Official Title of Study:

A Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) After Failure of Autologous Stem Cell Transplant (ASCT) or After Failure of At Least Two Prior Multi-Agent Chemotherapy Regimens in Subjects Who Are Not Candidates for ASCT

NCT Number: NCT02038933

Document Date (Date in which document was last revised): Oct 20, 2017

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 DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) AFTER FAILURE OF AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) OR AFTER FAILURE OF AT LEAST TWO PRIOR MULTI-AGENT CHEMOTHERAPY REGIMENS IN SUBJECTS WHO ARE NOT CANDIDATES FOR ASCT

(CHECKMATE 139: CHECKPOINT PATHWAY AND NIVOLUMAB CLINICAL TRIAL EVALUATION 139)

PROTOCOL CA209-139

VERSION # 2.1

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

LIST OF FIGURES

[redacted]

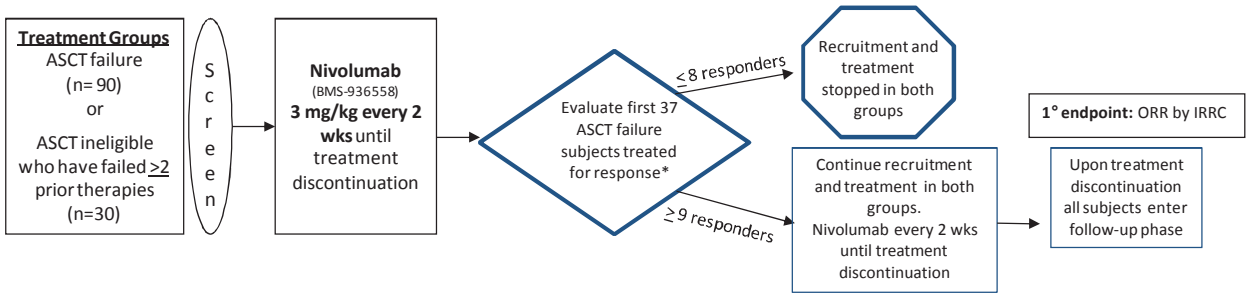
2 STUDY DESCRIPTION

2.1 Study Design

This is a single-arm Phase 2 study in subjects ≥18 years old with relapsed or refractory DLBCL, or transformed lymphoma (TL), after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in subjects who are not ASCT candidates. Approximately 120 subjects will be treated with nivolumab 3 mg/kg IV every 2 weeks. Subjects will be placed into cohorts based on prior ASCT failure [n=90] or ASCT ineligibility [n=30].

For the ASCT-failed cohort, a two-stage design will be used to test whether nivolumab yields a clinically compelling objective response rate. In the first stage, responses will be evaluated by the IRRC on the first 37 subjects treated. If there are 8 or fewer responses in these 37 subjects, the study will be stopped. In this case, the study will be terminated in both the ASCT-failed cohort as well as the ASCT ineligible cohort. Otherwise, approximately 53 additional subjects will be accrued into the ASCT-failed cohort to target a total of 90 treated subjects. Recruitment and treatment of subjects in both cohorts (ASCT failed and ASCT ineligible) will continue as described during the evaluation of the first 37 ASCT failed subjects treated. The tolerability of the regimen will continue to be evaluated by the sponsor with the investigators to ensure that it is acceptable for continued enrollment. For the ASCT ineligible cohort a single stage design will be used to estimate the objective response rate using approximately 30 treated subjects.

Figure 2.1-1: Study Design Schematic



* Recruitment and treatment of subjects in both groups (ASCT failure and ASCT ineligible) will continue as described during the evaluation of the first 37 ASCT failure subjects treated.

Note: Stage 1 data review will be conducted internally by BMS senior management for decision to proceed to second stage.

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 ORR, using the 2007 revised International Working Group Criteria for Malignant Lymphoma criteria. Secondary endpoints include IRRC-assessed duration of response (DOR), as well as complete remission rate (CRR), partial remission rate (PRR) and their duration and progression free survival (PFS) as determined by IRRC assessment and ORR based on investigator assessment.

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

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**
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 3 mg/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 02 (Incorporates Amendment 03)	23-Jul-2014	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 [redacted] and assessments to be performed on subjects that discontinue study treatment to receive an allogeneic SCT or ASCT
Revised Protocol 01 (Incorporates amendment 01)	06-Dec-2013	Per FDA mandatory recommendation: The protocol title and other sections have been updated to indicate that subjects who are not candidates for ASCT must

Table 2.4-1: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
		have failed at least 2 prior multi-agent chemotherapy regimens in order to meet eligibility requirements 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 Subjects that received ≥ 1000 mg of carmustine (BCNU) as part of their pre-transplant conditioning regimen 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	30-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 DLBCL or TL who are refractory or have relapsed following ASCT or after failure of at least two prior multi-agent chemotherapy regimens in ASCT ineligible patients.

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

[redacted]

[redacted]

4 ENDPOINTS

4.1 Primary endpoint ORR (IRRC-assessed)

The primary objective will be measured by the primary endpoint of IRRC-assessed objective response rate (ORR). It is defined as the number of subjects with a best overall response (BOR) of complete remission (CR) or partial remission (PR), according to the 2007 revised International Working Group Criteria for Malignant Lymphoma (see Table 4.1-1), divided by the number of treated subjects. The final analysis of the primary endpoint will occur at least 6 months after the last enrolled subject's first dose of study therapy (primary data lock time). 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 revised International Working group Criteria for Malignant Lymphoma or the date of subsequent therapy, whichever occurs first. Stem Cell Transplant will be considered as subsequent therapy. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial 2007 IWG defined progression. 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 (CR or PR), 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 > 1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

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

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 initiation of the subsequent anticancer therapy. Stem Cell Transplant will be considered as subsequent therapy. This endpoint will only be evaluated in subjects with objective response of CR or PR.

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 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 initiation of the subsequent anti-cancer therapy. Stem Cell Transplant will be considered as subsequent therapy.

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

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments and no death	First Dosing date	Not Progressed
No on study tumor assessments and no death	First Dosing date	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
Clinical progression without evidence of progression per 2007 IWG criteria or No progression	Date of last tumor assessment with no documented progression	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	Date of death	Progressed

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.

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

The planned sample size for this study will be approximately 120 treated subjects, separated into two cohorts based on prior ASCT failure [n= approx. 90] or ASCT ineligibility [n= approx. 30].

For the ASCT-failed cohort, a modified Simon's two-stage design will be used to test the null hypothesis that the true ORR is ≤ 20% (not considered clinically compelling). In the first stage, 37 treated subjects will be accrued. If there are 8 or fewer responses in these 37 subjects, the study will be stopped. In this case, the study will be terminated in both the ASCT-failed cohort as well as the ASCT ineligible cohort. Otherwise, approximately 53 additional subjects will be accrued into the ASCT-failed cohort to target a total of 90 treated subjects. The null hypothesis will be rejected if 25 or more responses are observed in 90 treated subjects. This design yields a one-sided type I error rate of 5% and power of 90% when the true response rate is 35%. The interim stopping rule for this design is identical to Simon's "optimal" 2-stage design[25], thereby limiting the expected number of subjects who receive treatment when the true response rate is not of clinical value. However, the sample size at the final analysis is larger than required by Simon's optimal design in order to provide additional subjects for safety evaluation. Table 5-1 provides the probabilities of stopping at different ORR using this rule.

Table 5-1: Operating Characteristics of Stopping Rule

True ORR	P(early stop)
15%	0.91
20%	0.69
25%	0.40
30%	0.18
35%	0.06
40%	0.01

For the ASCT ineligible cohort, the sample size of 30 treated subjects is determined to achieve a confidence interval (CI) width around the ORR estimate with a sufficient level of precision. If the observed number of subjects with ORR is 10 (33%), the width of the exact 2-sided 95% CI is 36%

with a lower bound of 17.3%. Such an observation would provide evidence in support that the true ORR is greater than or equal to 17.3% with a Type I error rate of 5%.

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[21].

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[21].

6.2 Treatment Regimens

All subjects will be treated with nivolumab.

6.3 Populations for Analyses

6.3.1 Study Cohorts

ASCT-failed cohort: All subjects with prior ASCT (per CRF)

ASCT ineligible cohort: All subjects without prior ASCT (per CRF)

6.3.2 Analysis Populations

Within each cohort 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.

[redacted]

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)[26,27]. Rates at fixed time points will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula[28] for variance derivation and on log-log transformation applied on the survivor function S(t) [29].

7.2 Study Conduct

7.2.1 Accrual

The following will be summarized on the enrolled population for the 2 cohorts separately and on the pooled 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, refractory DLBCL, or transformed lymphoma (TL)
- Subject without measurable disease at baseline
- Subject with baseline ECOG >1

On-Study:

- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, surgical resection of lesions, non palliative radiation therapy, or standard or investigational agents for treatment of cancer).

A summary table will be produced for the 2 cohorts separately and on the pooled population. A by subject listing will be produced.

7.3 Study Population

Analyses from this section will be produced for the 2 cohorts separately and on the pooled 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, ≥65)
- Gender, Race/Ethnicity
- Region (US/Canada vs. Europe vs. Rest of World)
- ECOG PS
- weight
- Smoking Status (Yes/No/Unknown)
- Initial disease diagnosis (Diffuse Large B-Cell Lymphoma, Follicular Lymphoma)

- Time from the initial diagnosis to first transplant (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 4 year, 4 - < 5 year, ≥ 5 year) (only for ASCT failed cohort)
- Time from the most recent transplant to first dose of nivolumab) (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 4 year, 4 - < 5 year, ≥ 5 year) (only for ASCT failed cohort)
- Time from initial disease diagnosis to first dose of nivolumab (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 4 year, 4 - < 5 year, ≥ 5 year)
- Disease stage at initial diagnosis (Stage I-II-III-IV)
- Revised International Prognostic Index (IPI) Score (0, 1, 2, 3, 4, 5) at initial diagnosis
- Lymphoma involvement in bone marrow at baseline (Yes/No/Not Available)
- Disease diagnosis at enrollment (DLBCL/Transformed Lymphoma, 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 product 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 (excluding preparative regimen for ASCT):
  - 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 and second lines of therapy (e.g. R-CHOP, ICE)
- Number of subjects by type of regimen (BEAM, CBV, Other) received for preparation to ASCT (for ASCT failed cohort only)
- Number of prior systemic regimen received (0, 1, 2, 3, ≥4), excluding preparative regimen for ASCT subjects
- Best response to most recent prior regimen (CR vs PR vs SD vs Relapse/PD vs Unable to Determine vs Not reported)
- Best response before transplant (for ASCT failed cohort)
- Best response to ASCT (for ASCT failed cohort)

- Best response to regimen post ASCT (for ASCT failed cohort)
- Time from completion of most recent prior regimen to treatment (< 3, 3 - 6, > 6 months)
- Prior radiotherapy (yes or 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 for the 2 cohorts separately and on the pooled population.

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	3 mg/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 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.

[redacted]

7.5 Efficacy

Unless otherwise specified analyses from this section will be produce by cohort separately.

7.5.1 Primary endpoint of ORR (IRRC-assessed)

The IRRC-assessed ORR (using 2007 revised International Working Group Criteria for Malignant Lymphoma criteria) will be summarized on the all subjects treated population by a binomial response rate. The method proposed by Atkinson and Brown will be used to estimate the CI for the ASCT-failed cohort if the responders at interim analysis are above the critical value, which is 8 responders. This confidence interval takes into account the group sequential nature of the two

stage modified Simon design. The two-sided 90% CI will be presented, corresponding to the nature of the 1-sided 5% alpha from the modified Simon design. In addition, per protocol, the two-sided 95% CI will be presented. However, if the responders are below the critical value and we don't stop the study, we are no longer following the two-stage design. The two-sided confidence intervals for binomial proportions will be derived using the Clopper-Pearson method.

The Clopper-Pearson[30] method will be used to estimate the two-sided 95% CI for the ASCT ineligible cohort, as well as 90% and 95% confidence intervals for ORR at interim analysis (IA).

In the ASCT failed cohort, the null hypothesis will be rejected if 25 or more responses are observed in 90 treated subjects at the final analysis (FA). In case not exactly 90 treated subjects are available, success will be referenced to a 2-sided 90% CI lower bound greater than 20%.

Success of the ASCT ineligible cohort will be referenced to a 2-sided 95% CI lower bound greater than 17.3%.

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 (for subjects in the ASCT failed cohort only):

- Age (<65, ≥ 65, ≥ 65 and < 75, ≥ 75)
- Region (US/Canada, Europe, Rest of the world).
- Gender (Male, Female)
- Race (white, black, Asian, and other)
- Smoking status (yes/no)
- ECOG (0, 1)
- Time from the initial diagnosis to transplant (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 4 year, 4 - < 5 year, >=5 year)
- Number of prior therapies (1, 2, 3, >=4) excluding preparative regimen
- Time from most recent prior regimen to first dose of nivolumab (< 3 months, 3 - 6 months, >6 months)
- Refractory, Relapsed Lymphoma
- DLBCL, Transformed Lymphoma

- IPI Score (0,1, 2, 3, 4,…)

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 categories (responders versus non-responders versus non-evaluable or no evidence of disease versus not reported) 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 by cohort 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 DOR 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.

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 Endpoint of Complete Remission Rate and Duration (IRRC-assessed)

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

To further characterize CRR, the duration of CR will be summarized by cohort 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 cohort 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 by cohort 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 by cohort 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 month will be estimated using KM estimates on the PFS curve. PFS rates at 6, 12, 18 and 24 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.

Subject listings of PFS will be produced.

7.5.5.1 Sensitivity analyses of PFS

Sensitivity analyses of PFS based on IRRC assessment will also be performed using the following modification of PFS primary definition.

- PFS accounting for assessment after subsequent therapy: PFS will be defined similarly to the primary definition except that events (progression or death) and tumor assessments that occurred after subsequent anti-cancer therapy will be considered (no time point truncation).

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

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

[redacted]

[redacted]

[redacted]

7.6 Safety

All analyses from the Core Safety SAP[21] will be produced for the ASCT-failed and ASCT ineligible cohorts pooled and for the ASCT-failed cohort separately.

7.6.1 Deaths

See Core Safety SAP[21]

7.6.2 Serious Adverse Events

See Core Safety SAP[21]

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP[21]

7.6.4 Adverse Events Leading to Dose Modification

See Core Safety SAP[21]

7.6.5 Adverse Events

See Core Safety SAP[21]

7.6.6 Select Adverse Events

See Core Safety SAP[21]with the exception that most of the analyses of select adverse events will be limited to the 30 days safety windows and will not be repeated with the 100 days safety windows. Plots of time to onset of select adverse events and tables of rates by timepoint of select adverse events will not be produced. Summary of any select, drug-related select, select endocrine, drug-related select endocrine AE by worst CTC grade will be produced. Summary of any select, drug-related select, select endocrine and drug-related select endocrine AE leading to discontinuation by worst CTC grade will also be produced.

7.6.7 Immune modulating medication

See Core Safety SAP[21]

7.6.8 Multiple Events

See Core Safety SAP[21]

7.6.9 Clinical laboratory evaluations

See Core Safety SAP[21] with the exception that scatterplots for total bilirubin will not be produced.

7.6.10 Vital Signs, Pulse Oximetry and Medical Procedures

See Core Safety SAP[21]. A by-subject listing of the medical prodecures will be produced.

7.6.11 Immunogenicity Analysis

See Core Safety SAP[21]

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[21]

7.6.14 Adverse Events by Subgroup

See Core Safety SAP[21]

7.6.15 Immune-mediated Adverse Events Analysis

IMAE analyses will include events, regardless of causality, occurring within 100 days of the last dose. These analyses are limited to subjects who received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which will be included in the analysis regardless of treatment since these events are often managed without immunosuppression.

IMAEs, serious IMAEs, IMAEs leading to discontinuation, and IMAEs leading to dose delay or reduction will be summarized by worst CTC grade and presented by IMAE Category/PT.

Time to onset, time to resolution, time to resolution with completion of immunosuppressive medication will be defined and summarized by IMAE category in the same manner as for select AEs (see Section 7.6.6) except that, other than for the endocrine category, the longest duration of IMAEs has to be associated with the use of an immune-modulating medication. Time to Resolution for Longest Any Grade or Grade 3-5 IMAE cluster per subject will be listed.

Use of immune-modulating medications for IMAE management will be summarized by IMAE category in a similar manner as for the select AEs (see Section 7.6.7).

IMAE rechallenge will be also summarized.

7.6.16 Other Events of Special Interest

In addition to select AE and immune-mediated AE, categories of other events of special interest (OESI) have been defined (i.e. myasthenic syndrome, Guillain-Barre syndrome, demyelination, pancreatitis, uveitis, encephalitis events). Worst CTC grade of any and drug-related OESI (both safety windows) will be summarized along with the time to onset and resolution. In addition, worst CTC grade of serious OESI and OESI leading to discontinuation will be summarized (both safety

windows). Lastly, OESI occurring within 100 days of the last dose in subjects who received immunosuppressive medication for treatment of the events will be tabulated by worst CTC grade and the time to onset and resolution will be provided.

[redacted]

[redacted]

7.10 Interim Analysis

As per the 2-stage design of this study, one interim analysis of IRRC-assessed ORR in the ASCT failed cohort will be performed when 37 ASCT-failed subjects have been treated and those subjects

still on treatment have completed 8 weeks follow-up (after the first scheduled tumor assessment). If there are 8 or fewer responses in these 37 subjects, the study will be stopped (in both the ASCT-failed and the ASCT ineligible cohorts). Otherwise, approximately 53 additional subjects will be accrued to target a total of 90 treated subjects in the ASCT failed group. Accrual and treatment will continue during the time period that the interim analysis is being conducted. This may result in more than 37 treated subjects in the event that the study is terminated for lack of efficacy. The tolerability of the regimen will continue to be evaluated by the sponsor with the investigators to ensure that it is acceptable for continued enrollment.

The following analyses will be performed at interim analysis on the first 37 ASCT-failed cohort treated subjects.

- Pre-Treatment Subject Status Summary
- End of treatment period subject status summary
- Demographic characteristics summary
- Baseline Physical Measurements summary
- Other baseline characteristics summary
- Prior cancer therapy summary
- Cumulative dose and relative dose intensity summary
- Best overall response, per IRRC
- Time to response and duration of response, per IRRC
- Event Chart for Tumor Response, Tumor Progression, Duration of Therapy and Death
- Waterfall plot of best reduction in Target Lesion, per IRRC
- Spider plot of Tumor Burden Change, per IRRC
- Best overall response, per investigator
- Kaplan Meier plot of PFS, per IRRC
- Kaplan Meier plot of overall survival
- Status of Censored Subjects, OS Analysis
- Subsequent cancer therapy summary
- Death summary
- Summary of any adverse events by worst CTC grade (any grade, grade 3-4, grade 5), 5% cutoff, 30 days safety window
- Summary of Drug-Related Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5), no cutoff, 30 days safety window
- Summary of Serious Adverse Events by Worst CTC Grade (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, unknown grade, any grade), no cutoff, 30 days safety window
- Summary of Drug-Related Serious Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5), no cutoff, 30 days safety window

- Summary of Adverse Events Leading to Discontinuation by Worst CTC Grade (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, unknown grade, any grade), no cutoff, 30 days safety window
- Summary of Any Select Adverse Events by Worst CTC Grade (Any Grade Grade 3-4 Grade 5), no cutoff, 30 days safety window
- Summary of Drug-Related Select Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5), no cutoff, 30 days safety window

In addition, the following analyses will be also performed at interim analysis.

- Demographic characteristics summary (ASCT Ineligible cohort and pooled with ASCT-Failed 37 subjects)
- Best overall response, per investigator (ASCT Ineligible cohort)
- Summary of Tumor Specimen Acquisition and Characteristics for PD-L1 (ASCT-Failed 37 subjects and ASCT Ineligible cohort pooled)
- Best Overall Response and Objective Response per Investigator for each PD-L1 Expression Status Group (ASCT-Failed 37 subjects, ASCT Ineligible and pooled)
- Box Plot of PD-L1 Expression versus Response Status (ASCT-Failed 37 subjects and ASCT Ineligible cohort pooled)
- Kaplan-Meier Plot of Overall Survival by PD-L1 Status at Baseline Kaplan-Meier Plot of Progression Free Survival per investigator by PD-L1 Status at Baseline (ASCT-Failed 37 subjects and ASCT Ineligible cohort pooled)
- Kaplan-Meier Plot of Progression Free Survival per investigator by PD-L1 Status at Baseline (ASCT-Failed 37 subjects and ASCT Ineligible cohort pooled)
- Best Overall Response and Objective Response per Investigator for each Cell of Origin Subtype (ASCT-Failed 37 subjects and ASCT Ineligible cohort pooled)
- Best Overall Response and Objective Response per Investigator by Double-Hit Status (ASCT-Failed 37 subjects and ASCT Ineligible cohort pooled)
- Best Overall Response and Objective Response per Investigator by Epstein-Barr virus (EBV) Status (ASCT-Failed 37 subjects and ASCT Ineligible cohort pooled)

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[31]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in BMS Non-Study Medication Domain Requirements Specification[32].

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	[redacted]	Initial version 02-Jun-2014
2.0	[redacted]	01-Sep-2014: updates based on revised protocol 02 Section 2.1: - Clarification that the 2007 revised IWG criteria is used. - Addition of partial remission rate and duration in the list of secondary endpoints Section 3.2: Addition of duration of CR and PR rate and duration Section 3.3: [redacted] Section 4.1: - Clarification that the 2007 revised IWG criteria is used. - Clarification that for subjects treated beyond progression the BOR is recorded up to the initial progression Section 4.2.1: Clarification that the 2007 revised IWG criteria is used. Section 4.2.2: Addition of duration in section title Section 4.2.3:Section added for the PR rate and duration endpoints descriptions Section 4.2.4 : Clarification that the 2007 revised IWG criteria is used. Table 4.2.4-1: clarifications added to the censoring scheme for PFS Section 4.3.2: Clarification that the 2007 revised IWG criteria is used. Section 4.3.7: [redacted] Section 4.3.8: [redacted] Section 6.3.2: addition of subjects treated beyond progression population Section 7.1: Remove last paragraph about analyses by cohort Section 7.2.1: specify that analyses will be for the 2 cohorts separately and on the pooled population Section 7.2.2: Specify that a summary table will be produced for the 2 cohorts separately and on the pooled population Section 7.3: specify that Analyses from this section will be produced for the 2 cohorts separately and on the pooled population Section 7.3.2: - addition of >65 years old category - clarification that the sum of product diameter is used Section 7.4: Specify that the analyses will be done for the 2 cohorts separately and pooled Section 7.5: Specify that Unless otherwise specified analyses from this section will be produce by cohort separately Section 7.5.1: Clarification that the 2007 revised IWG criteria is used Section 7.5.2: addition of range of DOR analysis

Table 10-1: Document History

Version Number	Author(s)	Description
		Section 7.5.3: addition of duration of CR in title and range if duration of CR Section 7.5.4: section added to include PR rate and duration analyses Section 7.5.5.1: Clarification that sensitivity for PFS will take into account assessments AFTER subsequent therapy Section 7.5.8: [redacted] Section 7.8 [redacted] Section 7.8.1: Specify that Unless otherwise specified all analyses from this section will be performed on the two cohorts separately Section 7.8.1.1: [redacted] Section 7.8.1.2: - [redacted] - Addition of the following analyses based only on pooled ASCT-failed 37 subjects and ASCT ineligible cohorts at IA - Frequency and percentage BOR based on investigator assessment - ORR based on investigator assessment will be computed along with exact 95% CIs using the Clopper-Pearson method. - OS curves will be estimated using the Kaplan-Meier product limit method. Two-sided, 95% confidence intervals for median OS will be computed. - PFS based on investigator assessment curves will be estimated using the Kaplan-Meier product limit method. Two-sided, 95% confidence intervals for median PFS will be computed. Sections 7.8.2, 7.8.3, 7.8.4 [redacted] Section 7.10: Addition of the following tables/figures at IA: - Spider plot of Tumor Burden Change, per IRRC (on 37 ASCT-failed cohort treated subjects) - Demographic characteristics summary (ASCT Ineligible cohort and pooled with ASCT-Failed 37 subjects) - Best overall response, per investigator (ASCT Ineligible cohort) - [redacted]

Table 10-1: Document History

Version Number	Author(s)	Description
		- [redacted]
2.1	[redacted]	○ Section 2.1: Note to the Subjects discontinue study therapy by proceeding to allogeneic SCT or ASCT for the tumor assessment schedule added under table 2.1-1 ○ Section 3.1 and 3.2: Objective added to the two titles after primary and secondary. PR and ORR full name added. ○ Section 4.1: while defining TTR, CR or PR added after the first response. ○ Section: 4.2.1: Stem Cell Transplant will be considered as subsequent therapy added. ○ Section 4.2.4: Censoring scheme related to anticancer treatment for PFS has been updated last evaluable assessment updated by last assessment. ○ Section 4.3.1.1: Immune-Mediated Adverse Events has been added ○ Section 4.3.3: The definition of overall survival rate at time T has been added. ○ Section 4.3.7: [redacted] ○ Section 6.3.2: [redacted]

Table 10-1: Document History

Version Number	Author(s)	Description
		○ Section 7.3.2: Time from initial disease diagnosis to first dose of nivolumab or to transformation, time from transformation to first dose of nivolumab have been removed. ○ Section 7.3.4: Number of subjects by type of prior therapy and Best response to most recent prior regimen have been updated ○ Section 7.5.1.2: BOR categories (responders versus non-responders versus non-evaluable or no evidence of disease versus not reported) will be cross-tabulated by assessment type (Investigator vs IRRC) has been added Subject-level graphics removed. 90% CI has been removed. ○ Section 7.5.5: Subject listings of PFS will not be produced. ○ Section 7.5.6: Investigator-assessed BOR and time to response, cumulative response rate and etc has been added. ○ Section 7.5.7.2: Subsequent therapy has been added. ○ Section 7.5.7.3: other efficacy analysis has been added. ○ Section 7.6.6: select adverse events added. ○ Section: 7.6.9: added with the exception that scatterplots for total bilirubin will not be produced. ○ Section 7.6.10: title updated. Added A by-subject listing of the medical prodecures will be produced. ○ Section 7.6.15: immune-mediated adverse events analysis added. ○ Section: 7.6.16: other events of special interest added. ○ Section 7.8 and 7.8.1: per Dako IHC assay added. ○ Section 7.5.1: Confidence interval for primary endpoints updated. ○ Section 7.5.1.1: IPI score is 0, 1, 2, 3, 4…