivolumab Dose Modifications

There will be no dose escalations or reductions of nivolumab allowed. Dose delay is the primary method for managing nivolumab-related toxicities.

6.4.3. Guidelines for Dose Modification

Guidelines for dose modifications following occurrence of general toxicities are listed in Table 8. For immune-related adverse events and other events of clinical interest, guidelines for dose modification are listed in Table 9.

Of note: **Guidelines for the management of immune-related adverse events and adverse events of clinical interest** are provided in Section 8.

If the criterion to resume treatment is met, the subject should restart treatment at the next scheduled timepoint per protocol.

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in the protocol.

Table 8: Dose Adjustments for Related Non-hematologic and Related Hematologic Toxicities

Adverse Event	CTCAE Grade	Ibrutinib and Nivolumab *
*For immune-related toxicities please see Table 9. Additional information may also be found in the latest IB sections (appendix on nivolumab adverse event management, algorithm management sections) Recommendations for the management of immune-related adverse events and adverse events of clinical interest are provided in Section 8.		
Non-Hematologic Toxicity [see separate table for Immune-related toxicities and adverse events of clinical interest)		
General	**Grade 1**	Continue therapy.
	Grade 2	Persistent[a] ≤12 weeks: Continue study therapy. Persistent[a] >12 weeks: Discontinue study therapy
	Grade 3	**1st event:** Hold study therapy until resolution to Grade ≤ 1 • Persistent[a] ≤12 weeks: Resume at same dose • Persistent[a] >12 weeks: Discontinue study therapy **2nd event:** discontinue study therapy
	Grade 4	Discontinue study therapy
Fatigue	**Grade 1**	Continue study therapy
	Grade 2	Persistent[a] ≤12 weeks: Continue study therapy. Persistent[a] >12 weeks: Discontinue study therapy
	Grade 3	**1st event:** Hold study therapy until resolution to Grade ≤ 1 • Persistent[a] ≤12 weeks: Resume at same dose • Persistent[a] >12 weeks: Discontinue study therapy **2nd event:** Discontinue study therapy
Alopecia	**Grade 1**	Continue study therapy
	Grade 2	Persistent[a] ≤12 weeks: Continue study therapy. Persistent[a] >12 weeks: Discontinue study therapy
Hemorrhagic events	**Grade 1**	Continue study therapy; contact sponsor.
	Grade 2	Persistent[a] ≤12 weeks: Continue study therapy; contact sponsor.. Persistent[a] >12 weeks: Discontinue study therapy
	Grade 3	**1st event:** Hold study therapy until resolution to Grade ≤ 1 • Persistent[a] ≤12 weeks: Resume at same dose • Persistent[a] >12 weeks: Discontinue study therapy **2nd event:** discontinue study therapy
	Grade 4 or SAE of bleeding any grade	Discontinue study therapy
Lab values	**Grade 1**	Continue study therapy and monitor in close intervals.
	Grade 2	Persistent[a] ≤12 weeks: Continue study therapy. Persistent[a] >12 weeks: Discontinue study therapy
	Grade 3	**1st event:** Hold study therapy until resolution to baseline or Grade ≤1 • Persistent[a] ≤12 weeks: Resume at same dose • Persistent[a] >12 weeks: Discontinue study therapy **2nd event:** Discontinue study therapy
	Grade 4	Discontinue study therapy
Adverse Event	**CTCAE Grade**	**Ibrutinib and Nivolumab ***
Hematologic Toxicity		
Neutropenia	**Grade 1-3**	Continue study therapy; supportive therapy as per local/institutional guidelines
	Grade 4	Supportive therapy as per local/institutional guidelines (hematology assessments twice weekly up to recovery). Any event not recovering to Grade ≤1 within 7 days (±2 days): discontinue study therapy.

Table 8: Dose Adjustments for Related Non-hematologic and Related Hematologic Toxicities

		For events recovering to Grade ≤1 within 7 days (±2 days):		
		Toxicity Occurrence	**Starting dose = 560 mg**	**Starting Dose = 420 mg**
		First	Restart at 560 mg	Restart at 420 mg
		Second	Restart at 420 mg	Restart at 280 mg
		Third	Restart at 280 mg	Discontinue study therapy
Febrile neutropenia	**Grade 3**	Hold study therapy until resolution; supportive therapy as per local/institutional guidelines. Any event not recovering to ≤ Grade 1 within 7 days: discontinue study therapy. For events recovering to Grade ≤1 within 7 days:		
		Toxicity Occurrence	**Starting dose = 560 mg**	**Starting Dose = 420 mg**
		First	Restart at 560 mg	Restart at 420 mg
		Second	Restart at 420 mg	Restart at 280 mg
		Third	Restart at 280 mg	Discontinue study therapy
	Grade 4	Discontinue study therapy.		
Thrombocytopenia	**Grade 1-3**	Continue study therapy; supportive therapy as per local/institutional guidelines		
	Grade 4	Hold study therapy until baseline or Grade 1; supportive therapy as per local/institutional guidelines:		
		Toxicity Occurrence	**Starting dose = 560 mg**	**Starting Dose = 420 mg**
		First	Restart at 560 mg	Restart at 420 mg
		Second	Restart at 420 mg	Restart at 280 mg
		Third	Restart at 280 mg	Discontinue study therapy

a. Persistent treatment-related adverse event that do not recover to Grade ≤1 within 12 weeks after last dose of nivolumab.

Table 9: Dose Adjustments for Immune-related Adverse Events

Recommendations for the management of immune-related adverse events and adverse events of clinical interest are provided in Section 8.		
Adverse Event	**CTCAE Grade**	**Ibrutinib and Nivolumab**
Immune-related AE (irAE)	**Section 8: Guidelines for Management of Immune Related Adverse Events**	
	Grade 1	Continue study therapy.
	Grade 2	Consider hold study therapy until resolution to Grade ≤1 Persistent[a] ≤12 weeks: Continue therapy at same dose and schedule. Persistent[a] >12 weeks: Discontinue study therapy
	Grade 3	**1st event:** hold study therapy, resume only after discussion/agreement with sponsor and resolution to Grade ≤1 **2nd event:** discontinue study therapy
	Grade 4	Discontinue study therapy.
Recommendations for the management of immune-related adverse events and adverse events of clinical interest are provided in Section 8.		
Adverse Event	**CTCAE Grade**	**Ibrutinib and Nivolumab**
Infusion Reaction	**Section 8.11(Table 18): Management of Nivolumab Related Infusion Reactions**	
	Grade 1	Continue study therapy.
	Grade 2	Hold study therapy until resolution to Grade ≤1 **1st event:** resume at same dose and schedule. **2nd event** (despite pre-medication, antihistamines, non-steroidal anti-inflammatory drugs, corticosteroids, bronchodilators, IV fluids;

Table 8: Dose Adjustments for Related Non-hematologic and Related Hematologic Toxicities

		prophylactic medications indicated for <24 hours]): discontinue study therapy.
	Grade 3 and 4	Discontinue study therapy.
Enterocolitis or diarrhea	**Section 8.1. (Table 10): Management of Gastrointestinal Adverse Events**	
	Grade 1	Continue study therapy.
	Grade 2	**1st event:** Hold until resolution to Grade ≤1. • **Improvement to ≤ Grade1:** Resume study therapy at same dose and schedule. • **Worsening or persistence >3 days from day of onset despite oral steroid treatment:** discontinue study therapy. **2nd event:** discontinue study therapy
	Grade 3 and 4	Discontinue study therapy.
Renal/Creatinine	**Section 8.5. (Table 14): Management of Renal Adverse Events**	
	Grade 1	Continue study therapy.
	Grade 2 and 3	**1st event:** Hold until resolution to Grade ≤1. • **Improvement to ≤Grade1:** Resume study therapy at same dose and schedule. • **Worsening or persistence >7 days from day of onset:** Discontinue study therapy. **2nd event:** discontinue study therapy
	Grade 4	Discontinue study therapy.
Pneumonitis	**Section 8.7. (Table 16): Management of Pulmonary Adverse Events**	
	Grade 1	Consider holding study therapy. **Improvement to baseline:** resume dosing. **Worsening or persistence >7 days from day of onset:** hold study therapy and treat as Grade 2.
	Grade 2	Hold study therapy until resolution to Grade ≤ 1 **Improvement to Grade ≤ 1 within 2 weeks:** resume dosing. **Persistence for >2 weeks from day of onset:** Discontinue study therapy.
	Grade 3 and 4	Discontinue study therapy.
Hepatic alteration	**Section 8.2. (Table 11): Management of Hepatic Adverse Events**	
	Grade 1	Continue study therapy. **Worsening or persistence >7 days from day of onset:** hold study therapy and treat as Grade 2.
	Grade 2	Hold study therapy until resolution to Grade ≤ 1 . **Improvement to Grade ≤1 within 2 weeks:** resume at same dose and schedule. **Persistence for >2 weeks from day of onset:** Discontinue study therapy.
	Grade 3 and 4	Discontinue study therapy.
AST/ALT and Bilirubin	**Section 8.2. (Table 11): Management of Hepatic Adverse Events**	
	Grade 1	Continue study therapy. If worsens treat as Grade 3.
	Grade 2	Consider hold study treatment until resolution to Grade ≤ 1 Persistent[a] ≤12 weeks: Continue therapy at same dose and schedule. Persistent[a] >12 weeks: Discontinue study therapy
	Grade 3 and 4	Discontinue study therapy
Recommendations for the management of immune-related adverse events and adverse events of clinical interest are provided in Section 8.		
Adverse Event	**CTCAE Grade**	**Ibrutinib and Nivolumab**
Endocrinopathy	**Section 8.3. (Table 12): Management of Endocrinopathies**	
	Asymptomatic	Continue study therapy.
	Symptomatic	**Abnormal lab values and pituitary MRI scan:** Hold study therapy until improvement to Grade ≤1; resume at same dose and schedule.

Table 8: Dose Adjustments for Related Non-hematologic and Related Hematologic Toxicities

	Suspicion of adrenal crisis	Hold study therapy; discontinue study therapy if no improvement after adrenal hormone replacement.
Rash	**Section 8.4. (Table 13): Management of Rash**	
	Grade 1	Continue study therapy.
	Grade 2	Persistent[a] ≤12 weeks: Continue therapy at same dose and schedule. Persistent[a] >12 weeks: Discontinue study therapy
	Grade 3	Hold study therapy until resolution to ≤ Grade 1 Persistent >2 weeks or inability to reduce steroid ≤10 mg/day >12 weeks: Discontinue study therapy. Discontinue if Grade 3 rash recurs.
	Grade 4	Discontinue study therapy
Neurological	**Section 8.6. (Table 15): Management of Neurological Adverse Events**	
	Grade 1	Continue study therapy.
	Grade 2	Hold study therapy until improvement to Grade ≤1; then resume study therapy.
	Grade 3 and 4	Discontinue study therapy.
Uveitis or visual complaints	**Section 8.8. (Table 17): Management of Uveitis and Visual Complaints**	
	Grade 1	Consider hold study therapy.
	Grade 2	Hold study therapy until improvement to Grade ≤1; then resume study therapy. **Persistence for >2 weeks from day of onset despite symptomatic treatment:** Discontinue study therapy.
	Grade 3 and 4	Discontinue study therapy.

a. Persistent treatment-related adverse event that do not recover to Grade ≤1 within 12 weeks after last dose of nivolumab.

7. TREATMENT COMPLIANCE

Upon termination of the study, or at the request of the sponsor or its designee, the pharmacist must return the study drugs to the sponsor or its designee, after all drug supplies have been accounted for, unless it is destroyed at the site as agreed upon by both the sponsor and the site. Instructions regarding accountability for study drug are provided in the Site Investigational Product Procedures Manual.

Ibrutinib and nivolumab are to be prescribed only by the principal investigator or a qualified physician listed as a sub-investigator on required forms. Records should be kept on the study drug accountability form provided by the sponsor or its designee. Dispensing of ibrutinib and the administration of nivolumab must be recorded in the subject's source documents. The study drug may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

Drug supplies for each subject will be inventoried and accounted for throughout the study.

Subjects will be provided with a diary card to record ibrutinib intake at home. Site personnel are to instruct the subject to bring the ibrutinib diary card and any unused ibrutinib to the site at the beginning of each treatment cycle to check ibrutinib dosing compliance. Instructions for proper self-administration of ibrutinib and storage conditions will be provided. Precautions associated with the use of ibrutinib and prohibited concomitant medications will be reviewed. Site staff will

provide additional instruction to reeducate any subject who is not compliant with the ibrutinib schedule.

Nivolumab will be administered as an IV infusion by qualified study-site personnel and the details of each administration will be recorded in the eCRF; date, start and stop time of the infusions, dose, volume infused.

The site pharmacist will maintain a log of all nivolumab vials prepared for infusion and administration and all ibrutinib dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

8. GUIDELINES FOR MANAGEMENT OF IMMUNE RELATED ADVERSE EVENTS AND ADVERSE EVENTS OF CLINICAL INTEREST

Therapy with immuno-oncology agents such as nivolumab can lead to specific immune-related adverse events (eg, irAE) that differ in nature, severity and duration as compared to adverse events caused by agents with a different mode of action. A detailed summary of the irAE observed in the nivolumab program can be found in the IB.

Early recognition and management of these irAE may mitigate more severe toxicity. However, differential diagnoses including non-inflammatory etiologies as well as the impact of the underlying malignant disease and/or concomitant medication should be evaluated according to standard medical practice.

Management algorithms have been developed to assist investigators in assessing and managing specific irAE and additional details on these management algorithms can be found in the Nivolumab Investigator's Brochure, Appendix 2 "Management Algorithms".

Of note: **Guidelines for dose modifications** are provided in Section 6.4.3.

8.1. Gastrointestinal AE

Diarrhea and colitis have been observed in subjects receiving nivolumab. Early recognition and treatment of diarrhea and colitis are critical to their management. Subjects should be advised to seek immediate medical evaluation if they develop new-onset diarrhea, blood in stool, or severe abdominal pain or if they have worsening of baseline diarrhea. In subjects with pre-existing diverticulosis and/or diverticulitis receiving concomitant medication with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics together with nivolumab, diverticular perforation has been observed.

Table 10: Management of Immune-related Gastrointestinal Adverse Events

Management and Follow-up of Immune-related Gastrointestinal Adverse Events. For dose modification guidelines, refer to Table 8 and Table 9.	
Grade 1	Symptomatic treatment according to institutional standards Close monitoring; instruct subject to report worsening immediately and treat as Grade ≥2
Grade 2	**≤5 days:** Symptomatic treatment according to institutional standards **>5 days or recurrence:** 0.5–1.0 mg/kg/d methylprednisolone.; consider prophylactic antibiotics; **Persistence or worsening despite steroids >3 days:** treat as Grade 3/4 **Improvement to ≤Grade 1:** taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, resume study therapy per protocol
Grade 3-4	**Immediately:** 1.0–2.0 mg/kg/d methylprednisolone IV; consider prophylactic antibiotics and lower endoscopy **Persistence >3 days or recurrence:** add infliximab 5 mg/kg (if no contraindication such as perforation or sepsis) **Improvement to ≤Grade 2 within ≤3 days:** taper steroids over at least 1 month
General	The oral corticosteroid equivalent of the recommended IV dose may be considered for ambulatory patients; the lower bioavailability of oral corticosteroids need to be considered. Clinical caution should be exercised, for subjects receiving concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, be vigilant for signs and symptoms of potential perforation, especially in subjects with known diverticular disease. Narcotics should be used with caution as pain medicines may mask the signs of colonic perforation.

8.2. Hepatic Adverse Events

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, drug-induced-liver-injuries (DILI) have been observed following treatment with nivolumab. Early recognition and treatment of elevated LFTs and DILI are critical to their management. Subjects should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Physicians should monitor LFTs prior to each nivolumab treatment.

Table 11: Management of Immune-related Hepatic Adverse Events

Management and Follow-up of Immune-related Hepatic Adverse Events. For dose modification guidelines, refer to Table 8 and Table 9.	
Grade 1	Monitor LFTs as outlined in the protocol; **Worsening:** treat as Grade ≥2
Grade 2	Monitor every 3 days; **Returning to baseline:** resume per protocol monitoring **LFT elevation >5 days or worsening:** 0.5 – 1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics **LFT return to ≤Grade 1 or baseline:** taper steroids over at least 1 month; resume routine monitoring and resume study treatment per protocol
Grade 3-4	Monitor every ≤2 days; **Immediately:** 1. –2.0 mg/kg/d methylprednisolone IV or IV equivalent; start prophylactic antibiotics; consult gastroenterologist **Persistence >3 days or recurrence:** add mycophenolate mofetil 1g bid; if no response within ≤ 5 days consider other immunosuppressants per local guidelines **LFT return to Grade 2:** stop immunosuppressants **LFT return to ≤Grade 1:** taper steroids over at least 1 month

8.3. Endocrinopathies

Endocrinopathies have been observed following treatment with nivolumab. The events have typically been identified through either routine periodic monitoring of specific laboratories (eg, TSH) or as part of a work-up for associated symptoms (eg, fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (eg, hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Subjects should be advised to seek medical evaluation if they notice new-onset fatigue, lightheadedness, or difficulty with vision or if baseline fatigue worsens.

Table 12: Management of Endocrinopathies

Management and Follow-up of Endocrinopathies. For dose modification guidelines, refer to Table 8 and Table 9.	
Asymptomatic TSH elevation	**TSH <0.5xLLN** or **TSH >2xULN** or **TSH >ULN in two subsequent measurements:** include free T4 assessment prior/after subsequent cycles of nivolumab; consider endocrinology consult
Symptomatic endocrinopathy	Assess endocrine function with appropriate laboratory testing; consider pituitary MRI scan **With abnormal lab and pituitary scan:** 1.0–2.0 mg/kg/d methylprednisolone IV or oral equivalent; initiate appropriate hormone therapy; consider prophylactic antibiotics **Clinical and laboratory improvement:** taper steroids over at least 1 month; patients with adrenal insufficiency may need to continue steroids with mineralcorticoid component **Without abnormal lab and pituitary scan but symptoms persist:** repeat laboratory assessments in ≤3 weeks and MRI in 4 weeks
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	Rule out sepsis **Immediately:** initiate/stress dose of IV steroids with mineralocorticoid activity; fluids IV; consult endocrinologist **Adrenal crisis ruled out:** treat as symptomatic endocrinopathy
General	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. The lower bioavailability of oral corticosteroids need to be considered

8.4. Rash

Rash and pruritus were the most common skin irAEs observed following treatment with nivolumab. The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without intervention. Subjects should be advised to seek medical evaluation if they notice new-onset rash. Early consultation with a dermatology specialist and a biopsy should be considered if there is uncertainty as to the cause of the rash, or if there is any unusual appearance or clinical feature associated with it. A case of toxic epidermal necrolysis occurred in a subject receiving concomitant prophylaxis with trimethoprim/sulfamethoxazole, and it is possible that the initial rash was due to a sulfa-hypersensitivity reaction that was eventually augmented by nivolumab. This case highlights the possible importance of discontinuing other suspected drugs in the management of rash.

Table 13: Management of Rash

Management and Follow-up of Rash. For dose modification guidelines, refer to Table 8 and Table 9.	
Grade 1-2	**Immediately:** Symptomatic therapy (eg, anti-histamines, topical steroids) **Persistence ≤2 weeks or recurrence:** consider skin biopsy; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics **Improvement to ≤Grade 1:** taper steroids over at least 1 month **Worsening to >Grade 2:** treat as Grade 3-4
Grade 3-4	**Immediately:** consult dermatologist; consider skin biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics **Improvement to ≤ Grade 1:** taper steroids over at least 1 month
General	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. The lower bioavailability of oral corticosteroids need to be considered

8.5. Renal Adverse Events

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with nivolumab. Physicians should monitor creatinine regularly.

Table 14: Management of Renal Adverse Events

Management and Follow-up of Renal Adverse Events. For dose modification guidelines, refer to Table 8 and Table 9.	
Grade 1	Monitor creatinine weekly **Creatinine returns to baseline:** continue monitoring per protocol **Creatinine increases:** treat as Grade ≥2
Grade 2-3	Monitor creatinine every ≤3 days **Immediately:** start 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics; consider renal biopsy **Improvement to ≤Grade 1:** taper steroids over at least 1 month **Persistence >7 days or worsening:** treat as Grade 4
Grade 4	Monitor creatinine daily **Immediately:** consult nephrologist; consider renal biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics **Improvement to ≤Grade 1:** taper steroids over at least 1 month
General	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. The lower bioavailability of oral corticosteroids need to be considered

8.6. Neurological Adverse Events

Neurological AEs have been uncommonly observed following treatment with nivolumab Neurological AEs can manifest as central abnormalities (eg, aseptic meningitis or encephalitis) or peripheral sensory/motor neuropathies (eg, Guillain-Barre Syndrome). The onset has been observed as early as after a single treatment. Early recognition and treatment of neurologic AEs is critical to their management. Subjects should be advised to seek medical evaluation if they notice impairment in motor function (eg, weakness), changes in sensation (eg, numbness), or symptoms suggestive of possible central nervous system abnormalities such as new headache or mental status changes.

Table 15: Management of Neurological Adverse Events

Management and Follow-up of Neurological Adverse Events. For dose modification guidelines, refer to Table 8 and Table 9.	
Grade 1	Monitor per protocol **Worsening:** treat as ≥Grade 2
Grade 2	**Immediately:** treat symptoms according to institutional standards; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent **Worsening:** treat as Grade 3-4
Grade 3-4	**Immediately:** consult neurologist; treat symptoms according to institutional standards; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; prophylactic antibiotics **Worsening or atypical presentation:** consider immunoglobulins IV (IVIG) or other immunosuppressive therapies according to institutional standards **Improvement to ≤ Grade 2:** taper steroids over at least 1 month
General	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. The lower bioavailability of oral corticosteroids need to be considered

8.7. Pulmonary AE

Pulmonary AEs including radiographic changes (eg, focal ground glass opacities and patchy infiltrates) indicative of drug-related pneumonitis have been observed in subjects receiving nivolumab. These pulmonary AEs were either asymptomatic or associated with symptoms such as dyspnea, cough, or fever. The initial occurrence of pulmonary AEs may be as early as after a single dose of nivolumab or delayed after prolonged therapy. Early recognition and treatment of pneumonitis is critical to its management. Subjects should be advised to seek medical evaluation promptly if they develop new-onset dyspnea, cough, or fever or if they have worsening of these baseline symptoms.

Table 16: Management of Pulmonary Adverse Events

Management and Follow-up of Pulmonary Adverse Events. For dose modification guidelines, refer to Table 8 and Table 9.	
Grade 1	Monitor for symptoms every 2-3 days; consider pulmonary and infectious-disease consult; re-image every 3 weeks **Worsening:** treat as ≥Grade 2
Grade 2	Monitor symptoms daily; re-image every 1-3 days; pulmonary and infectious-disease consultation; consider bronchoscopy and lung biopsy; consider hospitalization **Immediately:** start 1.0 mg/kg/d methylprednisolone IV or oral equivalent; prophylactic antibiotics **Persistence for 2 weeks or worsening:** treat as Grade 3-4 **Improvement to ≤ Grade 1 or baseline:** taper steroids over at least 1 month
Grade 3-4	Hospitalize; pulmonary and infectious-disease consult; consider bronchoscopy and lung biopsy **Immediately:** 2-4 mg/kg/d methylprednisolone or IV equivalent; add prophylactic antibiotics; **Persistence for 2 days or worsening:** add immunosuppression (eg, infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil) **Improvement to ≤ Grade 2:** taper steroids over at least 6 weeks
General	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. The lower bioavailability of oral corticosteroids need to be considered

8.8. Uveitis and Visual Complaints

Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (eg, uveitis) is an uncommon, but clinically important, event. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause.

Table 17: Management of Uveitis and Visual Complaints

Management and Follow-up of Uveitis and Visual Complaints. For dose modification guidelines, refer to Table 8 and Table 9.	
Grade 1	Thorough eye examination Topical corticosteroids should be considered Persisting despite topical steroids, treat as Grade 3-4
Grade 2	
Grade 3-4	Thorough eye examination Systemic corticosteroids

8.9. Lipase/Amylase Elevations

Asymptomatic elevations in lipase and amylase have been reported in nivolumab studies in which systemic monitoring was used. Very few subjects reported associated symptoms (eg, abdominal pain) or radiographic findings (eg, stranding) consistent with pancreatitis. Thus, there does not seem to be clinical significance to the elevated laboratory values. The recommended management of nivolumab-related elevated lipase/amylase values centers around close observation. Physicians should ensure that subjects have no associated symptoms consistent with pancreatitis, such as abdominal pain. Corticosteroids do not seem to alter the natural history of lipase/amylase elevations. Laboratory values tend to fluctuate on a day-to-day basis and eventually return to baseline or low grade levels over the course of weeks, whether or not subjects receive corticosteroids. Asymptomatic elevations should be monitored approximately weekly.

8.10. Infection

Subjects with a documented infectious complication should receive oral or intravenous antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

Usage of antimicrobial prophylaxis in accordance with standard practice (eg, American Society of Clinical Oncology guidelines [Flowers 2013][19]) is permitted and should be considered in subjects who are at increased risk for opportunistic infections.

8.11. Treatment of Nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Management of infusion reactions is provided in Table 18.

All CTCAE Grade 3 or 4 infusion reactions should be reported within 24 hours to the medical monitor and reported as an SAE if criteria are met.

Table 18: Management of Infusion Reactions

Management and Follow-up of Infusion Reactions. For dose modification guidelines, refer to Table 8 and Table 9.	
Grade 1	No intervention indicated; remain at bedside and monitor subject until recovery from symptoms, Consider diphenhydramine 50 mg or equivalent and or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administration
Grade 2	**Stop nivolumab infusion**; start IV saline infusion; give diphenhydramine 50 mg (or equivalent) IV and/or paracetamol 325 to 1000 mg (acetaminophen); consider corticosteroids and bronchodilator therapy; remain at bedside and monitor subject until recovery from symptoms **Re-start infusion at 50% of initial rate:** if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate; monitor subject closely. **Symptoms recur:** stop and discontinue further nivolumab treatment at that visit; administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF.
Grade 3-4	**Stop nivolumab infusion**; start IV saline infusion; recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous 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. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).
General	**Prophylactic medications (after initial event):** diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations; if necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used Appropriate resuscitation equipment should be available in the room and a physician readily available during the infusion of nivolumab.

9. CONCOMITANT THERAPY

Concomitant medications and any medications used to treat or support AEs will be collected in the eCRF and recorded in the source documents throughout the study beginning with signing of informed consent form to 30 days after the last dose of ibrutinib, 100 days after the last dose of nivolumab, or, afterwards, during the follow-up of a related SAE (if applicable). Otherwise, in Follow-up Period, only subsequent anti-lymphoma/neoplastic therapy should be documented (see Section 9.5). The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered (eg, CYP3A inhibitors, vitamin K antagonists). All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the eCRF.

9.1. Supportive Care

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

9.2. Permitted Medications

All concomitant medications (except those listed in Section 9.3) for medical conditions other than those investigated in the study are permitted, as clinically indicated. For subjects receiving prostate cancer androgen-deprivation-therapy (ADT) prior to the enrollment into the study may be continued upon consultation and in agreement with the medical monitor. The use of growth factors and transfusion is permitted in this study according to institutional or other guidelines (eg, American Society of Clinical Oncology guidelines, Ozer 2000).[44] However, prophylactic use during the DLT evaluation period in Part A is not permitted. The use of glucocorticoids is allowed for clinical management of AEs. However, inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks is a reason for discontinuation of study therapy.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

There were isolated cases of leukostasis reported in patients treated with ibrutinib. Subjects at risk of leukostasis (>400000/mm^3 circulating lymphocytes) should be closely monitored and supportive care such as hydration and/or leukapheresis administered as indicated. Ibrutinib may be temporarily held and the medical monitor should be contacted.

9.3. Prohibited Medications

Other anticancer treatments are not allowed in this study. The medications listed in Table 19 are known or suspected to impact the bioavailability, pharmacokinetic and potentially safety as well as efficacy profile of the study medications. The concomitant use of these medications with study therapy is therefore prohibited.

Table 19: Prohibited Concomitant Medications

Antineoplastic Therapy
• Cytotoxic chemotherapy • Biological therapy (including but not limited to: therapeutic antibodies and cytokines) • Radiation therapy[1] • Investigational agents
Immunotherapy
• Immunotherapy for any indication • Live, attenuated vaccines (including but not limited to the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid)[2]
Immunosuppressive agents
• Immunosuppressive agents (except to treat a drug-related adverse event)
Anticoagulants
• Warfarin or other Vitamin K antagonists
Glucocorticoids
• Glucocorticoids used chronically (≥14 days)[3,4] • Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in Nivolumab IB or to treat a drug-related adverse event).

[1] Palliative radiation therapy may be allowed after consultation and in agreement with the study sponsor.
[2] Live, attenuated vaccines are prohibited 30 days prior to the first dose of study therapy and throughout study participation.
[3] Chronic (≥14 days) use of glucocorticoid for adrenal replacement is allowed.
[4] The use of physiologic doses of corticosteroids may be approved after consultation and in agreement with the study sponsor.

9.4. Concomitant Medications to be Avoided, or to be Used with Caution

The bioavailability and in consequence the safety as well as efficacy profile of the medications listed in Table 20 may be altered when co-administrated with study therapy. Therefore, these medications should be avoided, or should be administered with caution concomitantly with study therapy. Instructions for medications to be used with precaution are also provided in Attachment 7.

Table 20: Concomitant Medications to be Avoided or to be Used with Caution

CYP3A4 /5 Inducers and Inhibitors
• Strong and moderate CYP3A4/5 inducers[1]
• Strong and moderate CYP3A4/5 inhibitors[1]
• Grapefruit and Seville oranges
QT-Prolonging Agents
• Medications known to cause *Torsade's des Pointes*[2]
Supplements
• Fish oil
• Vitamin E preparations
P-gp Substrates
• P-gp substrates with narrow therapeutic index (eg, Digoxin)
Anticoagulants and Antiplatelet Agents[3]
• Other anticoagulants then listed in Table 19
• Other medication that inhibit platelet function then listed in Table 19
Surgical intervention
• held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding

[1] For a listing of CYP3A4/5 inhibitors and inducers see Attachment 8 and http://medicine.iupui.edu/clinpharm/ddis/main-table.

[2] For a listing of medications that cause QT prolongation see http://www.azcert.org/medical-pros/drug-lists/list-01.cfm?sort=Generic_name.

[3] Subjects requiring the initiation of therapeutic anticoagulation therapy (other than warfarin or a vitamin K antagonist) during the course of the study should have treatment with ibrutinib held, the sponsor's medical monitor should be contacted, and ibrutinib should not be restarted until the subject is clinically stable and the re-initiation of ibrutinib is approved by the sponsor's medical monitor. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

9.5. Subsequent Therapies

Administration of any other antineoplastic therapy, for reasons other than progressive disease is strongly discouraged until progressive disease is established according to the criteria described in Attachment 6. After progressive disease is established, subsequent therapy is permitted at the investigator's discretion. Subsequent therapy (including start date, end date, and best response) should be documented in the appropriate section of the eCRF.

10. STUDY EVALUATIONS

10.1. Efficacy (Assessment of Disease Response and Progressive Disease)

Efficacy assessments will be performed as outlined in Time and Events Schedule (Table 1). These assessments are to be conducted until disease progression (even if subsequent therapy is started prior to objective disease progression), withdrawal of consent from study participation, or the end of study. For subjects who discontinue study drug before disease progression is documented, disease assessments will continue in the Follow-up Period at least every 6 months until disease progression is documented or the start of subsequent therapy. The determination of disease status for continuation of treatment will be assessed by the investigator at the site based on the results of the efficacy assessments; the results will be recorded in the eCRF. Radiological and PET scans performed prior to the database lock for the final analysis may be transferred to the independent imaging laboratory for storage; the scans may be reviewed, if deemed necessary.

For all subjects, as soon as disease progression is confirmed the sponsor's study lead should be informed immediately. A tumor biopsy should be collected for biomarker evaluations at progression, depending on the indication and if clinically feasible.

The detailed description of efficacy measurements that will be obtained during the study are provided in Attachment 5. At all times, identical methodology should be used for disease assessment at baseline and throughout the course of the study.

The investigator will perform tests that will allow evaluation of response to therapy according to corresponding disease criteria in Table 21.

Table 21: Response Criteria

Criteria	PART A	PART B	Attachment
IWCLL[1]	Subjects with CLL	Cohort B1 (CLL)	6.1
Response Assessment of Non-Hodgkin Lymphoma[2]	Subjects with B-cell NHL, including SLL	Cohorts B1 (SLL), B2, B3, and B4	6.2

1 International Workshop on Chronic Lymphocytic Leukemia (Hallek 2008)[23]
2 Recommendations for Initial Evaluation, staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson 2014)[12]

The efficacy endpoints are defined as follows, based on the IWCLL or the Lugano Classification by Cheson (2014),[12] as appropriate for the disease:

- Overall response rate, which is defined as the proportion of evaluable subjects who achieve CR or PR, as assessed by the investigators,
- Duration of response will be calculated from the date of initial documentation of a response (CR, or PR) to the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death. Subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment.
- Progression-free survival is defined as the duration from the date of first dose of study drug until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death, whichever comes first. Subjects who are progression-free and alive or have unknown status will be censored at the last tumor assessment.
- Overall survival is measured from the date of first dose of study drug to the date of the subject's death. If the subject is alive or the vital status is unknown, the subject will be censored at the date the subject was last known to be alive.

10.2. Treatment After Initial Evidence of Disease Progression

The anti-tumor response patterns seen with the study treatment and other immunotherapeutic agents may extend beyond the typical time course of responses seen with cytotoxic agents. It is documented that clinical responses to nivolumab can be observed after an initial increase in tumor burden. Therefore, treatment with study therapy beyond tumor progression is possible. Following implementation of amendment 7, continuation on study treatment after disease progression will no longer be permitted.

Once the specific criteria of progressive disease outlined in Section 10.1 are met, the appropriate tumor assessment should be repeated at the next per-protocol scheduled assessment time-point or earlier if clinically necessary (but not earlier than 8 weeks later) in order to confirm progressive disease.

In confirming whether or not the tumor burden has increased/disease has progressed, investigators may consider all tumor manifestations. While awaiting confirmation of disease progression, subjects should continue to receive study therapy if their clinical status is considered to be stable by the investigator based on the following Clinical Stability Criteria:

- Absence of clinical signs and symptoms indicative of rapid disease progression
- Clinical disease progression not requiring immediate therapeutic intervention
- No decline in ECOG performance status

The decision to continue study treatment after the first evidence of disease progression is at the discretion of the investigator.

Table 22 provides guidelines to continue or discontinue study therapy based on the initial and subsequent assessments of the tumor and the clinical status.

Table 22: Study Therapy after First Evidence of Progressive Disease

	Initial Assessment	*Repeat Assessment*	
	First Evidence of PD	**PD**	**SD, PR, or CR**
Disease Assessment	Repeat Assessment[1]	No additional assessments	Continue assessments[3]
Study Therapy	Continue[2]	Discontinue	Continue[4]

1 The repeat disease assessment (in line with guidelines for each indication) may be performed at the next per-protocol scheduled assessment timepoint or earlier if clinically necessary; the time interval from the initial to the confirmatory assessment has to be at least 4 weeks.

2 Per investigator's discretion the study therapy may be continued while awaiting the confirmatory disease assessment.

3 Only for subjects continuing study therapy, the per-protocol scheduled tumor assessments will be continued until confirmed disease progression.

4 Per investigator's discretion the study therapy may be continued after SD/PR/CR is observed in the confirmatory assessment; re-starting of study therapy stopped due to progressive disease in initial assessment is possible after SD/PR/CR is observed in the confirmatory assessment but requires agreement with medical monitor.

10.2.1.1. Circumstances in which Post-progression Treatment is Permitted

Subjects meeting progression defined by relapsed disease (after CR) or progressive disease (after PR, SD) may continue receiving study medication beyond investigator assessed progression as long as they meet the following criteria:

- Continue to meet all other study protocol eligibility criteria
- Investigator-assessed clinical benefit, and do not have rapid disease progression
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression
- Patients will be re-consented with an informed consent document describing any reasonably foreseeable risks or discomfort and other alternative treatment options
- Tolerance of study therapy

The decision to continue treatment beyond investigator-assessed progression should be discussed with the Sponsor and documented in the study records. The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

10.2.1.2. Assessments for Subjects with Post-progression Treatment

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

Further progression is evaluated by a subsequent CT or MRI which is performed at least 4 weeks from previous CT or MRI. The tumor burden volume from time of initial progression should be used as the reference baseline for comparison with the post-progression assessment.

New lesions are considered measurable at the time of initial progression if the long axis is more than 15 mm regardless of the short axis. If a lymph node has a long axis of 11 to 15 mm, it should only be considered measurable if its short axis is more than 10 mm.

Any new lesion considered non-measurable at the time of or after initial progression may become measurable and therefore included in the tumor burden determination.

10.2.1.3. Radiographic Assessment for Subjects who Discontinue Study Drug during Post-progression Treatment

For subjects that discontinue post-progression treatment, no additional radiographic assessments will be required. Upon treatment discontinuation, these subjects will continue in the Follow-up Period of the study.

10.3. Pharmacokinetics

10.3.1. Sample Collection

The Laboratory Manual provides further information regarding handling and shipment of blood samples. Pharmacokinetic assessments will not be conducted post clinical cutoff. Following implementation of amendment 7, collection of PD or PK samples will no longer be required.

10.3.2. Evaluations

Blood samples will be collected from all subjects for determination of plasma concentrations of ibrutinib and the PCI-45227 metabolite (if possible and judged relevant), as well as serum concentrations of nivolumab according to the Time and Events Schedule (Table 2). These sparse samples may be used for the development of a population-based pharmacokinetic model.

Samples for pharmacokinetic and immunogenicity assessment will be collected for all subjects receiving nivolumab. Table 2 lists the sampling schedule to be followed for pharmacokinetics and immunogenicity. All timepoints are relative to the start of study drug administration. All on treatment PK timepoints are intended to align with days on which study drug is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected, but the dose is subsequently delayed, an additional predose sample should not be collected. Further details of blood collection and processing will be provided in the procedure manual.

10.3.3. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of ibrutinib and the metabolite PCI-45227 using a validated, specific, and sensitive LC-MS/MS method by or under the supervision of the sponsor. If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method.

Serum samples will be analyzed for nivolumab by a validated method. In addition, selected serum samples may be analyzed by an exploratory analytical method that measures nivolumab for technology exploration purposes; exploratory results will not be reported.

10.3.4. Pharmacokinetic Parameters

Population pharmacokinetic analysis of plasma/serum concentration-time data of ibrutinib and nivolumab may be performed using nonlinear mixed-effects modeling (NONMEM), with the aim of providing estimates of pharmacokinetic parameters (eg, oral clearance) or metrics of systemic exposure (eg, area under the plasma/serum concentration-time curve within the dosing interval). Model-derived plasma/serum concentrations or metrics of exposure parameters (eg, C_{max} or AUC) may be subjected to further analyses to explore pharmacokinetic correlation between exposure and relevant clinical or biomarker information.

If deemed useful, C_{max} and partial AUCs for ibrutinib and the dihydrodiol metabolite PCI-45227 may be derived using non-compartmental analysis, as well as metabolite/parent ratios.

10.4. Immunogenicity Assessment

Subjects will be monitored for anti-nivolumab antibodies throughout the study. Blood for serum anti-nivolumab antibody testing should be collected at the times specified in Table 2.

Analysis will be performed by a central laboratory. At all timepoints that anti-nivolumab antibodies are measured, serum concentrations of nivolumab will also be measured. Details on blood sample collection, processing, storage and shipping procedures are provided in the SIPPM.

10.5. Biomarkers

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

Biomarkers will be assessed in all subjects to further characterize the pharmacodynamic profile and to investigate the molecular efficacy of the ibrutinib and nivolumab combination regimen.

Biomarkers will be analyzed in:

- Tumor tissue
- Blood samples (collected serially)
- Fine-needle aspirates (from affected lymph nodes)
- Bone marrow aspirates or biopsies

After clinical cutoff, some biomarker assessments (bone marrow aspirate/biopsy) will no longer be required. Biomarker assessments are summarized in Table 23. Samples for biomarker analyses will be obtained at the timepoints listed in Table 1 and Table 2. Following implementation of amendment 7, collection of biomarker samples will no longer be required.

Table 23: Biomarker Assessments

Time	Material	Analysis
Tumor Biopsy[1]		
• Screening (mandatory) • During therapy (optional) • Progression (optional)	1 FFPE tumor tissue block (preferred) **OR** minimum of 10 FFPE unstained sections	• PD-L1 status[2] • Molecular mechanisms of action and resistance [3] • Tumor infiltrating lymphocytes (TILs)[4] • Tumor antigens[5] • Tumor geno- and phenotype[6]
Blood Samples		
• Screening	see Laboratory Manual for details	• Drug binding and molecular activity[7]

Table 23: Biomarker Assessments

Time	Material	Analysis
• During study therapy • End of study therapy		• Biomarkers of clinical response[8] • Immune cell subsets [9] • Molecular mechanisms of action and resistance [3] • Ex vivo functional assays[10] • SNP analysis[11]
Fine-needle Aspirates		
• Screening • During study therapy • End of study therapy	see Laboratory Manual for details	• Immune cell subsets[9]
Bone Marrow Aspirate / Biopsy[12, 13]		
Screening[12,13] During therapy and/or at CR[13,14]	see Laboratory Manual for details	• Disease status • Confirmation of CR • Molecular mechanisms of action and resistance [3]

1: Mandatory tumor biopsy for subjects with accessible lesions prior to therapy (ie, within 90 days prior enrollment); on-treatment biopsies are optional. If biopsy prior to enrollment cannot be provided the reason must be documented in the medical record AND the Medical Monitor must be contacted. Archival tissue, if available, should be submitted for these subjects. Submission of archival tissue is also encouraged for all subjects, irrespective of whether fresh biopsy tissue is available. All subjects may volunteer to undergo tumor biopsy at any time during therapy if clinically indicated (eg, upon progression). When tumor biopsy is performed, submission of tumor biopsy is optional, but strongly encouraged for the purposes of understanding mechanisms of resistance to therapy. Tumor samples from bone metastases are not acceptable for PD-L1 assessment. Contact study medical monitor for cases where only bone metastasis lesion are available.

2: Proprietary IHC analysis

3: Expression profiling of immune-related genes, mutational analysis, and intracellular BCR-/BTK- and alternative signaling pathway analysis by Affymetrix gene array technology and/or quantitative real-time polymerase chain reaction (qPCR) Analysis includes, but is not limited to, genes associated with immune-related pathways, such as T cell activation and antigen processing and presentation.

4: IHC analysis of composition of immune infiltrates before and after exposure to study therapy including, but not limited to, CD4, CD8, FOXp3, PD 1, PD L1, and PD-L2.

5: Analysis (by IHC, RNASeq, GEP, qRT-PCR, miRNA, methylation, or mutational analyses) of gene mutations, chromosomal translocations, aberrant expressions, and epigenetic modifications and correlation to efficacy of study therapy.

6: Analysis (by IHC, RNASeq, GEP, qRT-PCR, miRNA, methylation, or mutational analyses) of disease heterogeneity and subtypes in correlation to response to study therapy.

7: PD-1 expression and nivolumab binding. BTK occupancy and inhibition of downstream survival pathways (ERK1/2, PI3K, NF-kB, MAPK) as well as survival signals from the microenvironment.

8: Multiplex- and enzyme-linked immunosorbent assay (ELISA) of tumor antigen-specific responses associated with clinical response by including cytokines, chemokines, soluble receptors, and antibodies to tumor antigens quantified. Analyses include but are not limited to, soluble CD25, soluble PD-1, soluble LAG 3, CXCL 9, and soluble PD-L1.

9: Lymphocyte subsets and expression levels of T cell co-stimulatory markers (by flow cytometry). Analyses may include, but not be limited to, the proportion of T-, B-, and NK-cells, proportion of memory- and effector T-cell subsets, and expression levels of PD 1, PD L1, PD L2, ICOS, and Ki67. Analysis of the diversity of the T-cell repertoire in correlation to clinical efficacy.

10: Functional status of effector T cells isolated from cryopreserved peripheral blood mononuclear cells based on but not limited to, assays for interferon-gamma (IFN γ) and CD107.

Table 23: Biomarker Assessments		
Time	**Material**	**Analysis**

[11] Single nucleotide polymorphisms (SNP) associated with safety and efficacy of study therapy. SNP analysis will be limited to genes associated with the PD1/PD-L1 pathway and activated T cell phenotype.
[12] Disease manifestation in the bone marrow must be evaluated within 90 days prior to enrollment. Bone marrow aspirates will be obtained using institutional standards for these procedures. Samples will be assessed for phenotypic and functional status of immune cells and tumor cells.
[13] All subjects may volunteer to undergo bone marrow biopsy and aspirate at any time during therapy if clinically indicated. When bone marrow biopsy is done, submission of bone marrow aspirate is strongly encouraged.
[14] Only in subjects with disease manifestation in the bone marrow prior to or during screening.

10.6. Safety Evaluations

All subjects who receive study therapy will be considered evaluable for toxicity. Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, electrocardiograms, physical examinations, clinical laboratory tests and ECOG performance status at specified time points as described in the Time and Events Schedule (Table 1). Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. The study will be monitored by the SET. Details are provided in Section 12.7. The study will include the following evaluations of safety and tolerability:

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance.

Contraceptive Requirements

Azoospermic males and women of childbearing potential (WOCBP) who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

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 have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. More frequent clinical laboratory tests may be performed as indicated by the overall clinical condition of the subject and of abnormalities that warrant more frequent monitoring. Hematology and serum chemistry laboratory evaluations can be repeated as clinically indicated. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Screening laboratory results must be available to the investigator for evaluation before the first dose of any study drug.

The following tests will be performed by the local laboratory as per Table 1. The laboratory reports must be filed with the source documents.

Hematology Panel	
hemoglobin white blood cell (WBC) ANC	platelet count ALC
Coagulation Studies	
aPTT	INR and/or PT
Thyroid function	
TSH T3	Free T4
Serum Chemistry Panel	
sodium potassium magnesium creatinine total bilirubin glucose (at Screening only) lactate dehydrogenase	aspartate aminotransferase (AST) alanine aminotransferase (ALT) alkaline phosphatase lipase albumin amylase
Pregnancy test (serum beta-hCG or urine): for women of childbearing potential only	
Beta$_2$-microglobulin and serum immunoglobulin levels (IgG, IgM, IgA)	

Hepatitis B and C Screening

- Hepatitis B core antibody (Ab): if positive, further testing to rule out active disease or chronic carrier
  - Hepatitis B surface antigen or
  - Hepatitis B DNA by PCR
- Hepatitis C antibody

Electrocardiogram

Triplicate electrocardiograms (ECGs) will be performed locally for all subjects at the timepoints specified in the Time and Events Schedule (Table 1). Additional cardiovascular assessments should be performed as clinically appropriate to ensure subject safety. The clinical investigator will review the printout, including ECG morphology, for immediate management.

Abnormalities noted at Screening should be included in the medical history. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones).

Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. Twelve-lead ECGs will be recorded at a paper speed of 25 mm per second until 4 regular consecutive complexes are available. The ECGs will be performed and interpreted by qualified site personnel. The results must be recorded and filed in the source documents.

If vital signs or blood draws are scheduled at the same time points as ECG recordings, the sequence of procedures should be as follows: ECG first, vital signs measurement second, and any type of blood draw (eg, PK, safety, biomarker) third.

The measured QT data will be corrected for heart rate using Fridericia (QTcF) correction method,[21] according to the following formula/method (with QT, RR and QTc expressed in ms):

- Fridericia Correction[21]

$$QTcF = \frac{QT}{(RR/1000)^{(1/3)}}$$

Vital Signs

Temperature, heart rate, blood pressure, and pulse oximetry will be recorded at the following times: Screening, prior to and within 1 hour after each nivolumab infusion, at the end of treatment, and as clinically indicated. Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Physical Examination

A full physical examination will be performed at screening. Subsequently, directed physical examination (includes all organ systems that were previously abnormal or involved with disease and documentation of any clinically relevant abnormalities in any organ) will be performed at the timepoints specified in the Time and Events Schedule (**Table 1**). Height will be measured at Screening only; weight will be periodically measured. Lymphoma symptoms reported at screening should be reviewed and recorded during the directed physical examination.

Renal Toxicity Evaluation

The glomerular filtration rate (GFR) will be determined according to Modified Diet in Renal Disease Formula (Attachment 2). The GFR will be evaluated at screening and as clinically indicated.

ECOG Performance Status

The ECOG performance status scale will be used to grade changes in the subject's daily living activities. ECOG performance status scale is provided in Attachment 4. The frequency of ECOG performance status assessment is provided in Table 1.

11. SUBJECT COMPLETION/TREATMENT DISCONTINUATION/WITHDRAWAL

11.1. Completion

A subject will be considered to have completed the study if he or she has died, has not been lost to follow up, or has not withdrawn consent from the study at the time when the primary analysis will be conducted (6 months after the last patient's first dose).

11.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued, this will not result in automatic withdrawal of the subject from the study.

Study treatment should be discontinued if:

- The investigator believes that for safety reasons (eg, AE, for criteria that require discontinuation, please refer to Table 8 and Table 9 in Section 6.4.3) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject experiences overt disease progression or relapse
- Unacceptable toxicity
- Treatment interruption of >6 weeks (unless otherwise approved by the Sponsor for non-drug related reasons)
- The subject refuses further treatment
- A serious protocol violation has occurred, as determined by the principal investigator or the sponsor

If a subject discontinues study treatment before the onset of disease progression, end of treatment and posttreatment assessments should be obtained and follow-up of scheduled assessments should be continued, including assessment of anti-nivolumab antibodies and nivolumab exposure 100 days after discontinuation of nivolumab. The reason(s) a subject discontinues treatment will be recorded on the eCRF.

11.3. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- The sponsor discontinues the study

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. If a subject discontinues study treatment and

withdraws from the study before the onset of disease progression, end-of-treatment and post-treatment assessments should be obtained. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

12. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

Summary statistics for continuous variables will include the mean, standard deviation, median, and range. Categorical data will be presented as frequencies and percentages.

12.1. Subject Information

The analysis populations for this study are defined as:

- The Treated Population will consist of all subjects who receive at least 1 dose of study drug (either ibrutinib or nivolumab). The Treated Population will be used for all safety and efficacy analysis unless otherwise stated.
- The Response Evaluable Population will consist of all subjects who receive at least 1 dose of both study drugs (ibrutinib and nivolumab), and have a pretreatment, and at least 1 posttreatment disease assessment; unless no post-baseline scan was performed due to AE possibly related to treatment.
- The Pharmacokinetic/Pharmacodynamic Population will consist of all subjects who receive at least 1 dose of study drug (either ibrutinib or nivolumab) and have at least 1 posttreatment sample collected during treatment to determine the concentration or pharmacodynamic biomarker response.

12.2. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). Toxicities will be graded for severity according to NCI-CTCAE, version 4. All reported AEs with onset during the Treatment Period (ie, treatment-emergent adverse events [TEAEs], and AEs that have worsened since baseline) will be included in the analysis.

Specifically, the following will be summarized:

- Incidence of DLT (Part A)
- All adverse events
- Grade 3 or higher adverse events
- Serious adverse events
- Adverse events leading to discontinuation of treatment

- Adverse events leading to death
- Adverse events of special interest

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline. Parameters with predefined toxicity grades will be summarized. Change from baseline to the worst grade experienced by the subject during the study will be provided as shift tables.

Vital Signs

Descriptive statistics of heart rate and blood pressure (systolic and diastolic) (supine) values and changes from baseline will be summarized. The percentage of subjects with clinically important changes from baseline will be summarized.

12.3. Sample Size Determination

This is a Phase 1/2a dose optimization and expansion study. For Part A, a statistical design based on the approach described in Ji, et al. (2010)[30] and Ji and Wang (2013)[29,30] will be used. This method requires a definition of an equivalence interval (EI), [*0.25; 0.30*], in which any dose is considered as a potential candidate for the true MTD, where *0.30* is the targeted DLT rate. Defining an EI results in the partition of the unit interval (0, 1) into 3 subintervals; (*0; 0.25*), [*0.25, 0.30*], and (*0.30; 1*). Doses in these 3 intervals are deemed lower, close to, and higher than the MTD, respectively. At least 6, and up to 9 subjects may be treated in each cohort in Part A. Approximately 18 subjects may be enrolled in Part A.

Part B, Cohorts B1 (CLL/SLL), B2 (FL), B3 (DLBCL), and B4 (Richter syndrome) are designed to evaluate the feasibility and safety of treating subjects with ibrutinib in combination with nivolumab and to evaluate preliminary activity. The sample size is calculated based on the following assumptions (denoting the true response rate of ibrutinib in combination with nivolumab as p):

- The overall response rate under null hypothesis is 20%
- The overall response rate under alternative hypothesis is at least 38%
- The probability to mistakenly rejecting the null hypothesis when it is actually true is 0.1 (one-sided).
- The probability to correctly rejecting null hypothesis when alternative hypothesis is true is at least 0.8

Under the above assumptions, the study will enroll approximately 35 subjects to get at least 32 response-evaluable subjects in each cohort of Part B (dose expansion; Cohorts B1, B2, B3, and B4).

Approximately 158 subjects (with up to 18 subjects in Part A and approximately 140 subjects in the Part B, dose expansion) will be enrolled in this study.

12.4. Efficacy Analyses

Part A: Individual best tumor responses and duration of response (defined as the time from first response to progression) will be listed for each dose cohort.

Part B: The following efficacy analyses will be performed to explore the clinical activity of ibrutinib in combination with nivolumab in each cohort in the treated population unless otherwise stated:

- Overall response rate (CR or PR) will be calculated with 95% CI for each disease-specific cohort B1, B2, B3, and B4 on the response-evaluable population.
- Progression-free survival and overall survival at 1 year will be evaluated using Kaplan-Meier method.
- Duration of response and duration of stable disease will be evaluated if there are sufficient data for responders within each cohort.

12.5. Pharmacokinetic Analyses

The plasma concentration data for ibrutinib and, if possible and judged relevant, the metabolite PCI-45227, and serum concentrations of nivolumab at each timepoint will be summarized using descriptive statistics. Ibrutinib and nivolumab data will be listed by dose cohort for all subjects with available plasma/serum concentrations. Subjects will be excluded from the pharmacokinetic analysis if their data do not allow for accurate assessment of the pharmacokinetic (eg, incomplete administration of the study agent; concentration data not sufficient for pharmacokinetic parameter calculation due to missing pharmacokinetic draws at multiple visits; or early discontinuation from the study).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics and for the calculation of pharmacokinetic parameters. All subjects and samples excluded from the analysis will be clearly documented in the study report.

If non-compartmental analysis for ibrutinib/PCI-45227 is performed, results will be summarized using descriptive statistics.

Population pharmacokinetic analysis of ibrutinib plasma concentration-time data may be performed using NONMEM. Data may be combined with data from other studies to support a relevant structural population-based pharmacokinetic model. Available subject characteristics

(demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting pharmacokinetic parameters.

Model-derived exposure parameters may be subjected to further explore pharmacokinetic/pharmacodynamic correlation between exposure with relevant clinical or biomarker information.

Ibrutinib and nivolumab concentration data may be compared to observed concentration data and/or concentration estimates from the existing population PK models of ibrutinib/nivolumab, as appropriate.

If additional population PK analyses of ibrutinib and/or nivolumab are performed using data from this study, the results relevant for this study will be communicated, but an additional modeling report may be generated and will not be part of the study report for this study.

12.6. Biomarker Analyses

Analyses are planned to identify biomarkers that are indicative of the mechanisms of action of the drug or predictive of efficacy for the combination. The associations of biomarkers with clinical response or time-to-event endpoints will be assessed using the appropriate statistical methods (analysis of variance [ANOVA], categorical, or survival model), depending on the endpoint. Correlation of baseline expression levels or changes in expression levels with response or time-to-event endpoints will identify responsive (or resistant) subgroups.

12.7. Study Evaluation Team

The SET will monitor data on an ongoing basis during dose optimization to ensure the continuing safety of the subjects enrolled in the study. The SET will consist of the principal investigators, sponsor medical monitors, the sponsor's clinical pharmacologist, or their designees, and the sponsor's statistician. Medical safety assessment representatives or other functions experts will be consulted as needed.

The SET will convene regularly; and at a minimum after each dose level completes the DLT assessment period. The SET may convene at additional times for data review or for any safety-related issues; a SET meeting can be requested by any SET member. In addition the SET and additional functional representatives from Janssen, as applicable, may review the data for expansion cohorts (Part B) for the efficacy endpoints including but not limited to ORR along with any safety concerns.

See Section 3.3 for further details on the SET decision-making process.

13. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety

information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local and systemic events for which the subject is specifically questioned.

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the subject is specifically not questioned.

13.1. Definitions

13.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 13.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Development of a new malignancy that is not associated with the disease under study
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ibrutinib and nivolumab, the expectedness of an adverse event will be determined by whether or not it is listed in the respective Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 13.1.2.

13.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

13.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI CTCAE Version 4. Any adverse event or serious adverse event not listed in the NCI CTCAE Version 4 will be graded according to investigator clinical judgment by using the standard grades as follows:

Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity.

Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

Grade 4: Life-threatening of disabling adverse event

Grade 5: Death related to the adverse event

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

13.2. Special Reporting Situations

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

13.2.1. Nivolumab

For instructions on how to handle events of clinical interest related to nivolumab, please refer to Section 8 and the nivolumab Investigator's Brochure, Appendix 2. These events (Grade ≥3) will be reported using the same timelines used for reporting SAEs. These events include:

- Colitis
- Endocrine
- Uveitis
- Hepatic
- Pneumonitis
- Renal
- Skin
- Immune-related AEs

13.2.2. Other

Other safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

13.3. Procedures

13.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of ibrutinib or 100 days after the last nivolumab infusion, whichever is later. Afterwards, report only SAEs that are at least possibly related to study treatment. After the clinical cutoff, only SAEs and Grade ≥3 AEs will be collected. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study therapy, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 13.1.1). Death should not be recorded as an adverse event or serious adverse event, but as the outcome of an adverse event. The event that resulted in the death should be reported as a serious adverse event.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and eCRF; reporting on eCRF after CCO (per amendment #6 and 7 further revisions apply per Table 1[collection of SAEs and Grade ≥3 AEs, AEs leading to discontinuation or modification, laboratory assessments {Grade ≥3 or clinically significant}]). Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

13.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

13.3.3. Adverse Events of Special Interest (AESI)

Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities by the Sponsor. These events will be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious adverse events) following the procedure described above for serious adverse events and will require enhanced data collection.

13.3.3.1. Major Hemorrhage

Major hemorrhage is defined as: Treatment-emergent hemorrhagic adverse events of Grade 3 or higher.

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher. All hemorrhagic events requiring a transfusion of red blood cells should be reported as Grade 3 or higher AE per CTCAE.
- Any treatment-emergent serious adverse event of bleeding of any grade.
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade.

13.3.4. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, and congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must promptly discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

13.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

14. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

14.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 13.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

14.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

15. STUDY DRUG INFORMATION

15.1. Physical Description of Study Drug

Ibrutinib (PCI-32765) is provided as white opaque, size 0, hard gelatin capsules containing 140 mg of ibrutinib. All formulation excipients are compendia and are commonly used in oral formulations. Refer to the Ibrutinib Investigator's Brochure for a list of excipients.

Nivolumab (BMS-936558-01 Solution for Injection) is a clear to opalescent colorless to pale yellow liquid and may contain particles. Each vial contains 100 mg nivolumab in a 10 mL solution (10 mg/mL).

15.2. Packaging

Ibrutinib capsules are packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All bottles will utilize child resistant packaging.

Nivolumab (BMS-936558 100 mg, 10 mg/mL) will be packaged in an open-label fashion. Each BMS-936558, 10 mL vial is packaged in a carton, and are not subject or treatment arm specific. Vial assignments by subjects will be made through the IWRS to track usage and resupply.

15.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Study drug supplies will contain a study-specific label with a unique identification number.

15.4. Preparation, Handling, and Storage

The recommended storage condition for ibrutinib capsules is controlled room temperature (15ºC to 25ºC) with excursions permitted to 30°C (86°F). Current stability data indicate that the capsules will be stable for the duration of the clinical study under the labeled storage conditions. Study staff will instruct subjects on how to store medication for at-home use as indicated for this protocol.

Nivolumab should be stored at 2° to 8°C and protected from light and freezing.

Refer to the pharmacy manual/study site investigational product manual for additional guidance on study drug handling and storage conditions.

15.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability eCRF page. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate

environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug.

16. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure for ibrutinib
- Investigator Brochure for nivolumab
- Site Investigational Product Procedures Manual
- Laboratory manual
- NCI-CTCAE Version 4.0
- IWRS Manual
- Sample ICF
- Subject diaries

17. ETHICAL ASPECTS

17.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is estimated to be approximately 25 mL at screening and approximately 60 mL at baseline. Samples for PK and biomarker analysis from Cycle 3 to Cycle 25 total approximately 110 mL. Approximately 10 mL for safety laboratory testing will be collected every cycle. Within the first year the total amount of blood drawn is estimated to be 530 mL, a volume approximating the volume of a single blood donation (500 mL). Subjects in Cohorts B1 and B2 will have an additional 43 mL of blood collected for ibrutinib pharmacodynamics and biomarkers during the run-in visit.

17.2. Regulatory Ethics Compliance

17.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

17.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This

approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

17.2.3. Informed Consent

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and

understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

When prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or legally acceptable representative must be informed about the study as soon as possible and give consent to continue.

17.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate

technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory pharmacodynamic/biomarker/PK/immunogenicity research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

17.2.5. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 17.1, Study-Specific Design Considerations.

18. ADMINISTRATIVE REQUIREMENTS

18.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

18.2. Regulatory Documentation

18.2.1. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable

- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

18.2.2. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

18.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

18.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If an electronic source is utilized, references made to the CRF in the protocol include the electronic source system but information collected through electronic source may not be limited to that found in the CRF.

18.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. Electronic data capture (eDC) will be used for this study. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRFs in English. The CRF must be completed as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the study-site personnel.

18.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

18.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

18.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

18.9. Study Completion/Termination

18.9.1. Study Completion

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

18.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

18.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

18.11. Use of Information and Publication

All information, including but not limited to information regarding ibrutinib or nivolumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of ibrutinib or nivolumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study

site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENTS

Attachment 1: Modified Toxicity Probability Interval

The modified Toxicity Probability Interval (mTPI) method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current cohorts at the same dose level to determine where future cohorts should involve dose escalation, no change in dose, or dose de-escalation. The detailed dose-finding rules based on the mTPI are illustrated in the table below.

Number of dose-limiting toxicities (DLTs)	6	7	8	9
0	E	E	E	E
1	E	E	E	E
2	S	S	S	S
3	D	D	S	S
4	DU	DU	D	D
5	DU	DU	DU	DU
6	DU	DU	DU	DU
7		DU	DU	DU
8			DU	DU
9				DU
10				

Table Key:
E = escalate to the next higher dose cohort
S = stay at the current dose cohort
D = de-escalate to the next lower dose cohort
DU = the current dose cohort has unacceptably toxic; no more subjects can be treated at this dose cohort.

While the table above serves as a guideline for dose cohort escalation/stay/de-escalation decisions, the following additional points will be taken into consideration when such a decision is made:

- The Sponsor/SET may change a "Stay at current dose" to "De-escalate to prior lower level" or "De-escalate to prior lower level or Unacceptable toxicity" in Table 4 based on safety concerns
- The Sponsor/SET may stop the dose escalation part of the study when enough information is available for determining a RP2D or MTD or for other reasons

Reference: Ji and Wang, 2013

Attachment 2: Modified Diet in Renal Disease (MDRD) Formulas

For creatinine in mg/dL, the estimated glomerular filtration rate (e-GFR) for the modified diet in renal disease (MDRD) formulas is:

$$\text{e-GFR (MDRD)} = 186 \times [\text{serum creatinine}]^{-1.154} \times [\text{age}]^{-0.203} \times [1.212 \text{ if Black}] \times [0.742 \text{ if female}]$$

For creatinine in µmol/L, the estimated glomerular filtration rate (e-GFR) for the modified diet in renal disease (MDRD) formulas is:

$$\text{e-GFR (MDRD)} = 32788 \times [\text{serum creatinine}]^{-1.154} \times [\text{age}]^{-0.203} \times [1.212 \text{ if Black}] \times [0.742 \text{ if female}]$$

Creatinine levels in µmol/L can be converted to mg/dL by dividing them by 88.4. The 32788 number above is equal to 186×88.41.1.

Attachment 3: New York Heart Association Criteria

The following table presents the New York Heart Association (NYHA) classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Classification of Functional Capacity and Objective Assessment. Available at http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp. Accessed 22 January 2014.

Attachment 4: ECOG Performance Status Scale

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair (Oken, 1982).[42]

Attachment 5: Efficacy procedures

Evaluations

Radiographic Image Assessments

During the study, disease response will be assessed using CT scans with IV contrast of the neck, chest, abdomen, and pelvis and any other location where disease was present at Screening or whole body FDG-PET scans. Subjects who are intolerant of IV CT contrast agents will have CT scans performed with oral contrast. Endoscopy is required to confirm CR for subjects with gastrointestinal (GI) involvement at baseline.

A separate CT scan and PET scan are preferred but, if the only available modality is combined/dual PET/CT scanner, then the CT portion of a PET/CT may be submitted in lieu of a dedicated CT; however, the CT scanning must be done according to certain imaging requirements provided to the radiologist in the radiology manual to ensure that an optimized CT examination is done. Evaluation of other sites of disease by radiological imaging, physical examination, or other procedures as necessary (to be performed throughout the study using the same method of assessment used to assess disease at baseline), and review of hematology and clinical chemistry results may be performed at the site level, as determined by the investigator.

Magnetic resonance imaging may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations). For all other sites of disease, MRI studies do not replace the required neck, chest, abdomen, and pelvic CT scans. Brain MRI and lumbar puncture are required, only if clinically indicated.

Radiological assessments will be performed at Screening, every 5 cycles (starting Cycle 5) or approximately every 10 weeks up to 15 months after the start of study drug. Thereafter, scans will be performed every 12 cycles (approximately every 24 weeks) until disease progression, or death, or end of study, whichever comes first. A PET scan will be performed at Screening. For subjects who are PET-positive at baseline, PET scans will be done at the time of maximal tumor reduction (eg, CR or 2 consecutive CT scans showing no further tumor reduction), relapse from CR, and at suspected disease progression if new lesion was detected on CT.

Subjects who discontinue treatment prior to disease progression (for other reasons such as an adverse event) must continue to have regularly scheduled CT scans/efficacy assessments every 10 weeks up to 15 months after the start of study drug. Thereafter, scan will be performed every 24 weeks until disease progression, or death, or the end of the study, whichever occurs first. It is important that instances of progressive disease be reported to the sponsor's medical monitor within 24 hours by means of a form provided by the sponsor (see Contact Information pages provided separately).

Definition of Measurable and Assessable Disease

Eligible subjects must have at least 1 measurable site of disease. Measurable sites of disease are defined as lymph nodes, lymph node masses, or extranodal sites of lymphoma. Each measurable site of disease must be greater than 1.5 cm in the long axis regardless of short axis measurement or greater than 1.0 cm in the short axis regardless of long axis measurement, and clearly measurable in 2 perpendicular dimensions. Measurement must be determined by imaging evaluation. All other sites of disease are considered assessable, but not measurable.

Up to 6 measurable sites of disease, clearly measurable in 2 perpendicular dimensions, will be followed for each subject. Measurable sites of disease should be chosen such that they are representative of the subject's disease (this includes splenic and extranodal disease). If there are lymph nodes or lymph node masses in the mediastinum or retroperitoneum larger than 1.5 cm in 2 perpendicular dimensions, at least 1 lymph node mass from each region should always be included. In addition, selection of measurable lesions should be from as disparate regions of the body as possible.

All other sites of disease will be considered assessable. Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedures as necessary, but is not measurable as defined above. Examples of assessable disease include bone lesions; mucosal lesions in the GI tract; effusions; pleural, peritoneal, or bowel wall thickening; disease limited to bone marrow; and groups of lymph nodes that are not measurable but are thought to represent lymphoma. In addition, if more than 6 sites of disease are measurable, these other sites of measurable disease may be included as assessable disease.

Positron Emission Tomography (PET Scan)

PET using [18F]-fluorodeoxyglucose (FDG) is important for the complete assessment of response and progression in subjects with DLBCL. Whole body FDG-PET scan (skull base to the proximal femur) is recommended at Screening, at the time of maximal tumor reduction (eg, CR or 2 consecutive CT scans showing no further tumor reduction), and relapse from CR. For subjects with PET-negative tumors at baseline, the response evaluation will be based on the CT scan.

Assessment of PET results is based on published criteria.

Visual assessment is considered adequate for determining whether a PET scan is positive, and use of the standardized uptake value is not necessary. A positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardized uptake value cutoff. Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased FDG uptake at the site of moderate- or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen uptake, and diffusely increased bone marrow uptake within weeks after treatment.

Bone Marrow Assessment

Bone marrow aspirate is mandatory and biopsy is optional at Screening (see Table 1). Subjects with bone marrow involvement must have a repeat bone marrow evaluation at the time of CR (preferably within 30 days of the initial documentation of CR). If bone marrow involvement can be confirmed with morphology, IHC or flow cytometry need not be done; 1 bone marrow examination is necessary for complete documentation of the CR.

Attachment 6: Criteria for Response

The following sections provide a summary of response criteria. Please refer to published international guidelines for the most recent and complete details.

Attachment 6.1: International Workshop on Chronic Lymphocytic Leukemia (IWCLL)

The International Workshop on Chronic Lymphocytic Leukemia (IWCLL) recommendations for the management of CLL in clinical studies and general practice are presented below (Hallek 2008)[23].

Response Category	Definition
Complete Response (CR)	Group A[1, 2] • Lymphadenopathy[a]: none >1.5cm • Hepatomegaly: none • Splenomegaly: none • Blood lymphocytes: <4000/µL • Marrow[c]: Normocellular, <30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi Group B[1, 2] • Platelet count: >100,000/µL • Hemoglobin>11 g/dL • Neutrophils[c:] >1500/µL **Complete Response with an Incomplete Marrow Recovery (CRi)** is defined as a complete response with an incomplete recovery of the subject's bone marrow. Subjects who have a CRi fulfill the criteria for a CR, but continue to have persistent anemia, thrombocytopenia, or neutropenia, and a hypocellular bone marrow. These cytopenias are due to drug toxicity in the bone marrow and are not due to any evidence of CLL.
Partial Response (PR)	Group A[1, 3] • Lymphadenopathy[a]: Decrease ≥50% • Hepatomegaly: Decrease ≥50% • Splenomegaly: Decrease ≥50% • Blood lymphocytes: Decrease ≥50% from baseline • Marrow[c]: 50% reduction in marrow infiltrates or B lymphoid nodules Group B[1, 3] • Platelet count: >100,000/µL or increase ≥50% over baseline • Hemoglobin: >11g/dL or increase ≥50% over baseline • Neutrophils[c]: >1500/µL or increase ≥50% over baseline **Nodular Partial Response (nPR)** nPR is a response where subjects meet the criteria for a CR, but the bone marrow biopsy shows that there are still B-lymphoid nodules present. These nodules are residual disease and therefore the subject is termed an nPR. **Partial Response (PR) with Lymphocytosis** PR with lymphocytosis is a response where subjects meet the criteria for a PR and have persistent lymphocytosis.
Stable Disease (SD)	Not meeting criteria for CR, CRi, nPR, PR, or PD
Progressive Disease (PD)	Group A[1, 4] • Lymphadenopathy[a]: increase ≥50% or appearance of new lesions >1.5 cm

Response Category	Definition
	• Hepatomegaly: increase ≥50% or appearance of new hepatomegaly • Splenomegaly: increase ≥50% or appearance of new splenomegaly • Blood lymphocytes • Marrow[c]: increase ≥50% over baseline[d] Group B[1, 4] • Platelet count: Decrease of ≥50% from baseline secondary to CLL • Hemoglobin: Decrease of >2g/dL from baseline secondary to CLL • Neutrophils[c]
Other	**Treatment-related Lymphocytosis** Treatment-related lymphocytosis is defined as an elevation in blood lymphocyte count of ≥50% compared with baseline that occurs in the setting of unequivocal improvement in at least 1 other disease-related parameter, including lymph node size, spleen size, hematologic parameters (hemoglobin and platelet count), or disease-related symptoms. Treatment-related lymphocytosis is isolated lymphocytosis occurring when no other criteria for progressive disease are met. In this particular setting, it will not be considered PD.

[a]. Sum of the products of multiple lymph nodes (as evaluated by CT scans).
[b]. Defined as a decrease in lymph nodes of ≥50% either in the sum products of the diameter of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node detected prior to the therapy, as well as no increase in any lymph node and no new enlarged lymph nodes. Note: in small lymph nodes <2 cm, an increase of <25% is not considered to be significant.
[c]. This parameter is not relevant for the PD category.
[d]. Subjects with treatment-related lymphocytosis should remain on study treatment in the absence of other criteria for progressive disease.

[1]. Group A defines the tumor load and Group B defines the function of the hematopoietic system
[2]. CR: all of the criteria need to be met and patients have to lack disease-related constitutional symptoms. Bone marrow aspirate at least 2 months following the last dose of nivolumab is required to confirm CR.
[3]. PR: At least 2 criteria from Group A plus 1 of the criteria from Group B must be met. In all cases, in order for a response to be termed a PR, the blood lymphocyte count should be normalized or decreased >50% from baseline (if elevated at baseline).
[4]. PD: at least 1 of the above criteria from Group A or B are met; or transformation to more aggressive histology (eg, Richter's transformation). A new organ infiltrate, bone lesion, ascites, or pleural effusion confirmed due to CLL would also be considered PD.

Attachment 6.2: Evaluation, Staging, and Response Assessment for Non-Hodgkin Lymphoma: The Lugano Classification (according to Cheson 2014)

Evaluation, staging, and response criteria are summarized in 3 tables below.

Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies	PET-CT	Increased FDG uptake
		Non avid disease	CT	Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, solitary mass, miliary lesions, nodules
		Non avid disease	CT	> 13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, mass
		Non avid disease	CT	Nodules
CNS	Signs, symptoms		CT	Mass lesion(s)
			MRI	Leptomeningeal infiltration, mass lesions
			CSF assessment	Cytology, flow cytometry
Other (eg, skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT[a], biopsy	Lymphoma involvement

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
a: PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky[a]	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.
a: Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Criteria for Response Assessment of Non-Hodgkin's Lymphoma

Response	Site	PET-CT-Based Response	CT-Based Response
Complete	Lymph nodes and extralymphatic sites	Complete metabolic response	Complete radiologic response (all of the following)
		Score 1, 2, or 3[a] with or without a residual mass on 5PS[2] 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 determinate, IHC negative
Partial	Lymph nodes and extralymphatic sites	Partial metabolic response	Partial remission (all of the following)
		Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasured 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

Response	Site	PET-CT-Based Response	CT-Based Response
No response or stable disease	Lymph nodes and extralymphatic sites	No metabolic response	Stable disease
		Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	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
Progressive disease	Individual target nodes/nodal masses Extranodal lesions	Progressive metabolic disease 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	Progressive disease requires at least 1 of the following: PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir. 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
	Non measured lesions	None	New or clear progression of preexisting nonmeasured lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

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

[b]: PET 5PS: 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.

Attachment 7: Instruction for Concomitant Medications to be Used with Precaution

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased dose normalized exposure, C_{max} and AUC0-last, of ibrutinib by 29- and 24-fold, respectively. The maximal observed ibrutinib exposure (AUC) was ≤ 2-fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, and cobicistat) and moderate inhibitors (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) should be avoided. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, reduce the ibrutinib dose to 140 mg or withhold treatment temporarily (for 7 days or less). If a moderate CYP3A inhibitor must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Monitor subject closely for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

Coadministration of ibrutinib with strong inducers of CYP3A decreases ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

Examples of inhibitors, inducers, and substrates can be found at
http://medicine.iupui.edu/clinpharm/ddis/main-table/

Drugs that may have their plasma concentrations altered by ibrutinib

In vitro studies indicated that ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes in vitro. Therefore, it is unlikely that ibrutinib has any clinically relevant drug-drug interactions with drugs that may be metabolized by the CYP450 enzymes.

In vitro studies indicated that ibrutinib is not a substrate of P-gp, but is a mild inhibitor. Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available; therefore, co-administration of narrow therapeutic index P-gp substrates (eg, digoxin) with ibrutinib may increase their blood concentration and should be used with caution and monitored closely for toxicity.

Concomitant Use of Ibrutinib/Placebo and QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic monitoring with electrocardiograms (ECG) and electrolytes should be considered and, if needed, the medical monitor may be contacted.

Concomitant Use of Ibrutinib/Placebo and Antiplatelet Agents and Anticoagulants

Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements, such as fish oil and vitamin E preparation should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Subjects requiring the initiation of therapeutic anticoagulation therapy (other than warfarin or a vitamin K antagonist) during the course of the study should have treatment with ibrutinib/placebo held, the sponsor's medical monitor should be contacted, and ibrutinib/placebo should not be restarted until the subject is clinically stable and the re-initiation of ibrutinib/placebo is approved by the sponsor's medical monitor. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

Attachment 8: Inhibitors and Inducers of CYP3A

Examples of inhibitors and inducers of CYP3A can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/. The list below reflects information obtained from the Indiana University, Division of Clinical Pharmacology, Indianapolis, IN website on July 2013.

Inhibitors of CYP3A

Strong inhibitors:	**All other inhibitors:**
INDINAVIR	amiodarone
NELFINAVIR	NOT azithromycin[a]
RITONAVIR	chloramphenicol
CLARITHROMYCIN	boceprevir
ITRACONAZOLE	ciprofloxacin
KETOCONAZOLE	delaviridine
NEFAZODONE	diethyl-dithiocarbamate
SAQUINAVIR	fluoxetine-metabolite norfluoxetine
TELITHROMYCIN	fluvoxamine
Moderate inhibitors:	gestodene
aprepitant	imatinib
erythromycin	mibefradil
diltiazem	mifepristone
fluconazole	norfloxacin
grapefruit juice	norfluoxetine
Seville orange juice	star fruit
verapamil	telaprevir
Weak inhibitors:	troleandomycin
cimetidine	voriconazole

a. Azithromycin is unique in that it does not inhibit CYP3A

Inducers of CYP3A

efavirenz	phenobarbital
nevirapine	phenytoin
barbiturates	pioglitazone
carbamazepine	rifabutin
glucocorticoids	rifampin
modafinil	St. John's wort
oxcarbazepine	troglitazone

INVESTIGATOR AGREEMENT

JNJ-54179060 (ibrutinib)
Clinical Protocol PCI-32765LYM1002 Amendment 7

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Date: PPD
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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