STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A SINGLE-ARM, OPEN-LABEL PHASE 2 STUDY OF NIVOLUMAB (BMS-936558) IN SUBJECTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA (FL)

(CHECKMATE 140: CHECKPOINT PATHWAY AND NIVOLUMAB CLINICAL TRIAL EVALUATION 140)

PROTOCOL CA209-140

VERSION # 3.1

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[redacted]

Research Hypothesis:

Treatment with nivolumab will lead to clinical benefit, as demonstrated by an improved clinically meaningful objective response rate, including durable responses with substantial magnitude of tumor reduction in subjects with refractory FL who have failed therapy with both rituximab and an alkylating agent.

Schedule of Analyses:

The final analysis of the primary endpoint will occur at least 12 months after the last enrolled subject's first dose of study therapy. It is anticipated that accrual will last 18 months, with approximately 115 subjects enrolled (90 subjects treated). It is anticipated that the analysis of the primary endpoint will take place approximately 30 months from FPFT. Additional survival analysis will be conducted for up to 5 years beyond analysis of the primary endpoint.

2 STUDY DESCRIPTION

2.1 Study Design

This is a single-arm Phase 2 study in subjects ≥ 18 years old with relapsed FL after failure of at least two prior lines of therapy (each containing rituximab and/or an alkylating agent). Approximately 90 subjects will be treated with nivolumab 3mg/kg IV every 2 weeks.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to first dose. Each 14-day dosing period will constitute a cycle. Radiographic study evaluations will take place in accordance with Table 2.1-1. A PET scan is required at baseline for all subjects, and to confirm a complete response (CR). Baseline assessments should be performed within 28 days prior to the first dose, utilizing spiral CT or MRI. An independent radiology review committee (IRRC) will also be utilized. The primary endpoint of this study is IRRC-assessed objective response rate (ORR), using revised 2007 International Working Group (IWG) Criteria for Malignant Lymphoma criteria. Secondary endpoints include IRRC-assessed duration of response (DOR), as well as complete remission rate (CRR) and PFS as determined by IRRC assessment and ORR based on investigator assessment.

The study design schematic is presented in Figure 2.1-1

Figure 2.1-1: Study Design Schematic

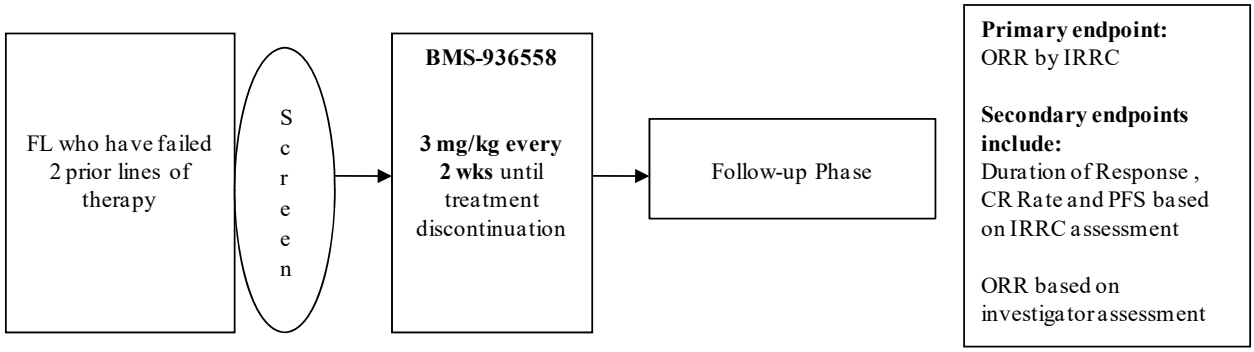

Table 2.1-1: Schedule of Spiral CT/MRI Tumor Assessments			
Time On Study	**Assessment Frequency**	**Assessment Week (day 1 of week shown)**	**Assessment Window**
Dose 1 to 8 Months	Every 8 weeks	9, 17, 25, 33	± 1 week
Month 9 to 2 Years	Every 12 weeks	45, 57, 69, 81, 93	± 2 weeks
> 2 Years	Every 6 months	119, 145, 171+	± 3 weeks

Note: Once subjects discontinue study therapy by proceeding to allogeneic SCT or ASCT, they will not undergo radiographic assessments as per the frequency described here, but will be followed using the following schedule. Tumor assessment (CR or non-CR) will be assessed by the investigator according to the 2007 IWG criteria and will be required on Day 100, at 6 months, 1 year and every year thereafter from the date of stem cell infusion until the first non-CR after SCT is documented.

2.2 Treatment Assignment

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Since this is a single arm study, all enrolled subjects who meet eligibility criteria will be treated with nivolumab at 3mg/kg IV every 2 weeks.

2.3 Blinding and Unblinding

Not applicable

2.4 Protocol Amendments

This SAP incorporates the following protocol amendments.

Table 2.4-1: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
Revised Protocol Number: 03 Incorporates amendment 04	21-JUL-2016	Update of Annex 1 of Protocol Algorithm for safety Management
Revised Protocol Number: 02 Incorporates amendment 03	23-JUL-2014	Removes the interim analyses and extends the duration of follow-up required for all subjects prior to performing the final analysis of the primary endpoint. Modifies a few eligibility criteria to facilitate enrollment.

Table 2.4-1: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
		Allows for continued treatment of subjects in certain instances where protocol-defined progression criteria have been met. The amendment also serves to clarify various protocol requirements to ensure consistency in the execution of the study including secondary and exploratory objectives, [redacted].
Revised Protocol Number: 01 Incorporates amendment(s) 02 and administrative letter 01	06-Dec-2013	Per FDA mandatory recommendation: Exclusion criteria have been added to exclude the following subjects Subjects that have received chest radiation ≤ 24 weeks prior to first dose of the study drug Additional updates were also made to the protocol including items such as correcting typographical and formatting errors, including errors in the biomarker sampling schedule in Table 5.6-1
Original Protocol	04-Oct-2013	Not applicable

2.5 Data Monitoring and Other External Committees

An IRRC will be utilized in this study for determination of IRRC-assessed primary (ORR) and secondary (DOR, CRR, PFS) endpoints. The IRRC will review all available tumor assessment scans for all treated subjects. Details of IRRC responsibilities and procedures will be specified in the IRRC charter.

There will be no data monitoring committee for this study.

3 OBJECTIVES

3.1 Primary objective

To assess the clinical benefit of nivolumab, as measured by independent radiologic review committee (IRRC) assessed objective response rate (ORR) in subjects with FL who have failed therapy with both rituximab and an alkylating agent.

3.2 Secondary objectives

- To assess the duration of response (DOR) based on IRRC assessments
- To assess the complete remission rate (CRR) and the duration of CR based on IRRC assessment

- To assess the partial remission (PR) rate and the duration of PR based on IRRC assessment
- To assess progression free survival (PFS) based on IRRC assessment
- To assess the objective response rate (ORR), based on investigator assessments

3.3 Exploratory Objectives

[redacted]

4 ENDPOINTS

4.1 Primary endpoint ORR (IRRC-assessed)

The primary objective will be measured by the primary endpoint of IRRC-assessed ORR. It is defined as the number of subjects with a best overall response (BOR) of CR or PR, according to the 2007 IWG criteria (see Table 4.1-1), divided by the number of treated subjects. The final analysis of the primary endpoint will occur at least 12 months after the last enrolled subject's first dose of study therapy. The BOR is defined as the best response designation recorded between the date of first dose and the date of initial objectively documented progression per the 2007 IWG criteria or the first subsequent therapy date per IRRC, whichever occurs first.

The first subsequent therapy date per IRRC is determined by the IRRC based on non-palliative radiotherapy, local tumor treatment, systemic anti-cancer therapy and Stem Cell Transplant with a start date on or after the first study therapy date.

For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. For purposes of analysis, if a subject receives one dose and discontinues the study without assessment or receives subsequent therapy prior to assessment, this subject will be counted in the denominator (as non-responder).

The IRRC-assessed objective response will be further characterized by the time to response (TTR). TTR is defined as the time from first dosing date to the date of the first response (PR or CR), as assessed by the IRRC.

Table 4.1-1: 2007 IWG Response Criteria for Malignant Lymphoma

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

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

4.2 Secondary Endpoints

4.2.1 Duration of Response (IRRC-assessed)

Duration of response (DOR) is defined as the time from first response (CR or PR) to the date of initial objectively documented progression as determined using the 2007 revised International

Working Group Criteria for Malignant Lymphoma or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the DOR will be censored on the date of their last evaluable tumor assessment. Subjects who start subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessments prior to or on the first subsequent therapy date per IRRC. This endpoint will only be evaluated in subjects with objective response of CR or PR. Ongoing responders are defined as responders who did not progress, did not die, are not off study and did not started a subsequent therapy.

Duration of Stable Disease will also be evaluated for subjects with SD as best response. Duration of SD is defined as the time between the first dose date to the date of the first documented progression, as determined by IRRC, or death due to any cause, whichever occurs first. Subjects who neither progress nor die will be censored at the same time they will be censored for the DOR analysis.

4.2.2 Complete Remission Rate and Duration (IRRC-assessed)

The complete remission rate (CRR) is defined as the number of subjects with a BOR of CR according to the 2007 revised International Working Group Criteria for Malignant Lymphoma, based on IRRC assessment, divided by the number of treated subjects.

To further characterize CRR, the duration of CR will also be evaluated in subjects with objective response of CR. Duration of CR is defined as the time from first documentation of CR (the date of first negative FDG-PET scan or the date of first documentation of no disease involvement in the bone marrow (if required), whichever occurs later) to the date of initial objectively documented progression as determined using the 2007 IWG criteria or death due to any cause, whichever occurs first. Censoring will be applied as per DOR definition.

4.2.3 Partial Remission Rate and Duration (IRRC-assessed)

The partial remission rate (PRR) is defined as the number of subjects with a BOR of PR according to the 2007 revised International Working Group Criteria for Malignant Lymphoma, based on IRRC assessment, divided by the number of treated subjects.

To further characterize PRR, the duration of PR will also be evaluated in subjects with objective response of PR. Duration of PR is defined as the time from first documentation of PR to the date of initial objectively documented progression as determined using the 2007 IWG criteria or death due to any cause, whichever occurs first. Censoring will be applied as per DOR definition.

4.2.4 Progression Free Survival (IRRC-assessed)

Progression free survival (PFS) is defined as the time from first dosing date to the date of the first documented progression, as determined by an IRRC according to the 2007 revised International Working Group Criteria for Malignant Lymphoma, or death due to any cause, whichever occurs first.

- Subjects who have no baseline tumor assessment will be censored at their first dosing date.

- Subjects who have baseline tumor assessment and who die without a reported progression will be considered to have progressed on the date of their death.
- Subjects who did not progress or die will be considered as not progressed and will be censored on the date of their last assessment.
- Subjects who did not have any on study assessments and did not die will be censored on the first dosing date.
- Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last assessment prior to or on their first subsequent therapy date.

Table 4.2.4-1: Censoring scheme used in primary analysis of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	First Dosing date	Not Progressed
No on study tumor assessments and no death	First Dosing date	Not Progressed
No progression per 2007 IWG criteria and no new anti-cancer treatment started	Date of last tumor assessment with no documented progression per the 2007 IWG criteria	Not Progressed
New anticancer treatment started without a prior reported progression per 2007 IWG criteria	Date of last tumor assessment prior or on the date of initiation of the subsequent anti-cancer therapy	Not Progressed
Progression per 2007 IWG criteria documented between scheduled visits or at scheduled visit without prior new anticancer treatment started	Date of the first documented tumor progression per the 2007 IWG criteria	Progressed
Death without progression per 2007 IWG criteria and without prior new anticancer treatment started	Date of death	Progressed

To further characterize PFS, progression by response to most recent prior systemic cancer therapy and progression by number of prior systemic cancer therapy lines may also be evaluated.

4.2.5 Objective Response Rate (Investigator-assessed)

Investigator-assessed ORR is defined similarly as described for the primary endpoint above (Section 4.1) and will be further characterized by TTR and DOR.

First subsequent therapy date per Investigator is defined as the earliest start date on or after the first study therapy date among systemic anti-cancer therapy, stem cell transplant, non-palliative radiotherapy and local tumor treatment (non-palliative radiotherapy or other).

4.3 Exploratory Endpoints

[redacted]

[redacted]

[redacted]

4.3.7 Outcome Research

4.3.7.1 EORTC-QLQ-C30

Health-related quality of life (HRQoL) will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire Version 3. It is a 30-item instrument that has gained wide acceptance in oncology clinical studies. The EORTC QLQ-C30 is composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom (fatigue, nausea and vomiting, and pain) and a global health status/QOL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups[30]. Except for the overall health status and global quality of life items, responses for all items are 4 point categorical scales ranging from 1 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales.

Data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual, as follows:

Functional scales:

- Physical functioning: (1 - ((Q1+Q2+Q3+Q4+Q5)/5 -1)/3) * 100
- Role functioning: (1 - ((Q6+Q7)/2-1)/3) * 100
- Emotional functioning: (1 - ((Q21+Q22+Q23+Q24)/4-1)/3) * 100
- Cognitive functioning: (1 - ((Q20+Q25)/2-1)/3) * 100
- Social functioning: (1 - ((Q26+Q27)/2-1)/3) * 100

Global health status:

- Global health status/QoL: ((Q29+Q30)/2-1)/6 * 100

Symptom scales/items:

- Fatigue: ((Q10+Q12+Q18)/3-1)/3 * 100
- Nausea and vomiting: ((Q14+Q15)/2-1)/3 * 100
- Pain: ((Q9+Q19)/2-1)/3 * 100

- Dyspnea: ((Q8-1)/3 * 100
- Insomnia: (Q11-1)/3 * 100
- Appetite loss: (Q13-1)/3 * 100
- Constipation: (Q16-1)/3 * 100
- Diarrhea: (Q17-1)/3 * 100
- Financial difficulties: (Q28-1)/3 * 100

Missing values will be imputed for missing items by "assuming that the missing items have values equal to the average of those items which are present" for any scale in which at least half the items are completed. A scale in which less than half of the items are completed will be treated as missing. This is the method proposed in the scoring manual. A questionnaire will be considered as received if at least one of the 15 scales is non-missing (after imputation).

All questionnaires completed at baseline and on-study will be assigned to a time-point according to the windowing criteria in Table 4.3.7.1-1 and included in the analysis. In case a subject has two on-study assessments within the same window, the assessment closest to the time-point will be used. And, in the case of two assessments at a similar distance to the time-point, the latest one will be chosen. In the event where the subject has no assessment at all in a specific window, the observation will be treated as missing for that time-point.

Table 4.3.7.1-1: Time Windows for EORTC-QLQ-C30 Assessments

Nominal Time-Point	Time Window
Week 1 (Baseline)	Prior to first dose on Day 1
Week 9	Day 2 thru Day 85, inclusive
Every 8 weeks up to week 25	Nominal Day (+ 28 days / - 27 days, inclusive)
Week 33	Day 198 thru Day 267, inclusive
Every 12 weeks thereafter	Nominal Day (+ 42 days / - 41 days, inclusive)
Follow-up 1	NA
Follow-up 2	NA

4.3.7.2 EuroQoL EQ-5D

Subjects' overall health status will be assessed using the EuroQol Group's self-reported health status measure (EQ-5D-3L)[31]. EQ-5D essentially has 2 components- the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. Once the data have been collected and a database created, a scoring function can be used to assign a value (i.e., EQ-5D index score) to self-reported health states from a set of population-based preference weights.

The EQ VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state)[32].

4.3.8 Biomarker Data

[redacted]

4.3.8.2 Other Biomarkers

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

The planned sample size for this study will be approximately 90 treated subjects. The sample size was determined based on two considerations: the ability to produce a CI which would exclude an ORR of 20%, which is not considered clinically relevant and provide sufficient information for a reliable understanding of the safety profile.

Assuming the true ORR is 35%, the study has approximately 87% power to reject the null hypothesis that the true ORR is ≤ 20%, considering a 2-sided alpha of 5%. In addition, Table 5-1 summarizes the 95% exact CI for the target ORRs ranging from 30% to 44% with sample size of 90. At observed ORR ≥ 30%, the lower bound of the 95% CI excludes 20%.

Table 5-1: Observed ORR with Exact 95% CI

True ORR	95% Exact CI
30%	[20.8%-40.6%]
34%	[24.7%-45.2%]
40%	[29.8%-50.9%]
44%	[34.0%-55.3%]

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple

assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will considered as baseline.

6.1.2 Post Baseline Period

On-treatment AEs will be defined as AEs with an onset date-time on or after the date-time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). An AE will be counted as on-treatment if the event occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment. Refer to Core SAP[29].

On-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. An evaluation will be counted as on-treatment if it occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment. Refer to Core SAP[29].

6.2 Treatment Regimens

All subjects will be treated with nivolumab.

6.3 Populations for Analyses

6.3.1 Analysis Populations

The following populations will be defined.

- **All enrolled subjects**: All subjects who signed an informed consent form and were registered into the IVRS.
- **All treated subjects**: All enrolled subjects who received at least one dose of nivolumab. This is the primary population for efficacy and safety.
- **All response evaluable subjects**: All treated subjects who have baseline and at least one on-study evaluable tumor measurement.
- **PK subjects**: All enrolled subjects with available serum time-concentration data from subjects dosed with nivolumab.
- **Immunogenicity evaluable subjects**: all treated subjects with baseline and at least one post baseline immunogenicity assessment.
- **All PD-L1 tested subjects**: All enrolled subjects who had a tumor tissue sample available for assessment of PD-L1 expression.
- **All PD-L1 evaluable subjects**: All treated subjects with quantifiable baseline PD-L1 expression
- **Biomarker subjects**: All treated subjects with available biomarker data.
- **Outcomes Research subjects**: all treated subjects who have an assessment at baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment (for EORTC QLQ-C30 and EQ-5D separately).

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, the bulleted titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category. Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized using the mean, standard deviation, median, minimum and maximum values.

Time to event distribution (e.g. progression free survival, overall survival, time to response, and duration of response) will be estimated using Kaplan Meier techniques. Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survivor function S(t)[33,34]. Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula[35] for variance derivation and on log-log transformation applied on the survivor function S(t) [36].

7.2 Study Conduct

7.2.1 Accrual

The following will be summarized on the enrolled population:

- Number of subjects accrued by country and investigational site
- Number of subjects accrued by month

A by subject listing of accrual will be produced.

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

At entrance:

- Subjects without documented relapsed or refractory FL.
- Subjects without treatment of FL consisting of ≥ 2 prior treatment lines; each of the two prior treatment lines must include a CD20 and/or an alkylating agent (e.g., bendamustine, cyclophosphamide, ifosfamide, chlorambucil, melphalan, busulfan, nitrosoureas). At least one of the prior treatment lines must include rituximab.
- Subject without measurable disease at baseline.
- Subject with baseline ECOG not in (0, 1).

On-Study:

- Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy, or standard or investigational agents for treatment of cancer).

A by subject listing will be produced.

7.3 Study Population

7.3.1 Subject Disposition

The total number of subjects enrolled (treated or not) will be presented along with the reason for not being treated.

Number of subjects who discontinued treatment along with corresponding reason will also be tabulated.

7.3.2 Demographics and Other Baseline Characteristics

Descriptive statistics will be summarized the following baseline characteristics for all treated subjects. All baseline presentations will identify subjects with missing measurements. Listings will also be provided.

- Age (descriptive statistics)
- Age categories (< 65, ≥ 65 and < 75, ≥ 75)
- Gender, Race/Ethnicity
- Region (US/Canada vs. Europe vs. Rest of World)
- ECOG PS (0, 1, >1, Not Reported)
- weight
- Smoking Status (current/former vs never smoker vs. unknown)
- Time from initial disease diagnosis to first dose of nivolumab (descriptive statistics and (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 5 year, 5 - < 7 year, 7 - < 10 year, ≥ 10 years)
- Disease stage at initial diagnosis (Stage I-II-III-IV)
- Follicular lymphoma international prognostic index (FLIPI) Score (0, 1, 2, 3, 4, 5) at initial diagnosis
- Lymphoma involvement in bone marrow at baseline (Yes/No/Not Reported)
- Disease status at study entry (Relapse, Refractory)
- All lesions (Investigator Tumor Assessments at Baseline): sites of diseases, number of disease sites per subject
- Target Lesions (Investigator Tumor Assessments at Baseline): Presence of target lesions, site of target lesion, sum of diameters of target lesions.

7.3.3 Medical History

General medical history will be listed by subject and pretreatment events will be tabulated.

7.3.4 Prior therapy

The following will be summarized:

- Number of subjects by type of prior therapy received:
  - Immunotherapy by Monoclonal Antibodies
  - Steroid
  - Chemotherapy – Anthracyclines
  - Chemotherapy – Other than Anthracyclines
  - Kinase Inhibitors
  - Immunomodulary Derivatives
  - Radioimmunotherapy
  - Other
- Number of subjects per type of regimen for first line of therapy (e.g. R-CHOP vs R-CVP vs OTHER)
- Number of prior systemic cancer therapy lines received (0, 1, 2, 3, 4, ≥ 5)
- Best response to most recent prior systemic cancer therapy (CR vs. PR vs. SD vs. Relapse/PD vs. Unable to Determine vs. Not Applicable vs. Not Reported) (Note: Not Applicable is used when the agent is a conditioning regimen for stem cell transplant)
- Time from completion of most recent prior regimen to treatment (< 3, 3 - 6, > 6 months)
- Prior radiotherapy (yes, no)
- Prior autologous transplant (yes, no)

Other Prior therapy:

- Prior/current non-study medication classified by anatomic and therapeutic classes.

Medication will be reported using the generic name. A listing by subject will also be provided.

7.3.5 Baseline Examinations

Percentage of subjects with abnormal baseline physical examination will be tabulated by examination criteria.

7.4 Extent of Exposure

Analyses in this section will be performed in all treated subjects.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics):

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.
- Number of doses received (summary statistics)
- Cumulative dose
- Duration of treatment: duration of treatment will be presented using a Kaplan-Meier curve whereby the last dose date will be the event date for subjects who discontinued study therapy. Subjects who are still on study therapy will be censored on their last dose date. Median duration of treatment and associated 95% CI will be provided.
- A by-subject listing of dosing of study medication (record of study medication, infusion details, dose change) and a listing of batch number will be also provided.

Table 7.4.1-1: Administration of study therapy: definition of parameters

	nivolumab
Dosing schedule per protocol	3mg/kg every 2 weeks
Dose	Dose (mg/kg) is defined as Total Dose administered (mg)/Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.
Cumulative Dose	Cum dose (mg/kg) is sum of the doses (mg/kg) administered to a subject during the treatment period.
Relative dose intensity (%)	Cum dose (mg/kg) / [(Last dose date - Start dose date + 14) x 3 /14] x 100
Duration of treatment	Last dose date - Start dose date + 1

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose delays

Treatment may be delayed for up to a maximum of 6 weeks from the last dose. A dose will be considered as actually delayed if the delay is exceeding 3 days (i.e., greater than or equal to 4 days from scheduled dosing date). Length of delay is defined as (duration of previous cycle in days - 14). Dose delays will be divided into following categories: 4 - < 8 days, 8 - < 15 days, 15 - < 42, ≥ 42 days. Reason for dose delay/omission will be retrieved from CRF dosing pages.

The following parameters will be summarized.

- Number of subjects with at least one dose delayed, number of dose delayed per subject, Length of Delay and Reason for Dose Delay

7.4.2.2 Infusion Interruptions and Rate Changes

The following parameters will be summarized:

- Number of subjects with at least one dose infusion interruption, number of infusion interruptions per subject and the reason for interruption.

- Number of subjects with at least one IV infusion rate reduction, number of IV infusion rate reduction per subject and the reason for reduction

7.4.2.3 Dose Reductions/Escalation

There will be no dose escalations or reductions of nivolumab allowed.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e. on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the WHO Drug Dictionary.

The following summary tables will be provided:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term).

A by-subject listing will accompany the table.

7.5 Efficacy

7.5.1 Primary endpoint of ORR (IRRC-assessed)

The IRRC-assessed ORR (using revised IWG Criteria for Malignant Lymphoma criteria) will be summarized on the all subjects treated population by a binomial response rate. The Clopper-Pearson[37] method will be used to estimate the two-sided 95% CI.

BOR will be summarized by response category.

Summary statistics of time to objective response will be provided for subjects who achieve PR or CR, as assessed by the IRRC. CR requires confirmation by PET. To assess tumor response kinetics, time to response will also be analyzed using the KM methodology for all treated subjects. Kaplan-Meier curve will represent the cumulative rate of response over time. For the non-responders, time to response will be censored at the maximum time of response + 1 day of all subjects. Cumulative Response Rates will be tabulated for Week 9, Month 4, 6, 8, 12 and 18, and overall Response Rate will be provided.

7.5.1.1 ORR Subgroups

To assess consistency of ORR, IRRC-assessed ORR (primary analysis) will be summarized for the following subgroups:

- Age (< 65, ≥ 65 and < 75, ≥ 75)
- Region (US/Canada, Europe, Rest of the world).
- Gender (Male, Female)
- Race (White, Black or African American, Asian, and Other (pooling all other possibilities)
- Smoking status (current/former vs never smoker vs unknown)

- ECOG (0, 1, >1, NOT REPORTED)
- Number of prior therapies (0, 1, 2, 3, 4, ≥ 5)
- Prior Autologous Transplant (Yes, No)
- Time from most recent prior systemic cancer therapy to first dose of nivolumab (< 3 months, 3 - 6 months, > 6 months)
- Refractory, Relapsed Lymphoma (which is the disease diagnosis status at study entry)
- FLIPI Score (0-1, 2, 3, 4-5)

Categories including less than 5 subjects may be collapsed. Analyses of subgroups of less than 5 subjects may not be provided.

7.5.1.2 Sensitivity analyses for ORR

- As sensitivity analysis, a summary of IRRC-assessed ORR based on response evaluable subjects instead of all treated subjects will also be presented. Clopper Pearson 95% CI will be used in this analysis.
- To assess concordance between IRRC (primary analysis) and investigator assessments, BOR will be cross-tabulated by assessment type (Investigator vs IRRC). Concordance Rate of Responders will be computed as the frequency with which Investigator and IRRC agree on classification of a subject as responder/non responder as a proportion of the total number of subjects assessed.

7.5.2 Secondary Endpoint of Duration of Response (IRRC-assessed)

The DOR will be summarized for subjects who achieve PR or CR as determined by IRRC using KM product-limit method. Two-sided, 95% confidence intervals for median DOR will be constructed based on log-log transformation. Range of duration of response and the number of ongoing responders will also be presented. In addition, the percentage of responders still in response at different time points (3, 6 and 12 months) will be presented based on the DOR KM plot.

The status of subjects who are censored in the duration of response analysis will be tabulated using the following categories:

- received subsequent anti-cancer therapy
- off-study (with reason)

Duration of stable disease will also be estimated using KM product-limit method for subjects with SD as best response. Two-sided, 95% confidence intervals for median duration of SD will be computed.

7.5.3 Secondary Enpoint of Complete Remission Rate (IRRC-assessed)

IRRC-assessed CRR will be summarized by a binomial response rate and its corresponding two-sided 95% exact CIs using the Clopper-Pearson[37] method.

To further characterize CRR, the duration of CR will be summarized for subjects who achieve CR as determined by IRRC using KM product-limit method. Two-sided, 95% confidence intervals for median duration of CR will be constructed based on log-log transformation. Range of duration of CR will also be presented.

7.5.4 Secondary Endpoint of Partial Remission Rate and Duration (IRRC-assessed)

IRRC-assessed PRR will be summarized by a binomial response rate and its corresponding two-sided 95% exact CIs using the Clopper-Pearson[31] method.

To further characterize PRR, the duration of PR will be summarized for subjects who achieve PR as determined by IRRC using KM product-limit method. Two-sided, 95% confidence intervals for median duration of PR will be constructed based on log-log transformation. Range of duration of PR will also be presented.

7.5.5 Secondary Endpoint of Progression Free Survival (IRRC-assessed)

IRRC-assessed PFS will be summarized descriptively using the Kaplan-Meier (KM) product-limit method. Median values of PFS, along with two-sided 95% CIs (based on the log-log transformation), will also be calculated.

The source of progression (death vs. progression) will be summarized.

The status of subjects who are censored in the PFS Kaplan-Meier analysis will be tabulated using following categories:

- Received subsequent anti-cancer therapy (Stem Cell Transplant, other)
- Still on-treatment
- Progression-free in follow-up
- Off-study: (lost to follow-up, withdrew consent, other).

KM curve of PFS will be generated. PFS rates per IRRC at 6, 9 and 12 months will be estimated using KM estimates on the PFS curve. PFS rates at 18, 24 and 36 months may also be estimated depending on whether minimum follow-up will be longer than timepoint to generate the rate. Associated two-sided 95% CIs will be calculated.

KM curves of PFS by response of most recent prior systemic cancer therapy as well as KM curves of PFS by number of prior systemic anti-cancer therapy lines will also be generated. Some categories may be collapsed to have sufficient number of subjects in each category. Median values of PFS in each category along with two-sided 95% CIs (based on the log-long transformation) will also be calculated.

7.5.6 Secondary Endpoint of Objective Response Rate (Investigator-assessed)

Investigator-assessed ORR will be summarized by a binomial response rate and its corresponding two-sided 95% exact CIs using the Clopper-Pearson[37] method.

Investigator-assessed BOR will be summarized by response category.

Summary statistics of time to objective response will be provided for subjects who achieve PR or CR, as assessed by the Investigator. CR requires confirmation by PET. To assess tumor response kinetics, time to response will also be analyzed using the KM methodology for all treated subjects. Kaplan-Meier curve will represent the cumulative rate of response over time. For the non-responders, time to response will be censored at the maximum time of response + 1 day of all subjects. Cumulative Response Rates will be tabulated for Week 9, Month 4, 6, 8, 12 and 18, and overall Response Rate will be provided.

7.5.7 Exploratory Endpoints

[redacted]

[redacted]

7.6 Safety

All analyses from the Core Safety SAP[29] will be produced.

7.6.1 Deaths

See Core Safety SAP[29].

7.6.2 Serious Adverse Events

See Core Safety SAP[29].

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP[29].

7.6.4 Adverse Events Leading to Dose Modification

See Core Safety SAP[29].

7.6.5 Adverse Events

See Core Safety SAP[29].

7.6.6 Select Adverse Events

See Core Safety SAP[29].

7.6.7 Immune modulating medication

See Core Safety SAP[29].

7.6.8 Multiple Events

See Core Safety SAP[29].

7.6.9 Clinical laboratory evaluations

See Core Safety SAP[29].

7.6.10 Vital Signs and Pulse Oximetry

See Core Safety SAP[29].

7.6.11 Immunogenicity Analysis

See Core Safety SAP[29].

7.6.12 Pregnancy

By-subject listing of pregnancy tests results will be provided

7.6.13 Clinical Safety Program (CSP)

See Core Safety SAP[29].

7.6.14 Adverse Events by Subgroup

See Core Safety SAP[29].

7.6.15 Immune-mediated Adverse Events Analysis

See Core Safety SAP[29].

7.7 Pharmacokinetics

The nivolumab concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop or refine a population PK model. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). In addition, model determined exposures may be used for exposure-response analyses. Results of population PK and exposure response-analyses will be reported separately.

7.8 Biomarker Analyses

[redacted]

7.9 Outcome Research Analyses

7.9.1 EORTC-QLQ-C30 Questionnaire

Unless otherwise specified, the analysis of EORTC QLQ C-30 will be performed in all treated subjects who have an assessment at baseline and at least one subsequent assessment. Analyses will be performed.

Baseline measures will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) for each QLQ-C30 item, as well as global and functional scales, based on subjects with a baseline measurement.

Change from baseline will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) for each QLQ-C30 item, as well as global and functional scales at each assessment time point. In addition, the percentage of subjects demonstrating a clinically meaningful deterioration (defined as a 10 point change from baseline) will be presented for each scale at each assessment timepoint. Percentages will be based on number subjects assessed at baseline and at assessment time point.

EORTC-QLQ-C30 questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (i.e., number of subjects on treatment or in follow up), will be calculated and summarized for each assessment time point.

A by subject listing of QLQ-C30 with each QLQ-C30 item, functional scales and global health status will be provided.

7.9.2 EQ-5D Questionnaire

Unless otherwise specified, the analysis of EQ-5D will be performed in all treated subjects who have an assessment at baseline and at least one subsequent assessment. Analyses will be performed.

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics (N, mean, SD, median, 25th and 75th percentiles, minimum, maximum).

Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem. Percentages will be based on number subjects assessed at assessment time point.

A by-subject listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS will be provided.

Results of EQ5D-Index will be presented separately and will be described in the GHEOR SAP.

7.10 Interim Analysis

No interim analysis planned. Interim analyses may be conducted if it is necessary in order to make decisions regarding further development. Summaries and listings of efficacy and safety will be provided. Interim analyses will not impact the study duration and the trial will continue as planned.

8 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates:

For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[38]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in BMS Non-Study Medication Domain Requirements Specification[39].

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known alive date and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known alive date
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known alive date

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

- In case, the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For other partial/missing dates, the following conventions will be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "July 1" will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time from first diagnosis to first dosing date, duration response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

9 CONTENT OF REPORTS

All analyses described in the SAP will be included in the Clinical Study Report(s) except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables, figures and listings

10 DOCUMENT HISTORY

Table 10-1: Document History

Version Number	Author(s)	Description
1.0	Cécile Dorange	Initial version 13-May-2014
2.0	Anne Sumbul	Updated on 25-Sep-2015
3.0	Anne Sumbul	Updated on 24-Apr-2017 • Reference to Protocol v3 (21JUL16) • Clarify PFS censoring scheme • Addition of definition of ongoing responder • Add PFS and OS rate at 9 and 36 months • Add Time to Next Treatment • Add PFS by response to most recent prior systemic cancer therapy

Table 10-1: Document History

		• Add PFS by number of prior systemic cancer therapy line • [redacted] • Clarify management of raw PD-L1 result = "<1%" • Analysis of IMAE is now referring to nivo core safety SAP • Clarify notion of subsequent therapy
3.1	Anne Sumbul	Updated on 27-Jun-2017 • Removed "not reported" for prior transplant and prior radiotherapy • Add "Not Applicable" to the codelist of best response to prior systemic cancer therapy • Add R-CVP as category for first line therapy • [redacted] • [redacted]

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