Protocol Number: CA2099GW
IND Number: 134,039
EUDRACT Number 2017-000367-33
Date 16-Feb-2017
Revised Date: 27-Jul-2018

Clinical Protocol CA2099GW

Phase 1/2 Study to Evaluate the Safety and Preliminary Efficacy of Nivolumab Combined with Daratumumab in Participants with Advanced or Metastatic Solid Tumors

Revised Protocol Number: 03
Incorporates Administrative Letters 02,03,04, and 05

Study Director/Medical Monitor
Von Potter, MD

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

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.
Administrative Letter 01	03-May-2017	[redacted]
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

Document	Date of Issue	Summary of Change
		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.
Original Protocol	16-Feb-2017	Not Applicable

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	[redacted]
[redacted] • Section 5.1 Overall Design [redacted]	This protocol has been revised to allow single agent treatment of nivolumab for on-study participants with non-small cell lung cancer (NSCLC). In addition, only TNBC and PAC participants who are deriving clinical benefit will continue to be treated with the nivolumab plus daratumumab combination therapy.	
• Synopsis: Study Population, Number of Participants • Section 5.2 Number of Participants. • Section 10.1 Sample Determination	Enrollment in all tumor cohorts is closed, as of 26-May-2018. Total final study enrollment is now included in the protocol.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	[redacted]
• Synopsis Objectives and Endpoints • Synopsis, Treatment Arms and Duration • Section 2, Schedule of Activities Table 2.-3, Follow-up Procedural Outline (CA2099GW) • Section 4 Objectives and Endpoints; Table 4.-1 Objectives and Endpoints • Section 9.4.5 Safety Assessments	[redacted]	
• Synopsis, Overall Design • Section 5.1 Overall Design	Central collection of scans has been discontinued. Possible blinded independent review has been deleted from the study design.	
	Pharmacokinetic, immunogenicity, [redacted] will no longer be collected in this study.	
	Tumor biopsy at Week 7 deleted. Section 5.1 only.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	[redacted]
• Synopsis Study Schematic • Section 5.1 Study Schematic	Updated to reflect the closure of enrollment in all tumor types, nivolumab monotherapy for NSCLC participants, the continuation of treatment with nivolumab and daratumumab for on-study TNBC and PAC participants who are deriving clinical benefit, and the removal of survival follow-up.	
• Section 2, Schedule of Activities Table 2.-2, On Study Procedural Outline (CA2099GW) • Section 2, Schedule of Activities Table 2.-3, Follow-up Procedural Outline (CA2099GW)	Tumor biopsy at Week 7 deleted. (On Study Procedural Outline only) Pharmacokinetic, immunogenic, [redacted] collection deleted.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	[redacted]
• Section 2, Schedule of Activities Table 2.-2, On Study Procedural Outline (CA2099GW), Radiographic Tumor Assessment • Section 5.1 Overall Design • Section 9.1.1,Imaging Assessment for the Study Table 9.1.1-2: Schedule of Spiral CT/MRI Tumor Assessments for advanced and Metastatic Cohort	Specific week(s) for imaging assessment removed.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	[redacted]
• Section 2, Schedule of Activities Table 2.-2, On Study Procedural Outline (CA2099GW) • Section 7.1 Treatments Administered; Table 7.1-1: Study Drug Dosing Schedule • Section 7.2 Method of Treatment Assignment	Text added to each section listed to specify change in drug treatment for all on-study participants.	
• Section 6.1 Inclusion Criteria 3) Age and Reproductive Status	Azoospermic males are not exempt from contraceptive requirements presented in Appendix 4.	
• Section 7.1.4 Criteria to Resume Treatment	Now specified that adrenal insufficiency of Grade ≥ 3 regardless of control with hormone replacement requires discontinuation of treatment.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	[redacted]
• Section 7.5 Preparation/Handling/ Storage/Accountability, Nivolumab Preparation and Administration	Specifics removed and reference to pharmacy manual included.	
Section 7.7 Prohibited Medication	Addition of any live/attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose to list of prohibited medication.	
• Section 7.7.2.4 Surgical Resection Following Initial Response	Information on processes for tissue specimen deleted.	
• Section 8.1.1 Nivolumab Discontinuation Criteria	Recommendations for adverse events that should or must result in discontinuation have been incorporated.	
• Section 8.1.2 Daratumumab Discontinuation Criteria	BMS medical monitor must be consulted before re-initiation of treatment after a dose delay of 6 weeks rather than 8 weeks.	
• Section 8.1.3 Post Study Treatment Follow-up	Updated per deletion of overall survival as study endpoint.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03	
Section Number & Title	**Description of Change**
• Section 9.1 Efficacy Assessments; Table 9.1.1-1 Acceptable Imaging Assessment Methods for Different Anatomic Regions	Central collection of scans has been discontinued and blinded independent review has been deleted from the study design.
• Section 9.2.1 Time Period and Frequency for Collection AE and SAE Information • Section 9.2.7 Potential Drug Induced Liver and Injury (DILI)	Redundant text removed.
• Section 9.4.5 Safety Assessment	Text removed for weight and ECOG assessments.
• Section 9.5 Pharmacokinetic [redacted] • Section 9.8.2, Immunogenicity Assessments	Content of these sections has been deleted as samples for these evaluations are no longer being collected, as of Revised Protocol 03.
• Section 10.3.4 Interim Analyses	Interim analyses for NSCLC cohort has been deleted.
Throughout the protocol	[redacted]

TABLE OF CONTENTS

1. SYNOPSIS

Protocol Title: Phase 1/2 Study to Evaluate the Safety and Preliminary Efficacy of Nivolumab Combined with Daratumumab in Participants with Advanced or Metastatic Solid Tumors

Study Phase: 1/2

[redacted]

Study Population: Men or women, ≥ 18 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1, with histologically or cytologically-confirmed diagnosis of advanced or metastatic cancer who also meet the corresponding requirements for the respective cohort (see Section 6), and who are treatment-naive to immune checkpoint inhibitors and CD38 blockers will be eligible to participate in the study. 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. 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.

Objectives and Endpoints:

Objectives	Endpoints
Primary To establish the tolerability of the combination of nivolumab and daratumumab in participants with advanced or metastatic solid tumors.	Incidence of adverse events (AE), serious adverse events (SAE) and specific laboratory abnormalities (worst grade).
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	• ORR, duration of response (DOR), best overall response (BOR) in each cohort, based on RECIST 1.1 criteria (Appendix 7). • Median PFS in each cohort • Pharmacokinetic parameters, influence of intrinsic and extrinsic covariates and potential exposure-response relationship will be characterized using integrated analyses. • Immunogenicity of nivolumab and daratumumab will be assessed by ADA positivity

Overall Design: This is an open-label, multi-center, phase 1/2 study to investigate 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). As of 13-June-2018, only TNBC and PAC participants who are deriving clinical benefit will continue to be treated with the nivolumab plus daratumumab combination therapy; NSCLC participants will be treated with nivolumab monotherapy. Eligible participants in each indication cohort will receive treatment for a maximum of 24 months as long as they experience clinical benefit per RECIST 1.1 criteria and do not meet the criteria for discontinuation (i.e., disease progression, unacceptable toxicity, consent withdrawal).

All safety data will be monitored on an ongoing basis during the treatment and the safety follow-up periods of the study. Disease assessments will be performed using computed tomography (CT) and/or magnetic resonance imaging (MRI), as appropriate. Investigator assessed response to therapy will be based on RECIST 1.1 criteria.

Number of Participants:

Enrollment of all tumor types closed, as of 26-May-2018. 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.

188 participants were enrolled in the study to ensure a total of 40 participants treated in each cohort, which assumed a screen failure rate of 25%. The NSCLC cohort was closed before this target was attained.

Treatment Arms and Duration: Participants in each cohort (TNBC, NSCLC, PAC) will receive treatment for a maximum of 24 months or until disease progression, unacceptable toxicity, consent withdrawal or the study is stopped.

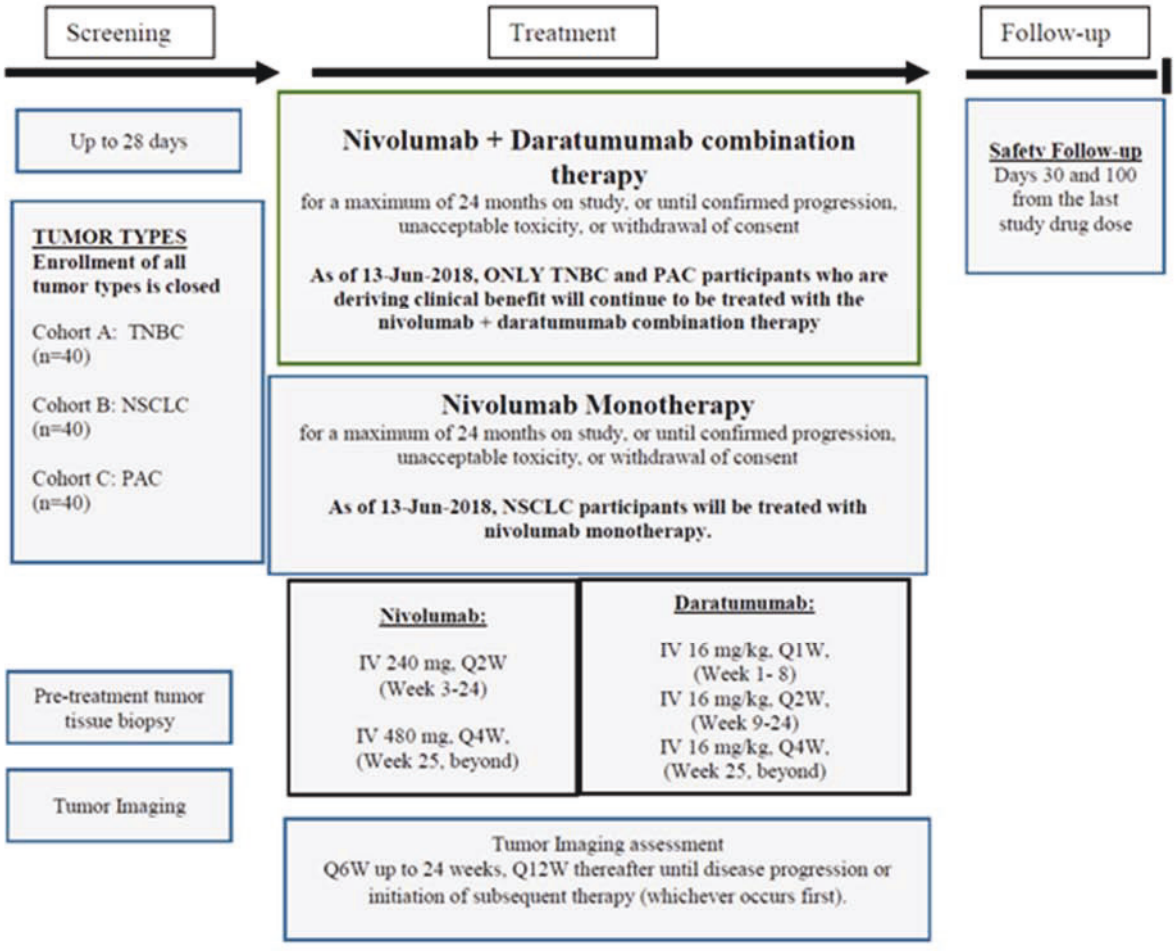
The duration of the study is anticipated to be approximately 3 years.

Please refer to Section 7.8 for study termination criteria.

Study treatment:

Study Drug for CA2099GW		
Medication	**Potency**	**IP/Non-IP**
Nivolumab (BMS -936558)	100 mg (10 mg/ml) and 40 mg (10 mg/mL)	IP
Daratumumab	100 mg (20 mg/mL) and/or 400 mg (20 mg/mL)	IP

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

2. SCHEDULE OF ACTIVITIES

Table 2.-1: Screening Procedural Outline (CA2099GW)

Procedure	Local Lab (LL) or Central Lab (CL)	Screening Visit (Day -28)	Notes
Eligibility Assessments			
Informed Consent		X	Prior to any screening procedures. Register in Interactive Response Technology (IRT) system to obtain participant number.
Inclusion/Exclusion Criteria		X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Medical History		X	
Document EGFR and ALK mutational status		X	EGFR and ALK for participants with NSCLC
Tumor Tissue Sample (biopsy)	CL	X	Fresh tissue biopsy at screening is required. Alternatively, tumor tissue collected after the completion of the most recent prior therapy is accepted.
Performance Status (ECOG)		X	Within 14 days prior to first dose. See Appendix 5 for ECOG scale.
Interactive Response Technology (IRT)		X	After informed consent form is signed, call IRT to enroll participant.
Safety Assessments			
Physical Examination		X	Within 14 days prior to first dose: full physical examination including weight measurement.

Table 2.-1: Screening Procedural Outline (CA2099GW)

Procedure	Local Lab (LL) or Central Lab (CL)	Screening Visit (Day -28)	Notes
Vital Signs		X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate must be measured after the participant has been resting quietly for at least 5 minutes.
Assessment of Signs and Symptoms		X	Within 14 days prior to first dose.
[redacted]		[redacted]	[redacted]
Adverse Events Assessment		X	Collection from the time of informed consent. NSAEs and SAEs must be collected up to 100 days after study drug discontinuation.
ECG	LL	X	ECGs should be recorded after the participant has been supine for at least 5 minutes.
Laboratory Tests			
Pregnancy Test	LL	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and within 24 hours of first dose of study therapy.
Blood type Assessment (ABO, Rh, and indirect anti-globulin testing)	LL	X	Prior to first dose of daratumumab.
CBC with Differential and Platelets	LL	X	Within 14 days prior to first dose.

Table 2.-1: Screening Procedural Outline (CA2099GW)

Procedure	Local Lab (LL) or Central Lab (CL)	Screening Visit (Day -28)	Notes
Serum Chemistry	LL	X	Within 14 days prior to first dose. Chemistry panel includes LDH, AST, ALT, ALP, albumin, total bilirubin, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, glucose, phosphate, carbon dioxide or bicarbonate. Amylase and lipase: only for participants with pancreatic adenocarcinoma.
Creatinine Clearance Assessment	LL	X	By Cockcroft-Gault formula or from 24 hour urine
Thyroid Function Tests	LL	X	TSH (reflex to free T3 and free T4 if abnormal result) to be performed within 28 days of first dose.
Urinalysis	LL	X	Total protein, glucose, blood, leukocyte esterase, specific gravity, and pH
Serology	LL	X	Hepatitis B surface antigen (HBV sAg, Australia antigen), and hepatitis C antibody (HCV Ab) or HCV ribonucleic acid (RNA) HIV-1 and -2 antibody. Testing for HIV must be performed at sites where mandated locally.

Table 2.-1: Screening Procedural Outline (CA2099GW)

Procedure	Local Lab (LL) or Central Lab (CL)	Screening Visit (Day -28)	Notes
Efficacy Assessments			
Body Imaging	LL	X	Tumor imaging assessment will occur at screening (within 28 days of first dose). CT or MRI chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at baseline. See Section 9.1
Brain Imaging (per clinical indication)	LL	X	Participants with active brain metastases or leptomeningeal metastases are not eligible for enrollment. Participants with brain metastases are eligible if brain metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. See Section 9.1
Bone Scan (per clinical indication)	LL	X	Participants with a history of bone metastasis may have a bone scan, if clinically indicated. See Section 9.1

Table 2.-2: On Study Procedural Outline (CA2099GW)

Procedure	Local Lab (LL) or Central Lab (CL)	Weeks 1-8		Weeks 9-24 Q2W	Week 25 and beyond Q4W	Notes Procedure Window ±2 Days Unless Specified Otherwise
		Weeks 1, 3, 5, 7	Weeks 2,4,6, 8			
Performance Status (ECOG)		X Weeks 1 and 5		X	X	Week 1 and then every 4 weeks thereafter. See Appendix 5 for ECOG scale.
Safety Assessments						
Physical Examination		X Weeks 1 and 5		X	X	Week 1 and every 4 weeks thereafter: targeted physical examination prior to dosing: include weight. Must include the following body systems: cardiovascular, gastrointestinal, pulmonary
Vital Signs		X	X	X	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate must be measured after the participant has been resting quietly for at least 5 minutes. For participants remaining on combination therapy, vital signs should be monitored extensively on Weeks 1 and 2 before, during, and after the infusion of daratumumab as follows: immediately before the start of the infusion; at 30 minutes, 1 hour, 90 minutes, 2 hours, and 3 hours 30

Table 2.-2: On Study Procedural Outline (CA2099GW)

Procedure	Local Lab (LL) or Central Lab (CL)	Weeks 1-8		Weeks 9-24 Q2W	Week 25 and beyond Q4W	Notes Procedure Window ±2 Days Unless Specified Otherwise
		Weeks 1, 3, 5, 7	Weeks 2,4,6, 8			
						minutes after the start of the infusion; at the end of the infusion; and 30 minutes, 1 hour, and 2 hours after the end of the infusion. All other cycles - Measure vital signs prior to administration of premedication of daratumumab, and pre-nivolumab and daratumumab and after the end of the infusion.
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Events Assessment		------ Continuously -------				NSAEs and SAEs must be collected up to 100 days after study drug discontinuation.

Table 2.-2: On Study Procedural Outline (CA2099GW)

Procedure	Local Lab (LL) or Central Lab (CL)	Weeks 1-8		Weeks 9-24 Q2W	Week 25 and beyond Q4W	Notes Procedure Window ±2 Days Unless Specified Otherwise
		Weeks 1, 3, 5, 7	Weeks 2,4,6, 8			
Laboratory Tests						
Pregnancy Test	LL	X Weeks 1 and 5		X	X	To be done within 24 hours of first dose of study therapy, and then at least once every 4 weeks (+/-1 week) regardless of dosing schedule.
CBC with Differential and Platelets	LL	X	X	X	X	Weeks 1-8:every week Weeks 9-24: every other week Week 25 and beyond: every 4 weeks
Serum Chemistry	LL	X		X	X	Weeks 1-24: every other week Week 25 and beyond: every 4 weeks Chemistry panel includes LDH, AST, ALT, ALP, albumin, total bilirubin, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, glucose, phosphate, carbon dioxide or bicarbonate. Amylase and lipase: only for participants with pancreatic adenocarcinoma.

Table 2.-2: On Study Procedural Outline (CA2099GW)

Procedure	Local Lab (LL) or Central Lab (CL)	Weeks 1-8		Weeks 9-24 Q2W	Week 25 and beyond Q4W	Notes Procedure Window ±2 Days Unless Specified Otherwise
		Weeks 1, 3, 5, 7	Weeks 2,4,6, 8			
Thyroid Function Tests	LL		X Week 8	X	X	TSH (reflex to free T3 and free T4 if abnormal result) to be performed every 8 weeks (±7 days) from first dose (starting at Week 8) regardless of dosing schedule
Clinical Drug Supplies						
IRT Drug Vials Assignment		X	X	X	X	Vials can be assigned up to 3 days prior to first dose date.
Dispense Study Treatment	**As of 13-June-2018, only on-study TNBC and PAC participants who are deriving clinical benefit will continue to be treated with the nivolumab plus daratumumab combination therapy; NSCLC participants will be treated with nivolumab monotherapy.**					
Daratumumab		X	X	X	X	Treatment schedule for both study therapies is specified in Table 7.1-1 Dose delay guidance for nivolumab: Section 7.1.1.1 and for daratumumab: Section7.1.2.1.
Nivolumab		Weeks 3, 5, 7		X	X	
Pre-infusion/Post-infusion medications for daratumumab		X	X	X	X	See Sections 7.5.1 and 7.5.2 for guidance on pre-infusion and post-infusion medications for daratumumab.
Oral Herpes Zoster Virus Prophylaxis		Initiate antiviral prophylaxis within 1 week after starting daratumumab. Continue antiviral prophylaxis during the Treatment Phase as per institutional guidelines, and for 3 months following treatment discontinuation of daratumumab.				

Table 2.-2: On Study Procedural Outline (CA2099GW)

Procedure	Local Lab (LL) or Central Lab (CL)	Weeks 1-8		Weeks 9-24 Q2W	Week 25 and beyond Q4W	Notes Procedure Window ±2 Days Unless Specified Otherwise
		Weeks 1, 3, 5, 7	Weeks 2,4,6, 8			
Efficacy Assessments						
Radiographic Tumor Assessment	LL	.	See Notes	X	X	Tumor imaging assessment will occur at screening, and then every 6 weeks from the date of first dose (+/-1wk) for the first 24 weeks, then every 12 weeks (+/-2wk) thereafter until PD (even if treatment is discontinued before progression). CT or MRI chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at baseline. Participants with a history of brain metastasis may have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated. See Table 9.1.1-1

Table 2.-3: Follow-up Procedural Outline (CA2099GW)

-	Local Lab (LL) or Central Lab (CL	Day 30, 100 Follow-up (±1 wk)	Notes
Performance Status (ECOG)		X	See Appendix 5 for ECOG scale.
Physical Examination		X	Targeted physical examination, include weight. Must include the following body systems: cardiovascular, gastrointestinal, pulmonary
Vital Signs		X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate must be measured after the participant has been resting quietly for at least 5 minutes.
[redacted]		[redacted]	[redacted]
Adverse Events Assessment		X	NSAEs and SAEs must be collected up to 100 days after study drug discontinuation.
Laboratory Tests			
Pregnancy Test	LL	X	
CBC with Differential and Platelets	LL	X	To be done at Follow-up 1. To be repeated at Follow-up 2 if study related toxicity persists.
Serum Chemistry	LL	X	Chemistry panel includes LDH, AST, ALT, ALP, albumin, total bilirubin, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, glucose, phosphate, carbon dioxide or bicarbonate. Amylase and lipase: only for participants with pancreatic adenocarcinoma. To be done at Follow-up 1. To be repeated at Follow-up 2 if study related toxicity persists.
Thyroid Function Tests	LL	X	TSH (reflex to free T3 and free T4 if abnormal result).

Table 2.-3: Follow-up Procedural Outline (CA2099GW)

-	Local Lab (LL) or Central Lab (CL	Day 30, 100 Follow-up (±1 wk)	Notes
			To be done at Follow-up 1. To be repeated at Follow-up 2 if study related toxicity persists.
Oral Herpes Zoster Virus Prophylaxis		X	Continue antiviral prophylaxis for 3 months following discontinuation of treatment with daratumumab.
Efficacy Assessments			
Body Imaging	LL	See Section 9.1	For participants who discontinue treatment before progression, tumor imaging assessment will continue to be conducted per the regular schedule until PD (ie, every 6 weeks from the date of first dose [+/-1wk] for the first 24 weeks, then every 12 weeks [+/-2 wk] thereafter until PD or initiation of new therapy, whichever occurs first.

[redacted]

4. OBJECTIVES AND ENDPOINTS

Table 4.-1: Objectives and Endpoints

Objectives	Endpoints
Primary To establish the tolerability of the combination of nivolumab and daratumumab in participants with advanced or metastatic solid tumors.	Incidence of adverse events (AE), serious adverse events (SAE) and specific laboratory abnormalities (worst grade).
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	• ORR, duration of response (DOR), best overall response (BOR) in each cohort, based on RECIST 1.1 criteria (Appendix 7). • Median PFS in each cohort • Pharmacokinetic parameters, influence of intrinsic and extrinsic covariates and potential exposure-response relationship will be characterized using integrated analyses. • Immunogenicity of nivolumab and daratumumab will be assessed by ADA positivity
[redacted]	[redacted]

5. STUDY DESIGN

5.1 Overall Design

Study CA2099GW is an open-label, multi-center, Phase 1/2 study investigating the safety and efficacy of nivolumab in combination with daratumumab in participants with advanced or metastatic tumor types including TNBC, NSCLC, and PAC. As of 13-June-2018, only TNBC and PAC participants who are deriving clinical benefit will continue to be treated with the nivolumab plus daratumumab combination therapy; NSCLC participants will be treated with nivolumab monotherapy, only.

Enrollment of all tumor types is closed, as of 26-May-2018. The enrollment of participants with NSCLC is 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.

Participants will be treated for a maximum of 24 months on study, or until confirmed progression, unacceptable toxicity, withdrawal of consent, or the study is discontinued by the sponsor. Study treatment can continue beyond initial investigator assessed progression as specified in Section 7.1.5

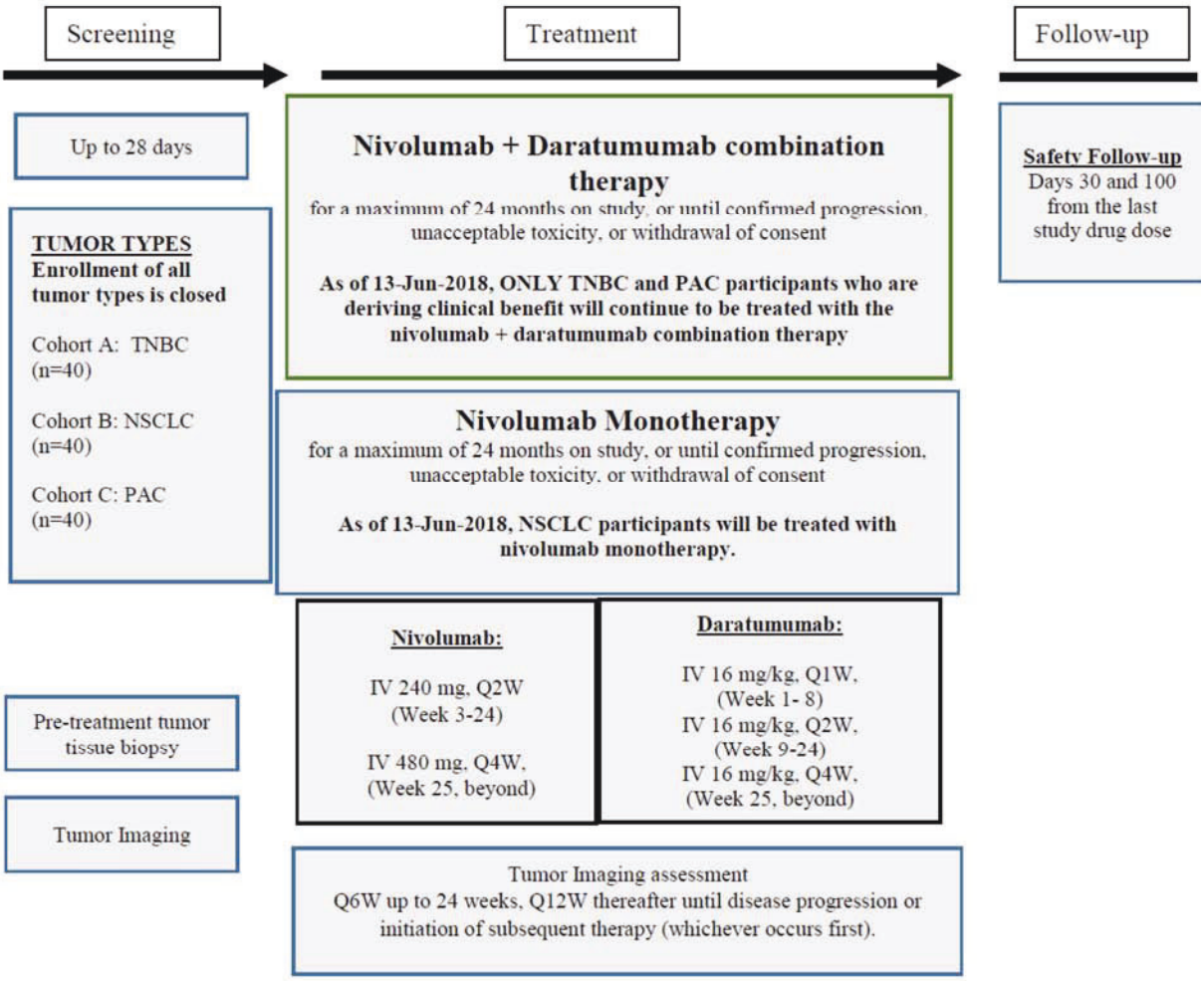
The study will consist of Screening, Treatment, and Follow-up. All safety data will be monitored on an ongoing basis throughout the study.

The duration of the study is anticipated to be approximately 3 years.

Please refer to Section 7.8 for study termination criteria.

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: 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

Screening Period (up to 28 days):

Participants will sign the informed consent form prior to undergoing any study-related procedures. Screening evaluations to determine eligibility will be performed within 28 days prior to the start of therapy (as outlined in Table 2.-1).

A baseline tumor imaging assessment will be performed prior to the start of therapy. Tumor tissue and peripheral blood must be provided for biomarker analysis. Sufficient, recent tumor tissue (fresh tumor biopsy or tumor tissue collected after the completion of the most recent prior therapy) obtained from a metastatic tumor lesion or from an unresectable primary tumor lesion which has

not been previously irradiated (formalin-fixed paraffin-embedded block (FFPE) or minimum of 25 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen) will be submitted to the central laboratory. If not enough tumor sample is available, the investigator has to contact the BMS study team to inform the BMS team if less than 25 charged unstained slides are available for the potential impact on biomarker testing.

Treatment Period:

During the Treatment period, (Table 2.-2) participants will receive (1) nivolumab 240 mg every 2 weeks from Week 3 to 24, then nivolumab 480 mg every 4 weeks from Week 25 and beyond, and (2) daratumumab 16 mg/kg every week for 8 weeks, then every 2 weeks for 16 weeks, and then every 4 weeks from week 25 onward, for a total treatment duration of 24 months. Due to the daratumumab infusion related reactions profile, the first 2 doses of daratumumab will be administered alone and nivolumab administration will start with the third dose of daratumumab. As of 13-June-2018, only TNBC and PAC participants who are deriving clinical benefit will continue to be treated with the nivolumab plus daratumumab combination therapy; NSCLC participants will be treated with nivolumab monotherapy. The treatment period will continue for a maximum of 24 months or until disease progression, occurrence of unacceptable toxicity, consent withdrawal, or the study is stopped by the Sponsor.

On-treatment tumor imaging assessments will occur every 6 weeks (+/-1 week) for the first 24 weeks, then every 12 weeks (+/- 1 week) until disease progression including participants who discontinue treatment due to unacceptable toxicity or until initiation of subsequent therapy, whichever occurs first. Treatment beyond initial investigator-assessed progression is permitted if the participant has an investigator-assessed clinical benefit and is tolerating study drug (Section 7.1.5). The investigator-assessed tumor response based on RECIST 1.1 criteria will be used for efficacy analyses. All participants will continue to be followed for safety after discontinuation of study medication during the Follow-up period. Participants who discontinue study drug due to toxicity will continue to have tumor assessments until disease progression or withdrawal of consent during Follow-up as specified in Table 2.-3.

Participants will be closely monitored for AEs and SAEs throughout the study. Participants who experience AEs that require discontinuation of one of the study drugs may be allowed to continue therapy with the other study drug, if deemed as in their best interest by both the PI and the BMS medical monitor. Participants must be deriving clinical benefit.

Participants may withdraw or discontinue at any time based on criteria in Section 8.1.

Follow-up Period:

All study participants who discontinue treatment will enter the Follow-up period, with visits scheduled on Days 30 and 100 from the last study drug dose, to monitor for AEs. Participants who discontinue study treatment due to toxicity will continue to be evaluated for efficacy until progression or initiation of subsequent therapy, whichever occurs first, as specified in Table 2.-3.

5.1.1 Data Monitoring Committee and Other External Committees

Not applicable [redacted]

5.2 Number of Participants

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. 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.

188 participants were enrolled in the study to ensure a total of 40 participants treated in each cohort, which assumed a screen failure rate of 25%. See Section 10.1 for sample size determination.

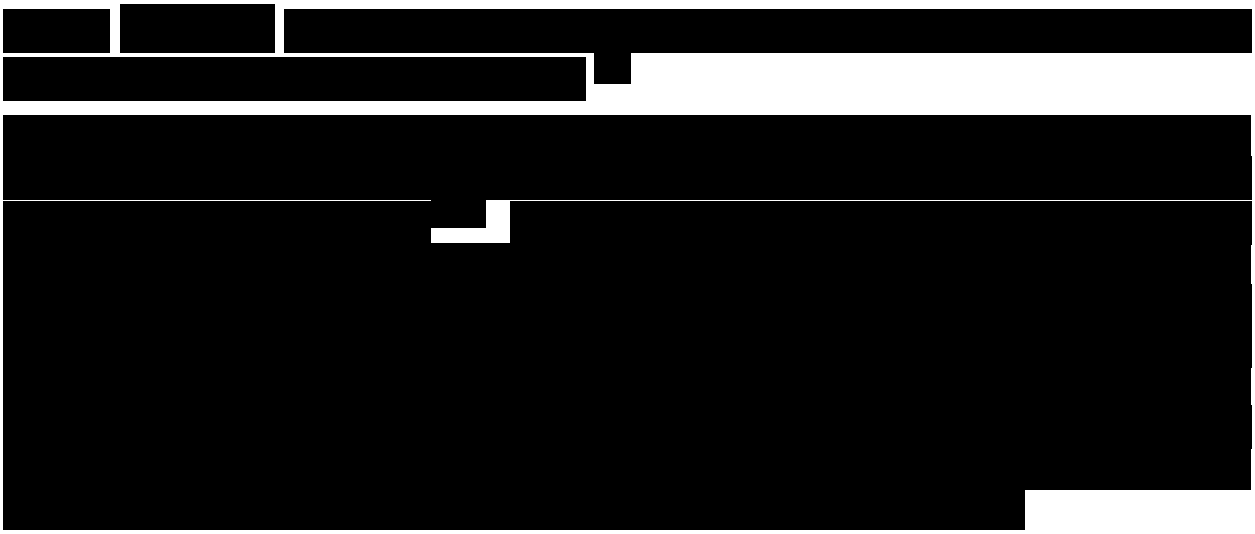
Participants at least 18 years old, who have histologic or cytological confirmation of the following solid tumors were enrolled:

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

5.3 End of Study Definition

The start of the trial is defined as first visit for first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities for the last participant.

[redacted]



5.6 Duration of Treatment: 24 months

The optimal duration of immunotherapy is currently unknown. However, because immunotherapy engages the immune system to control the tumor, continuous treatment as is required with targeted agents or cytotoxic therapy may not be necessary. Accumulating evidence from different clinical trials in different tumors types with nivolumab indicates that most of the responses are generally occurring early, with a median time to response of 2-4 months including in patients with NSCLC.[117,118] and a recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab for toxicity maintain disease control in the absence of further treatment.[119] For these reasons, in study CA2099GW, treatment will be given for up to 24 months in the absence of disease progression or unacceptable toxicity.

6. STUDY POPULATION

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal participant care.

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory **tests**, potential tumor biopsies, and other requirements of the study.

2) Type of Participant and Target Disease Characteristics

a) Women with histologically or cytologically confirmed breast carcinoma who must meet all of the following:

i. Tumor must be “triple receptor negative” defined as ER/PR negative and HER-2 negative defined per 2013 American Society of Clinical Oncologists and College of American Pathologists (ASCO-CAP) guidelines.[120]

AND

ii. Participants must have had received 1 to 4 prior regimens for the treatment of metastatic (Stage IV) or locally advanced disease. There must have been progression on or following the last regimen or unacceptable adverse events requiring discontinuation or therapy.

b) Participants with histologically or cytologically confirmed pancreatic adenocarcinoma who must meet the following:

i. Participants must not have clinically relevant ascites at baseline, such as ascites in need of paracentesis.

AND

ii. Participants must have received only 1 prior chemotherapy regimen for the treatment of metastatic (Stage IV) or locally advanced disease. There must have been progression on or following the last regimen or unacceptable adverse events requiring discontinuation or therapy.

c) Participants must have histologic or cytologic confirmation of NSCLC (per the seventh International Association for the Study of Lung Cancer [IASLC])[121] with squamous or nonsquamous histology that is advanced (metastatic and/or unresectable)

i. Participants must have no more than 2 prior lines of therapy including one line of platinum doublet chemotherapy.

ii. Participants who will receive study therapy as second line of treatment must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease.

a. First line therapy is defined as therapy used to treat advanced disease. Each subsequent line of therapy is preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity does not define the start of a new line of therapy.

b. Experimental therapies when given as separate regimen are considered as separate line of therapy and must have resulted in disease progression.

c. Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy and could comprise continuation of one or more of the agents used in the first-line therapy regimen or switch to another non cross-resistant agent. The initiation of maintenance therapy requires the lack of progressive disease with frontline therapy.

d. Treatment given for locally advanced disease is not considered as a line of therapy for advanced disease. Participants with recurrent disease > 6 months after platinum containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum doublet-based regimen given to treat the recurrence, are eligible. Adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) followed by recurrent or metastatic disease within 6 months of completing therapy is considered as first line therapy for advanced disease.

iii. Participants who will receive study therapy as third line of treatment must have experienced disease recurrence or progression during or after a separate EGFR or ALK tyrosine kinase inhibitor (TKI) regimen in addition to one prior platinum doublet-based chemotherapy regimen (regardless of order of administration).

a. Participants who received an EGFR TKI (erlotinib, gefitinib or experimental) in addition to a platinum-based chemotherapy must have a tumor with a known activating EGFR mutation.

b. Participants with a tumor with EGFR wild-type or unknown EGFR mutation status who received an EGFR TKI after failure of a prior platinum-based chemotherapy are excluded.

c. Participants who received an ALK inhibitor (crizotinib or experimental) in addition to a platinum-based chemotherapy must have a tumor with a known ALK translocation.

d) Participants must have measurable disease by CT or MRI per RECIST 1.1 criteria (radiographic tumor assessment must be performed within 28 days prior to first dose).

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

f) Life expectancy of at least 3 months

g) Must consent to tumor biopsy.

h) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, obtained within 3 months prior to first dose, with an associated pathology report, must be submitted to the core laboratory for inclusion. Central lab must provide Interactive Response Technology (IRT) with confirmation of receipt of evaluable tumor tissue prior to study treatment. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is unacceptable for submission. If not enough tumor sample is available, the investigator has to contact the BMS study team to inform the BMS team if less than 25 charged unstained slides are available for the potential impact on biomarker testing.

i) Prior focal palliative radiotherapy to an isolated bone or soft tissue metastasis must be completed at least 2 weeks before study drug administration.

j) All baseline laboratory requirements will be assessed and should be obtained within 14 days of first dose. Screening laboratory values must meet the following criteria:

i. WBCs $\geq$ 2000/μL (growth factors not permitted within 1 week of study drug administration; pegylated growth factors not permitted within 3 weeks of first study drug administration)

ii. Neutrophils $\geq$ 1500/μL (growth factors not permitted within 1 week of study drug administration; pegylated growth factors not permitted within 3 weeks of first study drug administration)

iii. Platelets $\geq$ 100 x 10^3/μL (transfusions not permitted within 72 hours prior to qualifying laboratory value)

iv. Hemoglobin $\geq$ 9.0 g/dL (transfusions not permitted within 72 hours prior to qualifying laboratory value; recombinant human erythropoietin not permitted within 3 weeks of study drug administration)

v. Estimated creatinine clearance by Cockcroft-Gault formula $\geq$ 30 mL/min

vi. AST and ALT levels $\leq$ 3 x ULN or $\leq$ 5 x ULN if liver metastases are present

vii. Total Bilirubin ≤ 1.5 x ULN (except participants with Gilbert Syndrome who can have total bilirubin < 3.0 mg/dL)

viii. Albumin ≥ 3 g/dL

ix. For participants with pancreatic adenocarcinoma

a. Lipase ≤ 1.5 x ULN. Participants with lipase > 1.5 x ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis

b. Amylase ≤ 1.5 x ULN. Participants with amylase > 1.5 x ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis

3) Age and Reproductive Status

a) Males and Females, ≥18 years of age

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug(s) plus approximately 5 half-lives of study drug(s) plus 30 days (duration of ovulatory cycle) for a total of 5 months post treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus approximately 5 half-lives of study drug(s) plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion.

f) WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements and still must undergo pregnancy testing as described.

Investigators shall counsel WOCBP and male participants who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male participants who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, participants must agree to the use one highly effective method of contraception as listed in Appendix 4.

6.2 Exclusion Criteria

1) Medical Conditions

a) Active brain metastases or leptomeningeal metastases. Participants with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

b) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair

the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.

c) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured or successfully resected, such as basal or squamous cell skin cancer, superficial bladder cancer, or gastric cancer, or carcinoma in situ of the prostate, cervix, or breast. Participants with active, known or suspected autoimmune disease. Participants with skin disorders (such as vitiligo, psoriasis, or alopecia), type I diabetes mellitus, hypothyroidism only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

d) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose. Inhaled or topical steroids, and adrenal replacement steroid doses are permitted in the absence of active autoimmune disease.

e) Vaccination with live attenuated vaccines within 4 weeks of first study agent administration

f) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Participants with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.

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

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

   ii) Uncontrolled or poorly controlled angina within the 3 months prior to consent

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

   iv) QTc prolongation > 470 msec

   v) history of other clinically significant heart disease (ie, cardiomyopathy, congestive heart failure with NYHA functional classification III-IV, pericarditis, significant pericardial effusion)

   vi) requirement for daily supplemental oxygen therapy

h) Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal

i) Known moderate or severe persistent asthma within the past 2 years, or uncontrolled asthma of any classification. Participants who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.

2) Prior/Concomitant Therapy

a) Prior therapy with any T cell co-stimulation or checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab and nivolumab; or other medicines specifically targeting T cells.

b) Prior therapy with anti-CD38 monoclonal antibodies.

c) Prior organ allograft.

d) Treatment with any chemotherapy, radiation therapy, (except for palliative radiation therapy as indicated in inclusion criterion 2.i above), biologics for cancer, or investigational therapy within 28 days of first administration of study treatment (participants with prior cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to Grade 1 (NCI CTCAE version 4).

3) Physical and Laboratory Test Findings

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

b) Positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Testing for HIV must be performed at sites where mandated locally.

c) Participants must not be dependent on continuous supplemental oxygen use**.**

4) Allergies and Adverse Drug Reaction

a) History of allergy to study drug components.

b) History of severe hypersensitivity reaction to any monoclonal antibody or fusion proteins

c) Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the daratumumab formulation

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.

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

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

6.3 Lifestyle Restrictions

Not applicable. No restrictions are required

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

Participant Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a screen failure (i.e., participant has not been treated). If re-enrolled, the participant must be re-consented.

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value). The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 2.-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7. TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation

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

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

The drugs used in combination therapy during this open-label study qualify as IPs, as per previous text, and their description and storage information are described in Table 7.-1.

Table 7.-1: Product Description for CA2099GW

Product Description / Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/ml) and 40 mg (10 mg/mL)	IP	Open label	Vial	Refer to the label on container and/or pharmacy manual.
Daratumumab Solution for Injection	100 mg (20mg/mL) and/or 400 mg (20 mg/mL)	IP	Open label	Vial	Refer to the label on container and/or pharmacy manual.

Further instructions with regard to the preparation, handling, and storage for nivolumab and daratumumab will be provided to sites separately as Pharmacy preparation instructions or a Pharmacy manual.

7.1 Treatments Administered

The selection and timing of dose for each participant is presented in Table 7.1-1.

Table 7.1-1: Study Drug Dosing Schedule

Cohort/Tumor Types*	Nivolumab + Daratumumab	Dose	Frequency of administration	Route of administration	Duration
A (n=40) TNBC B (n=40) NSCLC C (n=40) PAC	Nivolumab	240 mg flat dose	Every 2 weeks starting at Week 3	30 minutes Intravenous (IV) infusion	24 months or until progression, toxicity, or early discontinuation from study
		480 mg flat dose	then every 4 weeks starting at Week 25		
	Daratumumab	16mg/kg	Every week (Wks 1-8) then every 2 weeks (Wks 9-24), then every 4 weeks starting at Week 25	First infusion: approximately 8 hours Second and subsequent infusions: approximately 4 hours Intravenous (IV) infusion	

*** Enrollment in all tumor cohorts is closed.**

As of 13-June-2018, only on-study TNBC and PAC participants who are deriving clinical benefit will continue to be treated with the nivolumab plus daratumumab combination therapy; NSCLC participants will be treated with nivolumab monotherapy.

7.1.1 Nivolumab

Nivolumab should be administered before daratumumab. There are no pre-medications recommended for nivolumab.

Participants will receive nivolumab at a dose of 240 mg as a 30 minute infusion every 2 weeks from Week 3 to Week 24, then nivolumab 480 mg every 4 weeks from Week 25 and beyond for up to 24 months or until disease progression, occurrence of unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

Nivolumab can be delayed within a 3-day window during the every other week administration schedule, as long as the 12-day interval between 2 nivolumab doses is respected. During the every 4 weeks administration schedule, nivolumab can be delayed within a week, as long as the 21-day interval between 2 nivolumab doses is respected. The Week 25 dose (the first dose of the every 4 week dosing schedule) may be administered no less than 12 days from the previous dose and for subsequent doses it should be dosed no less than 21 days from the previous dose. Doses that fall outside the allowed window should be skipped.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.1.3.1.

There will be no dose escalations or reductions of nivolumab allowed. Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment.

If the dose of nivolumab is interrupted or discontinued due to a related AE, the treatment with daratumumab may continue as scheduled if deemed in their best interest by both the Principal Investigator and the BMS medical monitor. Participants must be deriving clinical benefit and the AE must clearly not be related to daratumumab. Please consult the BMS Medical Monitor or any questions regarding dose interruption or study therapy discontinuation.

7.1.1.1 Nivolumab Dose Delay Due to AEs

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related adverse event, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation (see Section 8.1)
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met. See Section 7.1.4.

7.1.2 Daratumumab

Daratumumab should be administered after nivolumab, and will start no sooner than 30 minutes after completion of the nivolumab infusion. All participants will receive pre-infusion and post-infusion medication for prevention of daratumumab infusion related reactions per the descriptions in Section 7.5. Participants should be carefully monitored for infusion reactions during daratumumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.1.3.2.

There will be no dose escalations or reductions of daratumumab allowed. Doses of daratumumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. See Table 7.1.2-1 for guidance on daratumumab dose delay.

If the dose of daratumumab is interrupted or discontinued due to a related AE, the treatment with nivolumab may continue as scheduled if deemed in their best interest by both the Principal Investigator and the BMS medical monitor. Participants must be deriving clinical benefit and the AE must clearly not be related to nivolumab. Please consult the BMS Medical Monitor or any questions regarding dose interruption or study therapy discontinuation.

During the weekly dosing schedule, daratumumab can be delayed within a window of -1 to +3 days. During the every other week dosing schedule, daratumumab dosing may be delayed for up to 1 week. During the every 4 week dosing schedule, daratumumab can be delayed within a 21-day window. Doses that fall outside the allowed windows should be skipped.

Table 7.1.2-1: Daratumumab Dose Delay Guidance

Weeks	Dosing Frequency	Skip dose window	Dosing Resumption
1 -8	Weekly (QW)	> 3 days	Next planned weekly dosing date
9-24	Biweekly (Q2W)	> 7 days	Next planned biweekly dosing date
25 and beyond	Every 4 weeks (Q4W)	> 21 days	Next planned every 4 weeks dosing date

Doses of daratumumab may be delayed up to 4 weeks during Weeks 1-24 or up to 6 weeks from Week 25 and beyond. Any adverse event deemed to be related to daratumumab that requires a dose hold longer than those specified above will result in permanent discontinuation of daratumumab. If a dose delay occurs, then pharmacokinetic and pharmacodynamic assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.

7.1.2.1 Daratumumab Dose Delays Due to AEs

The study treatment must be held if any of the following criteria below are met, to allow for recovery from toxicity. The criteria for a dose delay are:

- Grade 4 hematologic toxicity, except for grade 4 lymphopenia
- Grade 3 or higher thrombocytopenia
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

If daratumumab administration does not commence within the prespecified window (Table 7.1.2-1) of the scheduled administration date, then the dose will be considered a missed

dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

7.1.3 Treatment of Study Drug Related Infusion Reactions

7.1.3.1 Management of nivolumab infusion-related reactions

Since nivolumab is a fully human antibody, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4) guidelines.

Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Participants should be carefully observed until the complete resolution of all signs and symptoms. Following an infusion reaction, participants should be premedicated with acetaminophen and diphenhydramine for future treatments.

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

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

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

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

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

The following prophylactic premedications are recommended for future infusions:

- Diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If

necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

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

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

7.1.3.2 Management of daratumumab infusion-related reactions

Management of Daratumumab Infusion related reactions:

Participants should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions, and resources necessary for resuscitation must be available. Attention to staffing should be considered when multiple participants will be dosed at the same time.

For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may require further reduction in the rate of infusion, or treatment discontinuation of daratumumab.

Infusion-related reactions of Grade 1 or Grade 2: Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the participant does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate as outlined in Table 7.5-1.

Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the participant does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 7.5-1. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion-related reaction.

Grade 4 (life threatening): Permanently discontinue daratumumab treatment.

7.1.4 Criteria to Resume Treatment

Participants may resume nivolumab treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Participants with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 8.1.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by BMS Medical Monitor.

Participants with nivolumab-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. Grade ≥ 3 adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

7.1.5 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[7]

Participants will be permitted to continue treatment beyond initial RECIST 1.1 defined PD, assessed by the investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit.
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, central nervous system (CNS) metastases)
- Participant provides written informed consent prior to receiving additional treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment.

If the investigator feels that the participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to the Schedule of Activities in Section 2

For the participants who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

7.2 Method of Treatment Assignment

All participants were initially assigned to combination therapy. Enrollment of all tumor types is closed, as of 26-May-2018. As of 13-June-2018, only on-study TNBC and PAC participants who are deriving clinical benefit will continue to be treated with the nivolumab plus daratumumab combination therapy; NSCLC participants will be treated with nivolumab monotherapy.

Study treatment will be dispensed at the study visits as listed in Schedule of Activities: Table 2.-2.

After informed consent has been obtained, the subject must be screened into the study by logging into the Interactive Response Technology (IRT) to obtain a subject number. Every subject that signs the informed consent form must be assigned a subject number in the IRT. The investigator or designee will register the subject for screening by following the screening procedures established by BMS. During the screening visit, the IRT will assign a 5-digit participant number that will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001, (eg, 00001, 00002, 00003.... 00010). The patient identification number (PID) will ultimately be comprised of the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1, will have a PID of 0001 00001. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to assign the participant into the open dose panel of nivolumab plus daratumumab. Participants who withdraw from the study will not be replaced. Specific instructions for using IRT will be provided to the investigational site in a separate document.

The following information is required for drug vial assignment:

- Participant number

- Date of birth
- Gender at Birth

7.3 Blinding

This is an open-label study, blinding procedures are not applicable.

7.4 Dosage Modification

There will be no dose adjustments allowed for study drugs with the exception of changes due to fluctuations in weight for daratumumab.

7.5 Preparation/Handling/Storage/Accountability

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

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

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Storage facilities for controlled substances must be securely locked and substantially constructed, with restricted access to prevent theft or diversion, as applicable by local regulations.

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% sodium chloride injection, 5% dextrose injection) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the Investigator Brochure and/or pharmacy manual for complete storage, handling, dispensing, and infusion information for nivolumab, and daratumumab.

Nivolumab Preparation and Administration

Please refer to the current version of the IB and/or pharmacy manual for complete storage, handling, dispensing, and infusion information for nivolumab. Nivolumab vials must be stored at a temperature of 2° to 8°C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include use of laboratory coats and gloves. For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration,

please refer to the Nivolumab IB: "Recommended Storage and Use Conditions" and/or pharmacy manual.

Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy manual. Care must be taken to assure sterility of the prepared solution because the product does not contain any antimicrobial preservative or bacteriostatic agent.

Daratumumab Preparation and Administration

Daratumumab Infusion solution will be prepared as a 1,000-mL (first dose) or 500-mL (second and subsequent doses) dilution of daratumumab in sterile, pyrogen-free 0.9% NaCl. Preparation of infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 μM) during the infusion. Pharmacy manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to each pharmacy and site.

Because of this high risk of infusion related reactions daratumumab infusions will be administered per the Investigator's Brochure by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion reactions if they occur, and all participants will receive pre-infusion and post-infusion medication per the descriptions in Section 7.5

Before administration the drug product should be stored and prepared as per the instructions in pharmacy manual. Daratumumab (dose) will be administered as an IV infusion. All infusions will be planned as outpatient visits. Each participant's dose will be calculated based on the participant's weight at Week 1 rounded to the nearest kilogram. The dose of daratumumab to be administered to a participant will be calculated by multiplying the participant's weight (kg) by 16 mg/kg. The dose of daratumumab will remain constant throughout the study, unless the participant's weight changes more than 10% from Week 1. All infusions will be planned as outpatient visits. Participants will receive pre-infusion medications and post-infusion medications as detailed in the protocol (Section 7.5).

The infusion start and stop time will be recorded in the eCRF. If the infusion is stopped mid-session for any reason, the stop/start time must be recorded together with an explanation.

The dilution volumes, initial infusion rates, and increment for the first, second, and subsequent doses are provided in Table 7.5-1. The first infusion, with a volume of 1,000 mL, takes approximately 8 hours; the second and subsequent infusions, with volumes of 500 mL, take approximately 4 hours. The maximum infusion rate for all infusions is 200 mL/hour. Additional details for administration times and rates, as well as pre-infusion medications, will be provided in the pharmacy manual.

Vital signs should be monitored extensively on Week 1 and 2 before, during, and after the first infusion of daratumumab. For all other infusions, vital signs should be measured before the start of the infusion and at the end of the infusion. If a participant experiences any significant medical

event, then the investigator should assess whether the participant should stay overnight for observation. If the participant has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

Table 7.5-1: Daratumumab Infusion Rates

	Dilution Volume	Initial Infusion Rate (first hour)	Increments of Infusion Rate	Maximum Infusion Rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Modified rates should only be used if the first infusion of daratumumab was well tolerated as defined by an absence of > Grade 1 infusion-related reactions during the first 3 hours.

[b] Modified rates should only be used if the first 2 infusions of daratumumab were well tolerated as defined by an absence of > Grade 1 infusion-related reactions during a final infusion rate of ≥100 mL/hr.

7.5.1 Pre-Infusion Medication for Daratumumab

Daratumumab will be administered as described in the Schedule of Activities (Table 2.-2). On daratumumab infusion days, participants will receive the following medications approximately 1 hour prior to daratumumab infusion (can be administered before the nivolumab infusion):

- Paracetamol (acetaminophen) 650-1000 mg IV or PO
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent but avoid IV use of promethazine) (see Appendix 8 for list of antihistamines that may be used)
- Methylprednisolone 100 mg, or equivalent, administered intravenously. Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg). Substitutions for methylprednisolone are allowed, please refer to Appendix 9.
- Leukotriene Inhibitor (optional) on Cycle 1 Day 1: montelukast 10 mg PO, or equivalent.

If necessary, all PO pre-infusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion.

Pre-infusion medications for daratumumab may be administered before the start of nivolumab infusion. Daratumumab should be administered after nivolumab, and will start no sooner than 30 minutes after completion of the nivolumab infusion.

7.5.2 Post-Infusion medication for Daratumumab

For the prevention of delayed infusion-related reactions, all participants will receive long- or intermediate-acting corticosteroid orally (20 mg methylprednisolone or equivalent in accordance with local standards) on the 2 days following all daratumumab infusions (beginning the day after the infusion).

In the absence of infusion related AEs after the first 3 infusions, post-infusion corticosteroids should be administered per investigator discretion.

For participants with a higher risk of respiratory complications (eg, participants with mild asthma or participants with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history), the following post-infusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for participants with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for participants with COPD)

In addition, these at-risk participants may be hospitalized for monitoring for up to 2 nights after an infusion. If participants are hospitalized, then their spirometry test (FEV1) should be performed before discharge. If these participants are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all infusions. If no infusion-related reaction has occurred, the follow-up telephone call 48 hours after the infusion is not required. If the participant has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after participants are released from the hospital/clinic. If an at-risk participant experiences no major infusion-related reactions, then these post-infusion medications may be waived after 4 doses at the investigator's discretion.

Any post-infusion medication will be administered after the infusion has completed.

[redacted]

7.6 Treatment Compliance

Study treatment will be administered in the clinical facility by trained medical personnel. Treatment compliance will be monitored by treatment accountability, as well as by recording administration of each study treatment in the participants' medical records and eCRF.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.8 Treatment After the End of the Study

At the end of the study, BMS will not continue to provide BMS supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

BMS reserves the right to terminate access to BMS supplied study treatment if any of the following occur: a) the study is terminated due to safety concerns; b) the development of nivolumab or daratumumab is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives; c) the participant can obtain medication from a government sponsored or private health program. In all cases BMS will follow local regulations.

8. DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant ’s request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Documented and confirmed disease progression or clinical deterioration while receiving active study therapy
- Termination of the study by BMS as specified in Section 7.8.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- For discontinuation criteria related to nivolumab-and/or daratumumab-related adverse events, please see below.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. Please contact the Sponsor or designee within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All participants who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Table 2.-3. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the participant 's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate case report form (CRF) page.

Discontinuation of the study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined below or if the investigator believes that it is in best interest of the participant.

8.1.1 Nivolumab Discontinuation Criteria

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the Re-Treatment Period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Grade ≥ 3 adrenal insufficiency requires discontinuation regardless of control with hormone replacement (note: Hospitalization for diagnostic workup of adrenal insufficiency without severe symptoms
  - should not be considered a Grade 3 event).
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except for the following:
    - Grade 3 drug-related thrombocytopenia lasting > 7 days or associated with bleeding requires discontinuation
    - Grade ≥ 3 drug-related AST, ALT, or Total bilirubin requires discontinuation
    - Concurrent AST or ALT > 3× ULN and total bilirubin > 2× ULN

    *In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.
- Any drug-related Grade 4 endocrinopathy and Grade 3 adrenal insufficiency requires discontinuation.
- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis

  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued study drug dosing.

8.1.2 Daratumumab Discontinuation Criteria

Daratumumab treatment should be permanently discontinued for the following reasons:

- Grade 4 infusion reaction related to daratumumab.
- The 3rd occurrence of a Grade ≥ 3 daratumumab infusion related reaction
- Participants experiencing ≥ 8-week delay in all study drugs (nivolumab and daratumumab) due to an AE(s) related to study treatment must be discontinued from all study treatment. Participants experiencing delays unrelated to study therapy, for example due to palliative radiation therapy, may delay study treatment up to 84 days.
- Any daratumumab related AE that requires a dose hold of >4 weeks during Weeks 1-24 or >6 weeks during Week 25 and beyond will result in permanent discontinuation of daratumumab, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue as scheduled during such dosing delays.

The assessment for discontinuation of study drug should be made separately considering each study drug. If discontinuation criteria are attributed with only 1 drug used in this trial, once the participant meets criteria to resume therapy, the participant may continue dosing with the remaining study drug not attributed to criteria for discontinuation.

If a participant was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate CRF page.

Refer to the Schedule of Activities (Table 2.-3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

8.1.3 Post Study Treatment Study Follow-up

In this study, PFS is a secondary endpoint. Post-study treatment follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who

discontinue study drug must continue to be followed for collection of outcome follow-up data, as required and in line with Table 2.-3, withdrawal of consent, or conclusion of the study.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.

- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.

If a participant shows pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the participant should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm in the Nivolumab Investigator Brochure.

- Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.1 Efficacy Assessments

Study evaluations will take place in accordance with the schedule of activities presented in Section 2 and Table 9.1.1-1 and Table 9.1.1-2.

Chest, abdomen, pelvis and all known or suspected sites of disease should be assessed at all time points.

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 Version 1.1 (see Appendix 7).

At Screening, MRI of the brain without and with contrast is required for participants with known or suspected brain metastases. Participants with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

Participants with a history of bone metastasis may have a bone scan, if clinically indicated.

9.1.1 Imaging Assessment for the Study

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

CT and MRI are an essential part of the work-up to establish recurrence. The following imaging assessments should be performed at pre-specified intervals: CT of the chest, CT or MRI of the abdomen, pelvis, and other known sites of disease

- CT scans should be acquired with slice thickness of 5 mm or less with no intervening gap (continuous)
- Should a participant have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis and other sites of disease may be obtained. MRIs should be acquired with slice thickness of 5 mm or less with no gap (continuous).
- Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points.
- PET alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.

  Note: Use of CT component of a PET/CT scanner: Combined modality scanning, such as with FDG-PET/CT, is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low-dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically-based efficacy assessments, and it is, therefore, suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically-based RECIST (Appendix 7) measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

- Histology or cytological evidence of recurrence should be attempted in all cases except for brain metastases. Cytology and/or histology are mandatory to confirm recurrence in solitary or in equivocal lesions, any new lesions occurring in the kidney, and lymph nodes unless the lesion is too small to biopsy or the risk of biopsy is substantial (eg, inter-aortal node with risk of bleed after biopsy because of close proximity to the aorta and IVC) in which case the recurrence must be confirmed with a repeat scan 4 weeks later.

Study evaluations will take place in accordance with Table 9.1.1-2 and Appendix 7.

Tumor assessments will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria, see Appendix 7.

Table 9.1.1-1: Acceptable Imaging Assessment Methods for Different Anatomic Regions

Anatomic Region	Preferred Method	Alternative Methods
Chest, abdomen, and pelvis Note: Scan must cover lung apices to diaphragm, diaphragm through entire liver, and to below the pubic symphysis	CT with IV contrast	For chest: CT without contrast can be used only if the participant has a clinical contraindication for iodine-based IV contrast (eg, hypersensitivity, renal insufficiency) For abdomen and pelvis: MRI with gadolinium-based IV contrast is the first alternative method if the participant has a clinical contraindication for iodine-based IV contrast CT without contrast can be used as the second alternative method only if the participant has a clinical contraindication for both contrast-enhanced CT and MRI.
Brain	MRI with IV contrast	CT with IV contrast is the first alternative method if IV gadolinium is clinically contraindicated. MRI without contrast can be used as a second alternative method if a participant has clinical contraindications for both contrast-enhanced CT and MRI
Bone	Bone scintigraphy	PET (18F-fluoride NaF or FDG) or 99m Technetium SPECT

Notes:

1) CT scans must be performed with slice thickness of ≤ 5 mm. The reconstruction interval should be equal to slice thickness to avoid gap.
2) The same modality for a given anatomical coverage and the same scanning procedure (most importantly: reconstruction slice thickness, anatomic coverage, use of IV contrast) should be consistent between baseline and all subsequent follow-up scanning. If possible, the same scanner or an equivalent scanners should be used throughout the study.
3) For abdomen and pelvis CT scans, oral contrast is recommended as per institutional standards.
4) MRI should include both T1 and T2-weighted sequences with T1-weighted both pre- and post-contrast.
5) If bone scan shows hotspots indicative of metastases, further investigation with X-ray, CT, or MRI is warranted.
6) All scans generated should be exportable in electronic format (DICOM) to enable secure and rapid electronic transmission to the designated central imaging laboratory. No longer required per Revised Protocol 03.

Imaging restrictions and precautions are described in Section 7.7.2.6.

Table 9.1.1-2: Schedule of Spiral CT/MRI Tumor Assessments for advanced and Metastatic Cohorts

Tumor Assessment Frequency	*Assessment Window*
Tumor assessment at screening (within 28 days of first dose), and then every 6 weeks thereafter up to 24 weeks	± 1 week
Tumor assessment at week 24 and beyond will be every 12 weeks until PD.	± 2 weeks

For the 3 advanced metastatic tumor cohorts a baseline tumor assessments will be performed within 28 days prior to the start of treatment. Participants will then be evaluated for tumor response beginning 6 weeks from the date of first dose (± 1 week.), then every 6 weeks (± 1 week.) thereafter up to 24 weeks, then it will be every 12 weeks (+/- 2 weeks) until disease progression is documented, regardless of early treatment discontinuation due to reasons other than PD, or subsequent therapy is initiated (whichever occurs first).

Confirmation Scans are required as follows:

- Verification of Response: Confirmation of PR and/or CR is required after at least 4 weeks to ensure responses identified are not the result of measurement error.
- Verification of Progression: When not clinically burdensome to the participant, confirmation of PD is required after at least 4 weeks to ensure responses identified are not the result of measurement error.

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Immune-mediated adverse events are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant’s case report form.

Contacts for SAE reporting specified in Appendix 3

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment until 100 days after the last treatment, at the timepoints specified in the Schedule of Activities (Section 2).

Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. For participants assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of treatment assignment. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

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

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF section.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of this being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. (In order to prevent reporting bias, participants should not be questioned regarding the specific occurrence of one or more AEs.)

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for

disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

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

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

9.2.7 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.8 Other Safety Considerations

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

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 9.2).

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2).

9.4.1 Physical Examinations

Refer to Schedule of Activities: Section 2.

9.4.2 Vital signs

Refer to Schedule of Activities: Section 2.

9.4.3 Electrocardiograms

Refer to Schedule of Activities: Section 2.

9.4.4 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- A local laboratory will perform the analyses and will provide reference ranges for these tests. Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.
- Results of all laboratory tests required by this protocol must be provided to BMS, recorded either on the laboratory pages of the CRF or by another mechanism, as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF.

The laboratory tests that will be performed for study participants are shown in Table 9.4.4-1

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Blood type (ABO, Rh, and indirect antiglobulin testing) (screening only)	
Serum Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase Lactate dehydrogenase (LDH) Creatinine[a] Blood Urea Nitrogen (BUN) or serum urea level Glucose, Phosphate	Albumin Sodium Potassium Chloride Calcium Magnesium Creatinine clearance (CLcr)- screening only Carbon Dioxide or Bicarbonate[b] Amylase and lipase: only for participants with pancreatic adenocarcinoma
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick	
Thyroid Function Tests	
TSH (reflex to free T3 and free T4 if abnormal result)	
Serology	
Hepatitis B surface antigen (HBV sAg, Australia antigen), and hepatitis C antibody (HCV Ab) or HCV ribonucleic acid (RNA)HIV-1 and -2 antibody (screening only)	
Other Analyses	
Pregnancy test (WOCBP only: screening, predose, discharge).	
Follicle stimulating hormone (FSH) (screening only for women only)	

[a] Creatinine clearance measured by 24-hour urine collection or estimated from serum creatinine by the Cockcroft-Gault formula.

[b] To be done in sites where this is a standard part of the chemistry panel. In sites where testing for CO2/HCO3 is not standard, the test is optional.

9.4.4.1 Blood Typing

Blood Type, Rh factor, and Indirect Antiglobulin Test (IAT) should be done before the first dose of daratumumab. Participant RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion. Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Participants will receive a Participant Alert Card (PAC) for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Participant are to carry the PAC throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab IAT interference with IAT by treating reagent RBCs with dithiothreitol (DTT).[122]

Possible methods for blood banks to provide safe RBCs for transfusion to participants receiving daratumumab include:

a) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units
b) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice. Despite daratumumab binding to CD38 on erythrocytes, no indication of clinical significant hemolysis has been observed in daratumumab studies.

9.4.5 Safety Assessment

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include signs and symptoms, weight, ECOG Performance Status, BP, HR, temperature, and respiratory rate should be performed within 14 days prior to first dose except where noted in Table 2.-1. Concomitant medications will also be collected within 14 days prior to first dose and through the study treatment and follow-up periods. (See Table 2.-2 and Table 2.-3).

Baseline safety laboratory assessments should be done within 14 days prior to the first dose (see Table 2.-1). Pregnancy testing for WOCBP (done locally) to be done within 24 hours prior to first dose, and then every 4 weeks (+/– 1 week) regardless of dosing schedule, and at each safety follow up visit.

Determination of safety lab results is required prior to dosing. If there are delays with obtaining results for certain tests, please contact the medical monitor to determine clinical significance.

Participants will be evaluated for safety if they have received any study drug. Toxicity assessments will be performed continuously during the treatment phase. During the safety follow-up phase (see Table 2.-3) toxicity assessments should be done in person.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.

On treatment vital signs should be monitored extensively on Week 1 and 2 before, during, and after the first infusion of daratumumab as follows: immediately before the start of the infusion, at 30 minutes, 1 hour, 90 minutes, 2 hours, and 3 hours 30 minutes after the start of the infusion; at the end of the infusion, and 30 minutes, 1 hour, and 2 hours after the end of the infusion. For all other cycles, measure vital signs prior to administration of premedication of daratumumab, and pre-nivolumab and daratumumab and after the end of the infusion. The start and stop time of the nivolumab and daratumumab infusions should be documented. Physical examinations are to be performed at treatment visits as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

9.5 Pharmacokinetic

As of Revised Protocol 03, the collection of pharmacokinetic samples was discontinued.

[redacted]

9.8.2 Immunogenicity Assessments

As of Revised Protocol 03, the collection of immunogenicity samples is discontinued.

10. STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Sample size determination is not based on statistical power calculation.

40 participants were to be enrolled to each cohort; enrollment to the NSCLC cohort was closed before this target was attained. 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 10.1-1 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. At observed more than or equal to 9 responders, i.e., ORR ≥ 22.5%, the lower bound of the 95% CI excludes 10%. At observed more than or equal to 14 responders, i.e., ORR ≥ 35%, the lower bound of the 95% CI excludes 20%.

Table 10.1-1: 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%.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent
All Treated	All enrolled participants who received at least one dose of study drug. This will be both efficacy and safety population.
Safety	All treated participants who received at least one dose of study treatment. Participants will be included in the treatment group that they actually received
Pharmacokinetic Participants	All participants who receive at least one dose of study drug and have available serum concentration data
Immunogenicity Participants	All treated participants with baseline and at least one post-baseline immunogenicity assessment for nivolumab or daratumumab.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	NA
Secondary	ORR as defined as proportion of participants who achieved a best overall response (BOR) of CR or PR before taking any subsequent anti-cancer therapy, will be computed in each cohort along with the exact 95% CI using Clopper-Pearson method. BOR is defined as the best response designation recorded between the date of first dose and the date of the initial objectively documented tumor progression per investigator assessment using RECIST 1.1 criteria or the date of subsequent therapy, whichever occurs first Duration of response (or complete response) in each cohort will be estimated using KM product-limit method for participants who achieve PR or CR (or CR only). Median values along with two-sided 95% CI will be calculated. Investigator-assessed progression free survival (PFS) is defined as the time from first dosing date to the date of the first documented tumor progression, as determined by investigators (per RECIST 1.1), or death due to any cause. Participants who die without a reported progression will be considered to have progressed on the date of their death. Participants who did not progress or die will be censored on the date of their last tumor assessment. Participants who did not have any on study assessments and did not die will be censored on the randomization date. A participant who initiates a subsequent anti-cancer therapy will be censored on the date of last tumor assessment prior or on the start date of their subsequent anti-cancer therapy. The PFS curve, median and PFS rate at appropriate time points for each cohort will be estimated using the Kaplan-Meier product-limit method. Two sided, 95% confidence intervals for median PFS will be computed by Brookmeyer and Crowley method. A two-sided, 95% confidence interval for the PFS rates will be computed by Greenwood method for variance derivation and on log-log transformation applied on the survivor function S(t).
[redacted]	[redacted]

10.3.2 Safety Analyses

Safety analyses will be performed in all treated participants. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0. All on-study AEs, treatment-related, AEs, SAEs and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and MedDRA preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

10.3.3 Other Analyses

[redacted]

10.3.3.2 Immunogenicity Analysis

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]

10.3.4 Interim Analyses

An interim analysis of futility is planned. For TNBC or PAC cohort, if. 2 or less responders were observed among the first 20 participants after 4 months on treatment, the recruitment of the cohort will be assessed for potential stopping. If the true ORR is 10%, the probability of stopping the cohort is 68%. If the true ORR is 25%, the probability of stopping the cohort is 9%. At the time of interim analysis, disease control rate and duration of response, as well as progression free survival (PFS) will be also evaluated for each cohort. The stopping of the cohort for futility will be based on the totality of the evidence on efficacy.

Under the circumstance that data of some tumor types mature faster than others or a strong signal is observed in some tumor types, interim analyses may be 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 publication. These interim analyses will not impact the study duration or enrollment completion, and the trial will continue as planned.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ADA	antidrug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADP	adenosine diphosphate
AE	adverse event
ACLS	advanced cardiac life support
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
AIDS	acquired immunodeficiency syndrome
ALK	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
APC	anaphase-promoting complex.
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence

Term	Definition
%BE	percent biliary excretion
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BRCA	breast cancer 1, early onset
Bregs	regulatory B cells
BRt	Total amount recovered in bile
%BRt	Total percent of administered dose recovered in bile
BUN	blood urea nitrogen
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count
CDC	complement-dependent cytotoxicity
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	chloride
CLcr	creatinine clearance
CLD	dialysate clearance of drug from plasma/serum
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F (or CLT)	apparent total body clearance

Term	Definition
CLT/F/fu or CLT/fu	apparent clearance of free drug or clearance of free if (if IV)
Cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	minimum observed concentration
CMV	cytomegalovirus
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CR	complete response
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CT	computerized tomography
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
DCC	detected in colon cancer
D/C	discontinue
DEHP	di(2-ethylhexyl)phthalate
DILI	Drug Induced Liver Injury
dL	deciliter
DMC	Data monitoring committee
DOR	duration of response
DRt	total amount recovered in dialysate
%DRt	total percent of administered dose recovered in dialysate
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
EA	extent of absorption

Term	Definition
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
Eg	exempli gratia (for example)
EGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ER	estrogen receptor
ESR	Expedited Safety Report
F	bioavailability
Fb	fraction of bound drug
FDA	Food and Drug Administration
%FE	percent fecal excretion
FEV1	forced expiratory volume in 1 second
FFPE	formalin-fixed, paraffin-embedded
FI	fluctuation Index ([Cmax-Ctau)/Cavg])
Foxp3	forkhead box P3 transcription factor
FRt	total amount recovered in feces
%FRt	total percent of administered dose recovered in feces
FSH	follicle stimulating hormone
Fu	fraction of unbound drug
G	gram
GC	gas chromatography
GCP	Good Clinical Practice
G criteria	adjusted R^2 value of terminal elimination phase
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
H	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

Term	Definition
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HCO_3	bicarbonate
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR	heart rate
HRT	hormone replacement therapy
IASLC	International Association for the Study of Lung Cancer
IAT	
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
Ie	id est (that is)
IEC	Independent Ethics Committee
IFN-γ	interferon-γ
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
iNOS	inducible nitric oxide synthase
IP	Investigational product
IRB	Institutional Review Board
IRC	Independent Review Committee
IRRs	infusion related reactions
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K_3EDTA	potassium ethylenediaminetetraacetic acid
K^+	potassium
Kg	kilogram

Term	Definition
λσz	terminal disposition rate constant
L	liter
LAM	Lactation amenorrhea method
LC	liquid chromatography
LDH	lactate dehydrogenase
Ln	natural logarithm
Lz_Start	The time point starting the log-linear elimination phase defining the terminal half life
Lz_End	The time point ending the log-linear elimination phase defining the terminal half life
Lz_N	Number of time points in the log-linear elimination phase defining the terminal half life
MDSCs	myeloid-derived suppressor cells
Mg	milligram
Mg^{++}	magnesium
MI	myocardial infarction
MIC	minimum inhibitory concentration
Min	minute
mL	milliliter
MLR	mixed lymphocyte reaction
MM	multiple myeloma
mmHg	millimeters of mercury
MoA	multiple mechanisms of action
MR	medical research
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight
MR_AUC(TAU)	Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_Ctau	Ratio of metabolite Ctau to parent Ctau, corrected for molecular weight

Term	Definition
MRI	magnetic resonance imaging
MRT	mean residence time
MS	mass spectrometry
MST	medical safety team
MTD	maximum tolerated dose
μg	microgram
N	number of subjects or observations
Na^+	sodium
N/A	not applicable
Ng	nanogram
NIMP	non-investigational medicinal products
NK	natural killer
NKT	natural killer T
NO	nitric oxide
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PAC	pancreatic adenocarcinoma
PARP	poly ADP ribose polymerase
pAUCe	Extrapolated partial AUC from last quantifiable concentration to infinity
Pb	percent of bound drug
PBMC	peripheral blood mononuclear cell
PCP	Pneumocystis carinii pneumonia
pCR	complete pathological response
PD	pharmacodynamics; progressive disease
PD-L1	programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	promising clinical outcomes??? progression-free survival

Term	Definition
PID	patient identification number
PK	Pharmacokinetics
PO	per os (by mouth route of administration)
PPK	population PK
PR	progesterone receptor; partial response
PT	prothrombin time
PTT	partial thromboplastin time
Pu	percent of unbound drug
PVC	polyvinyl chloride
QC	quality control
QD, qd	quaque die, once daily
R^2	coefficient of determination
RBC	red blood cell
RCC	renal cell carcinoma
ROS	of reactive oxygen species
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation; stable disease
SOP	Standard Operating Procedures
sp.	Species
Subj	Subject
SUSAR	Suspected, Unexpected Serious Adverse Reaction
T	Temperature
T	Time
T3	tri-iodothyronine
T4	thyroxine
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T-cell receptor
T-HALF	Half life
T-HALFeff_AUC	Effective elimination half life that explains the degree of AUC accumulation observed

Term	Definition
T-HALFeff_Cmax	Effective elimination half life that explains the degree of Cmax accumulation observed)
TIA	transient ischemic attack
TID, tid	ter in die, three times a day
TIL	tumor-infiltrating lymphocytes
TKI	tyrosine kinase inhibitor
Tmax, TMAX	time of maximum observed concentration
TME	tumor microenvironment
TNBC	triple-negative breast cancer
TPC	treatment of physician's choice
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
Tregs	regulatory T cells
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UR	urinary recovery
%UR	percent urinary recovery
URt	total amount recovered in urine
%URt	total percent of administered dose recovered in urine
UV	Ultraviolet
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	Washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential
x g	times gravity

APPENDIX 2 STUDY GOVERANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

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

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

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

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

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

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

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

Subjects unable to give their written consent (e.g., stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

SOURCE DOCUMENTS

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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

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

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

RECORDS RETENTION

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

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

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

RETURN OF STUDY TREATMENT

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

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

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

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

CLINICAL STUDY REPORT AND PUBLICATIONS

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

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (e.g., among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: o a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) o elective surgery, planned prior to signing consent o admissions as per protocol for a planned medical/surgical procedure o routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) o medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases o admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) o admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study treatment is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 9.2.5 for reporting pregnancies).

EVALUATING AES AND SAES

Assessment of Causality
The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following: Related: There is a reasonable causal relationship between study drug administration and the AE. Not related: There is not a reasonable causal relationship between study drug administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms).
- The preferred method for SAE data reporting collection is through the eCRF.
- The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning.
    - In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. [c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal Sponge with spermicide
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus).
- Spermicide only
- Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting

APPENDIX 5 ECOG PERFORMANCE STATUS CRITERIA

0 Fully active; able to carry on all pre-disease performance without restriction

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work

2 Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours

3 Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours

4 Completely disabled; cannot carry on any selfcare; totally confined to bed or chair

5 Dead

[redacted]

APPENDIX 7 RECIST 1.1

Changes in tumor measurements and tumor responses will be assessed by the investigator using the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria.[1]

1. ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1 Measurable lesions

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- *Malignant lymph nodes*: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥15 mm in ***short*** axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the ***short*** axis will be measured and followed.

1.2 Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions.
- Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that in not measurable by reproducible imaging techniques.

1.3 Special considerations regarding lesion measurability

1.3.1 Bone lesions

- Bone scan, PET scan or plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

[redacted]

- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.3.2 Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

1.3.3 Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.4 Specifications by methods of measurements

1.4.1 Measurement of lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 30 days before the beginning of the treatment.

1.4.2 Method of assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

1.4.2.1 CT/MRI scan

CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT/MRI scan is based on the assumption that CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

1.4.2.2 Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

1.4.2.3 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

1.4.2.4 Ultrasound

Ultrasound is ***not*** useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

1.4.2.5 Endoscopy, laparoscopy

The utilization of these techniques for objective tumor evaluation is ***not*** advised.

1.4.2.6 Tumor markers

Tumor markers ***alone*** cannot be used to assess objective tumor response.

1.4.2.7 Cytology, histology

The results of cytology or histology may be utilized to inform individual timepoint response assessments.

2. BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

2.1 Target lesions

When more than one measurable lesion is present at baseline all lesions up to **a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions*** and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their **size** (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to ***reproducible repeated measurements*.**

A ***sum of the diameters*** (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the ***baseline sum diameters*.** If lymph nodes are to be included in the sum, then as noted below, only the ***short*** axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

2.1.1 Lymph nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes

that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

2.2 Non-target lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as **'present', 'absent', or in rare cases 'unequivocal progression'.** In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3. TUMOR RESPONSE EVALUATION

3.1 Evaluation of target lesions

Complete Response (CR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a **30% decrease in the sum of diameters of target lesions,** taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a **20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study*** (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an **absolute increase of at least 5 mm**. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

3.1.1 Special notes on the assessment of target lesions

3.1.1.1 Lymph nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a **short axis of ≥ 15 mm by CT scan**. Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

3.1.1.2 Target lesions that become 'too small to measure'

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

- if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

- if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

3.1.1.3 Target lesions that split or coalesce on treatment

- When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) above the normal limits.

Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

3.2.1 Special notes on assessment of non-target lesions

The concept of progression of non-target disease requires additional explanation as follows: Fluid Collections:

Effusions and Ascites: At each time point, radiologists will check for the presence or absence of effusions/ascites. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression.

3.2.1.1 When the subject also has measurable disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

3.2.1.2 When the subject has only non-measurable disease

- To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'.
- If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

3.2.1.3 Tumor markers

Tumor markers *alone* cannot be used to assess objective tumor responses.

3.3 New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. *If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.*

3.3.1 FDG-PET evaluation

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of the qualitative assessment of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression

occurring at that site (if so, the date of PD will be the date of the initial positive FDG-PET scan).

– If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

4. RESPONSE CRITERIA

4.1 Time point response

A response assessment should occur at each time point specified in the protocol.

For subjects who have **measurable disease** at baseline Table 1 provides a summary of the overall response status calculation at each time point.

Table 1: subjects with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE =not evaluable.

4.1.1 Missing assessments and not evaluable designation

When no imaging/measurement is done at all at a particular time point, the subject is **not evaluable (NE)** at that time point. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time point response.

- Confirmation of PR and CR is required after at least 4 weeks to ensure responses identified are not the result of measurement error.

4.1.2 Confirmation Scans

- **Verification of Response:** Confirmation of PR and/or CR is required after at least 4 weeks to ensure responses identified are not the result of measurement error.
- **Verification of Progression:** When not clinically burdensome to the subject, confirmation of PD is required after at least 4 weeks to ensure responses identified are not the result of measurement error.

4.2 Best overall response: All timepoints

The *best overall response* is determined once all the data for the subject is known. It is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Best response is defined as the best response across all time points with subsequent confirmation. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as specified in Table 2. When SD is believed to be best response, it must meet the protocol specified minimum time from baseline. Measurements must have met the SD criteria at least once after study entry at a minimum interval that is defined in the study protocol.

Table 2: Best overall response when confirmation of CR and PR IS required.

Overall response	Overall response	BEST overall response
First time point	**Subsequent time point**	
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD[b] duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD[b] duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD[b] duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD

Table 2: Best overall response when confirmation of CR and PR IS required.

Overall response	Overall response	BEST overall response
First time point	**Subsequent time point**	
PR	PD	SD provided minimum criteria for SD[b] duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD[b] duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[b] Minimum criteria for SD duration is 5 weeks (35 days).

4.3 Duration of response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.1 Duration of overall response

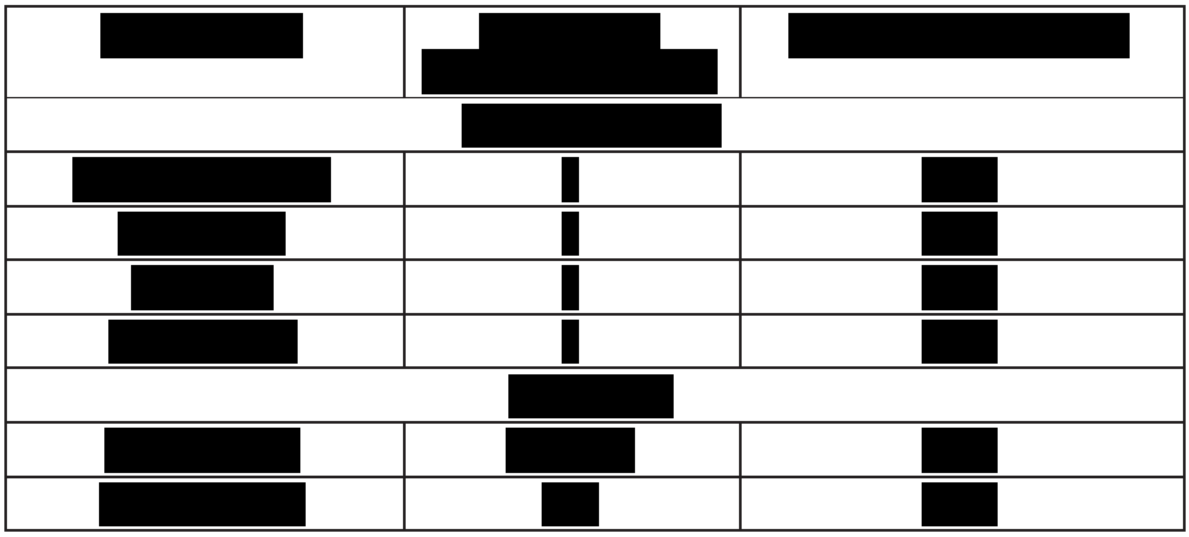
The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.3.2 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

[redacted]



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