Official Title of Study:

PHASE 1/2 STUDY TO EVALUATE THE SAFETY AND PRELIMINARY EFFICACY OF NIVOLUMAB COMBINED WITH DARATUMUMAB IN PARTICIPANTS WITH ADVANCED OR METASTATIC SOLID TUMORS

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STATISTICAL ANALYSIS PLAN
FOR SYNOPTIC CLINICAL STUDY REPORT

PHASE 1/2 STUDY TO EVALUATE THE SAFETY AND PRELIMINARY EFFICACY OF NIVOLUMAB COMBINED WITH DARATUMUMAB IN PARTICIPANTS WITH ADVANCED OR METASTATIC SOLID TUMORS

PROTOCOL(S) CA209-9GW

VERSION # 2.0

DATE: 16-SEP-2020

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[redacted]

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Schedule of Analyses:

Interim analyses for futility were planned, separately for TNBC, NSCLC and PAC. Analyses were to be based on the first 20 participants of each cohort, after 4 months on treatment. The database lock (DBL) for the PAC interim was planned for Q2 2018; and for TNBC was anticipated for Q3 2018.

Under the circumstance that data of some tumor types mature faster than others or a strong signal was observed in some tumor types, additional interim analyses may have been performed prior to the completion of the study in order to facilitate program decisions such as expanding the current study or starting phase 3 development and to support presentations or publications.

Final analyses of each fully-accrued cohort was to be conducted, separately for each cohort.

On 13-June-2018, investigators were informed that Protocol CA209-9GW would be amended to allow single agent treatment of nivolumab for on-study participants with non-small cell lung cancer (NSCLC). In addition, only triple-negative breast cancer (TNBC) and pancreatic adenocarcinoma (PAC) participants who are deriving clinical benefit would continue to be treated with the nivolumab plus daratumumab combination therapy.

The enrollment of participants with NSCLC was closed due to the lack of an efficacy signal. This decision was not related to any serious adverse events associated with the use of nivolumab in combination with daratumumab. The enrollment of participants with TNBC and PAC was previously closed as the study had met enrollment goals in these 2 cohorts.

At that time, the protocol defined interim analysis was done after 20 patients treated for each cohort for both TNBC and PAC. The combination was discontinued before 20 patients were treated in the NSCLC cohort, thus the protocol defined interim analysis was not performed.

Following the decision of BMS to stop enrollment, only a final close out analysis will be performed at the end of the study. This statistical analysis plan describes these.

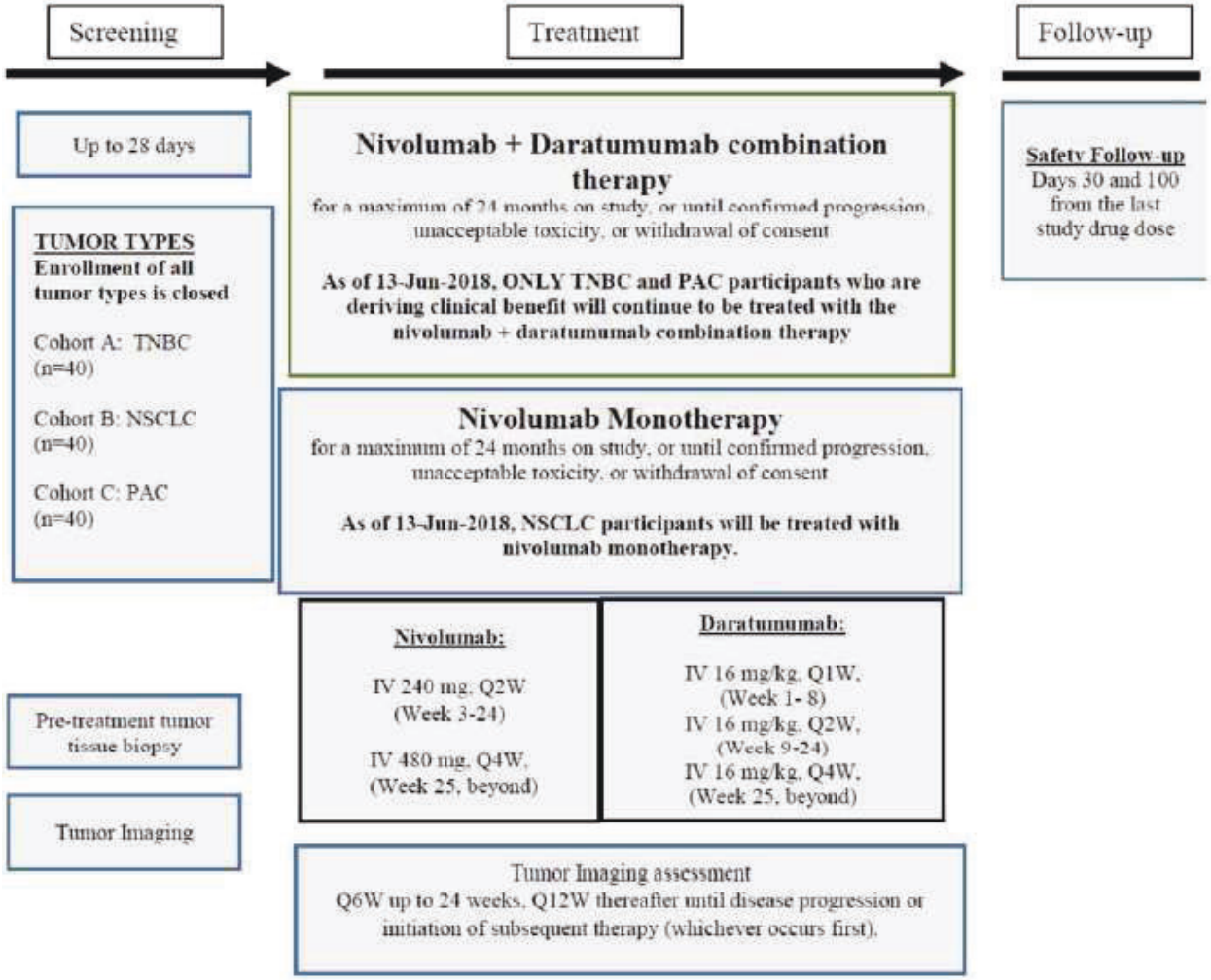
2 STUDY DESCRIPTION

2.1 Study Design

Study CA2099GW is an open-label, multi-center, Phase 1/2 study to investigate the safety and efficacy of nivolumab in combination with daratumumab in advanced or metastatic tumors including triple-negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), and pancreatic adenocarcinoma cancer (PAC). Treatment with nivolumab in combination with daratumumab is hypothesized to be well tolerated and to have clinical activity in participants with advanced or metastatic tumors, including TNBC, NSCLC, and PAC.

The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: Study Design Schematic



Abbreviations: NSCLC= non-small cell lung cancer; PAC= pancreatic adenocarcinoma; NCB= triple-negative breast cancer; CR = complete response; PR = partial response; SD= stable disease; PD= progressive disease; Pre-tx = pretreatment; Q1W = every week; Q2W = every 2 weeks; Q4W = every 4 weeks; Q6W = every 6 weeks; Q12W = every 12 weeks

Approximately 160 participants were planned to be enrolled in the study to ensure a total of 40 participants treated in each cohort, assuming a screen failure rate of 25%.

Participants at least 18 years old who have histologic or cytological confirmation of the following solid tumors will be enrolled:

- Triple negative breast cancer, TNBC (Cohort A)
- Non-small cell lung cancer, NSCLC (Cohort B)
- Pancreatic adenocarcinoma cancer, PAC (Cohort C)

All subjects will receive nivolumab administered IV at 240 mg every 2 weeks for weeks 3-24 and IV at 480 mg every 4 weeks after 25 weeks combined with daratumumab administered at 16 mg/kg every week for weeks 1-8, then daratumumab administered at 16 mg/kg every 2 weeks for weeks 9-24, then daratumumab administered at 16 mg/kg every 4 weeks after 25 weeks for a maximum of 24 months or until confirmed progression, unacceptable toxicity, or withdrawal of consent.

Upon notification regarding the LUC2001 study termination from Janssen, on 26-May-2018, BMS study teams issued a temporary hold to enrollment for studies evaluating daratumumab and nivolumab combination treatment in solid tumors. BMS implemented the enrollment hold as a precautionary step while safety and efficacy data from BMS studies with the combination of nivolumab and daratumumab were reviewed. Following a full review of all available relevant data for daratumumab in combination with nivolumab, a safety signal that would cause a significant risk for patients was not validated, based on the absence of a pattern of severe adverse events that could not be accounted for by underlying disease or prior therapy.

The cumulative efficacy data in over 100 patients in different solid tumor cohorts did not demonstrate an efficacy signal that would warrant continuation of the combination treatment in solid tumor trials. On 13-June-2018, investigators were informed that Protocol CA209-9GW would be amended to allow single agent treatment of nivolumab for on-study participants with non-small cell lung cancer (NSCLC). In addition, only triple-negative breast cancer (TNBC) and pancreatic adenocarcinoma (PAC) participants who are deriving clinical benefit would continue to be treated with the nivolumab plus daratumumab combination therapy.

The enrollment of participants with NSCLC was closed due to the lack of an efficacy signal. This decision was not related to any serious adverse events associated with the use of nivolumab in combination with daratumumab. The enrollment of participants with TNBC and PAC was previously closed as the study had met enrollment goals in these 2 cohorts.

This statistical analysis plan describes the analyses that will be included in the synoptic clinical study report at the end of the study.

2.2 Treatment Assignment

After the subject's informed consent has been obtained and eligibility is established, the subject will be enrolled, and a number will be assigned through an interactive voice response system (IVRS). If the subject's tumor type has not yet met the target cohort size of 40 participants, the subject will be assigned a treatment vial number and will receive study treatment.

Subjects in all cohorts will be assigned to the following dosing schedule.

Nivolumab IV:	240 mg, Q2W (Weeks 3-24); 480 mg, Q4W (Weeks 25+)
Daratumumab IV 16 mg/kg:	Q1W (Weeks 1-8); Q2W (Weeks 9-24); Q4W (Weeks 25+)

On 13-June-2018, investigators were informed that Protocol CA209-9GW would be amended to allow single agent treatment of nivolumab for on-study participants with non-small cell lung cancer (NSCLC). In addition, only triple-negative breast cancer (TNBC) and pancreatic

adenocarcinoma (PAC) participants who are deriving clinical benefit would continue to be treated with the nivolumab plus daratumumab combination therapy.

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

Table 2.4-1 below includes a list of the protocol amendments and administrateive letters.

Table 2.4-1: Protocol amendments and administrative letters

Document	Date of Issue	Summary of Change
Revised Protocol 03	27-Jul-2018	Revised Protocol 03 incorporates revisions to allow single agent treatment of nivolumab for on-study participants with non-small cell lung cancer (NSCLC). Only triple-negative breast cancer (TNBC) and pancreatic adenocarcinoma (PAC) participants who are deriving clinical benefit will continue to be treated with the nivolumab plus daratumumab combination therapy. Enrollment of all tumor types is closed, as of 26-May-2018. The enrollment of participants with NSCLC was closed due to the lack of an efficacy signal. The enrollment of participants with TNBC and PAC was previously closed as the study had met enrollment goals in these 2 cohorts. Pharmacokinetic, immunogenic, [redacted] will no longer be collected in this study. [redacted]
Administrative Letter 05	16-Feb-2018	Included additional available potencies for Daratumumab Solution for Injection to include 400mg potency.
Administrative Letter 04	26-Jan-2018	Clarified the eligibility criteria for the pancreatic adenocarcinoma (PAC) and triple negative breast cancer (TNBC) cohorts
Administrative Letter 03	17-Nov-2017	Clarified the eligibility criteria for the pancreatic adenocarcinoma cohort.
Administrative Letter 02	04-Aug-2017	Clarified protocol requirements for tumor tissue submission at screening and updated Medical Monitor
Revised Protocol 02	14-Jun-2017	Incorporates Amendment 03
Amendment 03	14-Jun-2017	[redacted] Adds clarification that prior focal radiation therapy as palliative treatment to a non-index lesion is permitted up to 2 weeks from starting study therapy. Added to the inclusion criteria are permitted time windows prior to start of study therapy for the use of supportive measures to achieve required screening laboratory values. Clarification of inclusion criteria for participants with triple negative breast cancer and pancreatic adenocarcinoma to include, in addition to history of progression or refractory disease, best response of stable disease to prior treatment regimens. Correction to remove height from baseline assessments. Modification in RECIST 1.1 (Appendix 7) to clarify minimum duration of stable disease.

Table 2.4-1: Protocol amendments and administrative letters

Document	Date of Issue	Summary of Change
Administrative Letter 01	03-May-2017	Clarification that the whole blood biomarker sample at screening is not required; the scheduled whole blood collection at Week 1/Day 1 will be used for baseline biomarkers assessments
Revised Protocol 01	18-Apr-2017	Incorporates Amendment 02
Amendment 02	18-Apr-2017	Adds American Society of Clinical Oncologists and College of American Pathologists (ASCO-CAP) guidelines as part of the inclusion criteria definition of HER2 negativity in triple negative breast cancer as requested by the FDA. Revision of creatinine clearance threshold for eligibility, as recommended by the FDA.

3 OBJECTIVES

This section includes only the primary and secondary objectives since these will be analyzed as part of the synoptic clinical study report. The study protocol includes the complete list of study objectives.

3.1 Primary

To establish the tolerability of the combination of nivolumab and daratumumab in participants with advanced or metastatic solid tumors.

3.2 Secondary

- To evaluate the objective response rate (ORR) of nivolumab combined with daratumumab in participants with advanced or metastatic tumors in each cohort.
- To assess progression free survival (PFS) of nivolumab combined with daratumumab in participants with advanced or metastatic tumors in each cohort.
- To characterize the pharmacokinetics of nivolumab and daratumumab in participants with advanced or metastatic tumors.
- To characterize the immunogenicity of nivolumab and daratumumab in participants with advanced or metastatic tumors

4 ENDPOINTS

This section includes only the endpoints that will be analyzed as part of the synoptic clinical study report.

4.1 Efficacy Endpoints

Efficacy endpoints are ORR and median PFS in each cohort in each cohort, based on RECIST 1.1 criteria. In addition, duration of response (DOR), best overall response (BOR) and disease control rate will also be analyzed, which are also described in this section.

4.1.1 Objective Response Rate

Objective Response Rate (ORR) is defined as the number of treated subjects who achieve a best response of complete response (CR) or partial response (PR) based on investigator assessments (using RECIST v1.1 criteria) divided by the number of all treated subjects. Best Overall Response (BOR) is defined as the best response, as determined by Investigator, recorded between the date of first dose and the date of objectively documented progression per RECIST v1.1 criteria or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination. Subsequent therapy includes any therapy (systemic cancer therapy, surgery, radiotherapy).

4.1.2 Disease Control Rate

Disease Control Rate (DCR) is defined as the number of treated subjects who achieve a best response of complete response (CR), partial response (PR) or stable disease(SD) based on investigator assessments (using RECIST v1.1 criteria) divided by the number of all treated subjects.

4.1.3 Duration of Response

Duration of Response (DOR) is defined as the time between the date of first documented response (CR or PR) to the date of the first documented tumor progression as determined by Investigator (per RECIST v1.1 criteria), or death due to any cause, whichever occurs first. 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. Subsequent therapy includes any therapy (systemic cancer therapy, surgery, radiotherapy).Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. For subjects who neither progress nor die, DOR will be censored on the date of their last evaluable tumor assessment. DOR will be evaluated for responders (CR or PR) only.

4.1.4 Progression-Free Survival

PFS rate at time *T* is defined as the probability that a subject has not progressed and is alive at time *T* following start of treatment. PFS rates at fixed time points (e.g. 6 months, depending on the minimum follow-up) are defined as the probability that a subject has not progressed and is alive at time *T* following start treatment date.

Disease assessment with CT and/or MRI, as appropriate, will be performed at baseline and every 6 weeks up to 24 weeks, and every 12 weeks thereafter until PD, the completion of follow-up, initiation of new therapy, or participant withdraw from the study. Tumor responses will be assessed by the investigator as defined by RECIST v1.1.

PFS is defined as the time between the date of treatment start day and the date of first documented tumor progression, based on Investigator assessments (per RECIST v1.1 criteria), 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. The following censoring rules will be applied for the primary definition of PFS:

- Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment.
- Subjects who did not have any on study tumor assessments and did not die will be censored on their first dosing date.
- Subjects who receive subsequent anti-cancer therapy prior to documented progression will be censored at the date of the last evaluable tumor assessment conducted on or prior to the date of initiation of the subsequent anti-cancer therapy.
- Subjects who did not have a documented progression and received subsequent anti-cancer therapy will be censored at the date of the last evaluable tumor assessment conducted on or prior to the initiation of the subsequent anti-cancer therapy.
- Subsequent therapy includes any therapy (systemic cancer therapy, surgery, radiotherapy).

Censoring rules for the primary definition of PFS are presented in Table 4.1.4-1.

Table 4.1.4-1: Censoring Scheme used in Primary Definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments*	Date of first dose	Censored
No on study tumor assessments and no death*	Date of first dose	Censored
Subsequent anti-cancer therapy started without death or progression per RECIST v1.1 reported prior or on the same day	Date of last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Documented progression per RECIST v1.1 and no new anti-cancer started before	Date of the first documented progression per RECIST v1.1 (excludes clinical progression)	Progressed
No progression and no death, and no new anti-cancer therapy started	Date of last evaluable tumor assessment	Censored
Death without progression per RECIST v1.1 and no new anti-cancer started before	Date of death	Progressed

* Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are not considered.

4.2 Safety endpoints

The assessment of safety will be based on the incidence of adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation, and deaths. In addition, specific laboratory abnormalities will be summarized and listed.

4.3 Pharmacokinetics

Pharmacokinetics will be measured using serum concentration-time data (both nivolumab and daratumumab).

4.4 Immunogenicity

Serum samples will be evaluated for development of nivolumab and daratumumab Anti-Drug Antibodies (ADA) by validated assays. Samples may also be analyzed for neutralizing antibodies.

Serum samples collected will be analyzed by a validated immunogenicity assay. Selected serum samples may be analyzed by an exploratory orthogonal method that measures anti-nivolumab.

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

Blood samples for immunogenicity analysis will be collected. Samples will be evaluated for development of Anti-Drug Antibody (ADA) by a validated electrochemiluminescent (ECL) immunoassay.

5 SAMPLE SIZE AND POWER

Sample size determination is not based on statistical power calculation.

40 participants were planned to be enrolled to each cohort. In this study, an ORR in excess of 10% will be considered of clinical interest for TNBC and PAC cohort. An ORR in excess of 20% will be considered of clinical interest for NSCLC cohort.

Assuming the true ORR is 25%, 40 participants in each tumor type can provide approximately 79.8% power to reject the null hypothesis that the ORR is 10%, considering a 2-sided alpha of 5%.

Assuming the true ORR is 40%, 40 participants in each tumor type can provide approximately 83.7% power to reject the null hypothesis that the ORR is 20%, considering a 2-sided alpha of 5%.

Table 5.1 shows the precision of the estimation of ORR based on the two-sided 95% exact CI using Clopper-Pearson methods based on 4, 8, 12, 16 and 20 responders out of 40 participants. If at least 9 responses are observed , i.e., ORR >=22.5%, the lower bound of the 95% CI excludes 10%. If at least 14 responses are observed, i.e., ORR >=35%, the lower bound of the 95% CI excludes 20%.

Table 5-1: Two-sided 95% exact CI using Clopper-Pearson Method Based on the Number of Observed Responses from 40 participants

Number of Observed Responses	4	8	12	16	20
Observed Response Rate	4/40 (10.0%)	8/40 (20.0%)	12/40 (30.0%)	16/40 (40.0%)	20/40 (50.0%)
95% exact CI (%)	(2.8, 23.7)	(9.1, 35.6)	(16.6, 46.5)	(24.9, 56.7)	(33.8, 66.2)

A sample size of 40 can also detect, with more than 87% probability, a safety event that occurs at an incident rate of 5%.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

- 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. Evaluations (laboratory test) on the same date and time of the first dose of study treatment will be considered as baseline evaluations. Events (AEs) on the same date and time of the first dose of study treatment will not be considered as pre-treatment events.
  - 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) will be defined as evaluations with a date on or prior to the day of first dose of study treatment.
- Post baseline period:
  - On-treatment AEs will be defined as AEs with an onset date and time on or after the date and 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). For subjects who are off study treatment, AEs will be included if event occurred within a safety window of 30 days (or 100 days depending on the analysis) after the last dose of study treatment. No "subtracting rule" will be applied when an AE occurs both pre-treatment and post-treatment with the same preferred term and grade.
  - On-treatment evaluations (laboratory tests) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. For subjects who are off study treatment, evaluations should be within a safety window of 30 days (or 100 days depending on the analysis) after the last dose of study treatment.

6.2 Treatment Regimens

For this non-randomized study, analyses will be based on the treatment group "as treated".

6.3 Populations for Analyses

- All Enrolled subjects: All subjects who signed the informed consent form and obtained a subject number.
- All Treated subjects: All enrolled subjects who received at least one dose of any study treatment. This will be both efficacy and safety population.
- Subjects Entered Follow-up: All subjects who entered the follow-up period as specified in subject status CRF pages.
- All Treated Subjects with Objective Response: All treated subjects with response of CR or PR per RECIST v1.1 per Investigator.

Unless otherwise specified, the efficacy and safety analyses will include all treated subjects.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, discrete variables will be tabulated by the frequency and proportion of subjects falling into each category, grouped by treatment. Percentages given in these tables will be rounded to the first decimal and, therefore, may not always sum to 100%. Percentages less than 0.1 will be indicated as '< 0.1'. Continuous variables will be summarized by treatment group using the mean, standard deviation, median, minimum, and maximum values.

Time-to-event variables (e.g. time-to resolution) will be analysed using the Kaplan-Meier technique. When specified, the median will be reported along with 95% CI using Brookmeyer and Crowley method[1] (using log-log transformation for constructing the confidence intervals[2]).

The conventions to be used for imputing missing and partial dates for analyses requiring dates are described in Section 8.

All analyses would be presented by tumor type:

- Triple negative breast cancer (TNBC)
- Non-small cell lung cancer (NSCLC)
- Pancreatic adenocarcinoma cancer (PAC).

7.1.1 Adverse Events, Serious Adverse Events

Serious adverse events consist of AEs deemed serious by the Investigator and flagged accordingly in the CRF and clinical database.

Adverse events leading to study drug discontinuation are AEs with action taken regarding study drug(s) = "Drug was discontinued".

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the most recent version of the dictionary at the time of the database lock will be used. Adverse events results will be graded for severity using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

In the AE summary tables, unless otherwise specified, subjects will be counted only once at the Preferred Term (PT), only once at the System Organ Class (SOC), and only once at subject level for the counting of total number of subjects with an AE. The AE tables will be sorted by the SOCs and then PTs. SOC will be ordered by descending frequency overall and then alphabetically. PTs will be ordered within SOC by descending frequency overall and then alphabetically. The sorting will be done based on the 'Any Grade' column of the experimental arm when arms are presented side-by-side.

Unless otherwise specified, the AE summary tables will be restricted to on-treatment events regardless of the causality.

7.1.2 Laboratory Tests

Clinical laboratory parameters (hematology, serum chemistry and thyroid function tests) will be evaluated.

Laboratory tests will be graded using the NCI Common Terminology Criteria NCI CTCAE version 4.0.

Clinical laboratory data will be summarized and listed both using the International System of Units (SI) and US conventional units.

In the laboratory summary tables, unless otherwise specified, subjects will be counted only once for each lab parameter according to their worst on treatment CTC grade (worst being the highest CTC grade).

The laboratory tables and listings will be sorted by laboratory category, laboratory subcategory and laboratory test code sequence number.

7.2 Study Population

7.2.1 Subject Disposition

The total number of subjects enrolled (treated or not treated) will be presented along with the reason for not being treated. This analysis will be performed on the all enrolled subjects population.

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by treatment group. Reason for discontinuation will be derived from subject status CRF page. This analysis will be performed only on the all treated subjects.

Number of subjects who discontinued study follow-up along with corresponding reason will be tabulated by treatment group. Reason for discontinuation will be derived from subject status CRF page. This analysis will be performed only on the all subjects entered follow-up population.

A by-subject listing for all enrolled subjects will also be provided, showing whether the subject was treated along with the reason for not being treated.

A by-subject listing for all treated subjects will be provided showing the subject's off treatment date and whether the subject continue in the treatment period/study along with the reason for going off treatment period/study.

A by-subject listing for subjects entered follow-up will be provided showing the subject's off study date and the reason for not continuing in follow-up.

7.2.2 Demographics and Other Baseline Disease Characteristics

The following demographic and baseline disease characteristics will be summarized and listed:

- Age (continuous)
- Age categorization (< 65, ≥ 65 and < 75, ≥ 75 and < 85, ≥ 85, ≥ 75, ≥ 65)
- Sex (Male vs. Female)
- Race (White, Black or African American, Asian, Other)
- Ethnicity (Hispanic/Latino and Not Hispanic/Latino)

- Disease stage at initial diagnosis
- Disease stage at study entry
- ECOG performance status
- Number of prior systemic cancer therapy regimens (0, 1, 2, 3, >=4, not reported)

7.3 Extent of Exposure

7.3.1 Administration of Study Therapy

Duration of study therapy for both nivolumab and daratumumab will be summarized in days (descriptive statistics). Subjects also will be categorized based on the duration of study therapy: 1-28, 29-56, 57-84, 85-168, more than 169 days.

The number and percentage of NSCLC patients who discontinued daratumumab and continued with single agent treatment of nivolumab as a result of the BMS decision communicated to investigators after 13-June-2018 will be summarized.

7.4 Efficacy

Analyses of progression free survival (PFS) and objective response rate (ORR) will be based on the Investigator evaluation.

CIs for endpoints will be at the two-sided 95% level. P-values will not be reported. Point estimates and confidence bounds for efficacy variables will be rounded to the second decimal place.

7.4.1 Analysis of Objective Response Rate and Disease Control Rate

One of the objectives of the study is to estimate the ORR per Investigator among all treated subjects.

The number and percentage of subjects in each category of BOR per Investigator (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or unable to determine [UTD]) will be presented. Estimates of response rate and disease control rate, along with its exact two-sided 95% CI by Clopper and Pearson[3] will be presented.

7.4.2 Duration of Response

Duration of response (DOR) will be evaluated for subjects who achieved PR or CR. The DOR will be estimated using the Kaplan-Meier (KM) product limit method and will be displayed graphically. The plot will also present number of events, number of subjects involved, medians, and 95% CIs for the medians. Median values of DOR, along with two-sided 95% CI in each treatment group will be computed based on a log-log transformation method.

7.4.3 Analysis of Progression-Free Survival

One of the objectives of the study is to estimate the progression-free survival (as determined by Investigator) for all treated subjects.

The PFS function for each tumor type will be estimated using the KM product limit method and will be displayed graphically. A two-sided 95% CI for median PFS will be computed via the log-log transformation method.

7.5 Safety

7.5.1 Deaths

A by-subject listing of deaths will be provided for all enrolled subjects population.

7.5.2 Serious Adverse Events

Serious adverse events will be summarized for all treated subjects:

- Overall summary of SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.
- The analysis will be conducted using the 30-day safety window.

A by-subject SAE listing will be provided for the "enrolled subjects" population.

7.5.3 Adverse Events Leading to Discontinuation of Study Therapy

AEs leading to discontinuation will be summarized:

- Overall summary of AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

The analysis will be conducted using the 30-day safety window.

A by-subject AEs leading to discontinuation listing will be provided.

7.5.4 Adverse Events

Adverse events will be summarized.

The following analyses will be conducted using the 30 days safety window only:

- Overall summary of any AEs by worst CTC grade (1, 2, 3, 4, 5, not reported, total) presented by SOC/PT.
- Overall summary of any AEs presented by worst CTC grade (1, 2, 3, 4, 5, not reported, total) by SOC/PT. This table will be restricted to events with an incidence greater or equal to 5% in any treatment group.

A by-subject AE listing will be provided.

7.5.5 Laboratory Parameters

The analysis population for each laboratory test is restricted to treated subjects meeting that laboratory test abnormality.

A summary as worst CTC grade on-treatment per subject and a by-subject listing of the following laboratory parameters abnormalities will be provided: hemoglobin, hematocrit, leukocytes, platelet count, ALT, AST, alkaline phosphatase (ALP), total bilirubin, lactate dehydrogenase, blood urea nitrogen (BUN) or serum urea level, creatinine, sodium, potassium, calcium, chloride, magnesium, creatinine clearance (CLcr), carbon dioxide or bicarbonate, amylase, glucose, phosphate, albumin, urinalysis labs, serology tests, FSH and lipase.

A summary and a by-subject listing of the following thyroid specific abnormalities will be provided: TSH, FT3, FT4.

A by-subject listing of differences in categorization of SI and US laboratory test results will be provided.

The analyses will be conducted using the 30-day safety window.

In addition, further analyses on specific laboratory parameters will be performed by treatment group:

Abnormal Hepatic Function Test

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized:

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN
- Total bilirubin > 2 x ULN
- ALP > 1.5 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 1.5 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 1.5 x ULN
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN

Abnormal Thyroid Function Test

The number of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized:

- TSH value > ULN and
  - with baseline TSH value ≤ ULN
  - with at least one FT3/FT4 test value < LLN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≥ LLN within 2-week window after the abnormal TSH test
  - with FT3/FT4 missing within 2-week window after the abnormal TSH test.
- TSH < LLN and
  - with baseline TSH value ≥ LLN
  - with at least one FT3/FT4 test value > ULN within 2-week window after the abnormal TSH test
  - with all FT3/FT4 test values ≤ ULN within 2-week window after the abnormal TSH test
  - with FT3/FT4 missing within 2-week window after the abnormal TSH test

7.6 Immunogenicity Analysis

[redacted]

Immunogenicity will be reported for ADA positive status (such as persistent positive, neutralizing positive, only last sample positive, baseline positive, and other positive) and ADA negative status,

relative to baseline. [redacted]

Incidence of ADA

Number (%) of subjects will be reported for the following parameters based on Evaluable Subjects.

- Baseline ADA-positive
- ADA-positive
  - Persistent Positive (PP)
  - Not PP-Last Sample Positive
  - Other positive
  - Neutralizing Positive
- ADA-negative

A listing of all ADA assessments will be provided. A separate listing of ADA assessments for subjects with neutralizing positive will also be provided as appropriate.

Clinical implications

Clinical implications of nivolumab immunogenicity will be primarily focused on subjects with persistent ADA-positive relative to ADA-negative. Subjects with any ADA-positive samples after initiation of treatment (relative to baseline) may be used to explore clinical implications. Effect of immunogenicity on safety will be explored by examining the frequency and type of AEs of special interest such as hypersensitivity/infusion reaction. Summary tables for incidence of overall and each of the preferred terms will be provided, if the number of subjects is of sufficient size (e.g., at least 10 subjects). Otherwise, individual subject's safety profile will be examined and described based on a listing.

7.7 Pharmacokinetics

Summary statistics will be calculated for nivolumab and daratumumab concentrations, and summarized by scheduled sample collection time.

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[4]
- For missing and partial adverse event resolution dates, imputation will be performed as follows:
  - If only the day of the month is missing, the last day of the month will be used to replace the missing day. If the imputed date is after the death date or the last known alive date, then the latest known alive date or death date is considered as the resolution date.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.

- Missing and partial non-study medication domain dates will be imputed using the derivation algorithm described in 4.1.3 of BMS Non-Study Medication Domain Requirements Specification[5].

[redacted]

- 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 date alive.
- For date of progression after start of study therapy, 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. In case of 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.
  - If the day and month are missing or a date is completely missing, it will be considered as missing.
- For date of progression to prior therapies, 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.
- For other partial/missing dates, the following conventions were 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-to onset, time-to resolution) will be calculated as follows:

Duration = (Last date - first date + 1)

Last known alive date will be defined based on all appropriate dates collected on the CRF.

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 this SAP will be included in the Synoptic Clinical Study Report. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

10 DOCUMENT HISTORY

Table 10-1: Document History

Version Number	[redacted]	Description
1.0	[redacted]	Original Issue
2.0	[redacted]	BMS has taken the decision to discontinue the study. A final close out synoptic CSR will be produced focused on key safety and efficacy. This version of the analysis plan focuses only on the analyses for the synoptic CSR, incorporates the latest IO Core SAP conventions and replaces the previous version of the SAP.