Official Title of Study:

A Phase 2, Open-label, Randomized Controlled Trial of BMS-986218 or BMS-986218 Plus Nivolumab in Combination with Docetaxel in Participants with Metastatic Castration-resistant Prostate Cancer

NCT Number: NCT05169684

Document Date (Date in which document was last revised): 18 February 2022

CLINICAL PROTOCOL CA022009

A Phase 2, Open-label, Randomized Controlled Trial of BMS-986218 or BMS-986218 Plus Nivolumab in Combination with Docetaxel in Participants with Metastatic Castration-resistant Prostate Cancer

Brief Title:

A Phase 2 Trial of BMS-986218 or BMS-986218/Nivolumab in Combination with Docetaxel in mCRPC

Protocol Amendment Number: 02

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IND: 157650
EudraCT/EU Trial Number: 2021-003990-74
UTN: U1111-1268-2566

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 02	18-Feb-2022	The overall purpose for Protocol Amendment 02 is to provide updated language introducing an additional "next-generation" anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) agent which may be incorporated into the study design via future amendment. An update was also made to the Bayesian Optimal Interval (BOIN) table.
Protocol Amendment 01	24-Nov-2021	The overall purpose of Protocol Amendment 01 was to provide updates to increase participant safety: • Clarified dose-limiting toxicity criteria and exceptions • Updated hepatic adverse event criteria for delay, resume, and discontinue of study treatments • Updated inclusion/exclusion criteria related to prior radium 223 treatment and superscans • Clarified that progression-free survival (PFS) endpoint refers to radiographic PFS
Original Protocol	02-Sep-2021	Not applicable

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 02:

The overall purpose for Protocol Amendment 02 is to introduce information regarding BMS-986288, an additional "next-generation" anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) monoclonal antibody (mAb). BMS-986288 may be incorporated into the study design via future protocol amendment to test further the central study hypothesis that addition of next-generation anti-CTLA-4 agents, with or without nivolumab, will improve outcomes compared to docetaxel alone. BMS-986288 is another non-fucosylated next-generation anti-CTLA-4 that shares the Fcγ receptor (FcγR)-dependent mechanisms of BMS-986218. BMS-986288 is identical to BMS-986218 except for an additional "Probody" design element that could decrease toxicity by preventing binding to sites outside of the tumor, and thus further improve the benefit/risk profile as compared to BMS-986218.

An update was also made to the Bayesian Optimal Interval (BOIN) table that eliminated criteria for 1 or 2 participants, as enrollment will be in groups of 3 to 4 participants at a time in Part 1a and Part 1b.

The Protocol Summary has been revised as applicable to align with the protocol changes.

This protocol amendment applies to all participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: On Study Treatment Procedural Outline, Body Imaging/Bone Scan Table 2-3: Long-term Follow-up Procedural Outline, Body Imaging/Bone Scan	Tumor assessments should occur every 9 weeks (± 7 days) from first dose, regardless of treatment schedule or dose delays for first 27 weeks (instead of 24 weeks).	Since images are completed every 9 weeks initially, the scans should be done at 9, 18, and 27 weeks, and thereafter every 12 weeks.
Table 2-2: On Study Treatment Procedural Outline, ECG	References to the Data Management Electrocardiogram (ECG) Study Guidelines were deleted.	This guideline does not exist for this study.
Section 3: Introduction Section 3.1: Study Rationale Section 3.2.2: BMS-986218 and BMS-986288 Mechanism of Action Section 3.2.5: BMS-986218 and BMS-986288 Clinical Activity Section 3.3.3: Overall Benefit/Risk Conclusion Section 5.4.2.1: Rationale for Docetaxel and BMS-986288 or BMS-986288 plus Nivolumab	Language was added introducing next-generation anti-CTLA-4 agents.	Based on emerging data from the ongoing CA043-001 study, BMS-986288 may be incorporated into the CA022-009 study design if BMS-986288 has a better benefit/risk profile than BMS-986218.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 5.1.2-1: Safety Lead-in Evaluation Guidance Based on BOIN Design	Columns for 1 or 2 participants were deleted from the BOIN table. The de-escalation criteria were modified.	Three to 4 participants will enroll at a time into Part 1a and Part 1b (see protocol Section 5.1.2). Therefore, criteria for n = 1 and n = 2 will not be needed in the study. Modifying the de-escalation criteria allows for all possibilities in the table.
Section 6.2: Exclusion Criteria, 1), o)	Added list of topical steroid types.	To clarify which types of topical steroids are allowed.
Section 10.2: Sample Size Determination, Sample Size Justification for Randomized, Controlled Portion (Part 2)	The percentages were corrected to 5% in control arm, 9% in the BMS-986218 + docetaxel arm, and 7% in the BMS-986218 + nivolumab + docetaxel arm.	Corrects typos.

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1 PROTOCOL SUMMARY

Protocol Title:

A Phase 2, Open-label, Randomized Controlled Trial of BMS-986218 or BMS-986218 Plus Nivolumab in Combination with Docetaxel in Participants with Metastatic Castration-resistant Prostate Cancer

Brief Title: A Phase 2 Trial of BMS-986218 or BMS-986218/Nivolumab in Combination with Docetaxel in mCRPC

Rationale:

In 2004, 2 Phase 3 studies (TAX 327 and SWOG 99-16) demonstrated that docetaxel-based chemotherapy regimens improved survival in participants with metastatic castration-resistant prostate cancer (mCRPC) that progressed after castration therapy. More recently, most patients have also received treatment with at least 1 novel antiandrogen therapy (NAT) prior to use of docetaxel for mCRPC. The target population for this study is participants with mCRPC that progressed after an NAT and have not received chemotherapy for mCRPC. Treatment with chemotherapy in this population has a modest benefit with regard to overall survival and does not produce long-term disease control. Several lines of evidence support the hypothesis that addition of "next-generation" anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) agents, with or without nivolumab, will improve outcomes compared to docetaxel alone.

Objectives and Endpoints:

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety, tolerability, and DLTs of docetaxel in combination with BMS-986218 or in combination with BMS-986218 plus nivolumab in participants with mCRPC (**Part 1**)	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, TRAEs, AEs leading to discontinuation, and deaths
• To compare the rPFS in mCRPC participants treated with docetaxel and either docetaxel in combination with BMS-986218 or docetaxel in combination with BMS-986218 and nivolumab (**Part 2**)	• rPFS for randomized participants is the time between randomization date and the first date of documented radiographic progression, or death due to any cause, whichever occurs first. The radiographic progression will be assessed by blinded independent central review (BICR) per PCWG3
Secondary	
• To assess the antitumor activity of the combination of docetaxel with BMS-986218 or BMS-986218 and nivolumab in mCRPC participants, based on ORR, TTR, and DOR (**Part 2**)	• Objective response rate per PCWG3 (ORR-PCWG3) is the proportion of participants who have a confirmed complete or partial best overall response (BOR) per PCWG3 among randomized participants who have measurable disease at baseline. The BOR is defined as the best response designation, as determined by the BICR, recorded between the date of randomization and the date of objectively documented radiographic progression, or last tumor measurement, whichever occurs first • Time to response per PCWG3 (TTR-PCWG3) is the time from randomization date to the date of the first documented CR or PR per PCWG3, as determined by BICR • Duration of response per PCWG3 (DOR-PCWG3) is the time between the date of first response (CR/PR per PCWG3) to the date of first documented radiographic progression per PCWG3 (as determined by BICR), or death due to any cause
• To assess PSA response rate (PSA-RR) and time to PSA progression (TTP-PSA; limited to participants with measurable PSA [defined as ≥ 2 ng/ml] at baseline) (**Part 2**)	• PSA-RR is the proportion of randomized participants with a 50% or greater decrease in PSA from baseline to any post-baseline PSA result. A second consecutive value obtained 3 or more weeks later is required to confirm the PSA response • TTP-PSA is the time between randomization date to the date of PSA progression per PCWG3 in randomized participants
• To assess overall survival (OS) (**Part 2**)	• OS for all randomized participants is the time between randomization date and the date of death from any cause

Table 1: Objectives and Endpoints

Objectives	Endpoints
• To characterize safety of BMS-986218 in combination with docetaxel, and with nivolumab and docetaxel in Part 2	• Overall safety and tolerability will be measured by the incidence of AEs, TRAEs, SAEs, AEs leading to discontinuation, and deaths

Abbreviations: AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CR, complete response; DLT, dose-limiting toxicity; DOR, duration of response; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; PR, partial response; PSA, prostate-specific antigen; PSA-RR, PSA response rate; rPFS, radiographic progression-free survival; SAE, serious adverse event; TRAE, treatment-related adverse event; TRR, time to response; TTP-PSA, time to PSA progression.

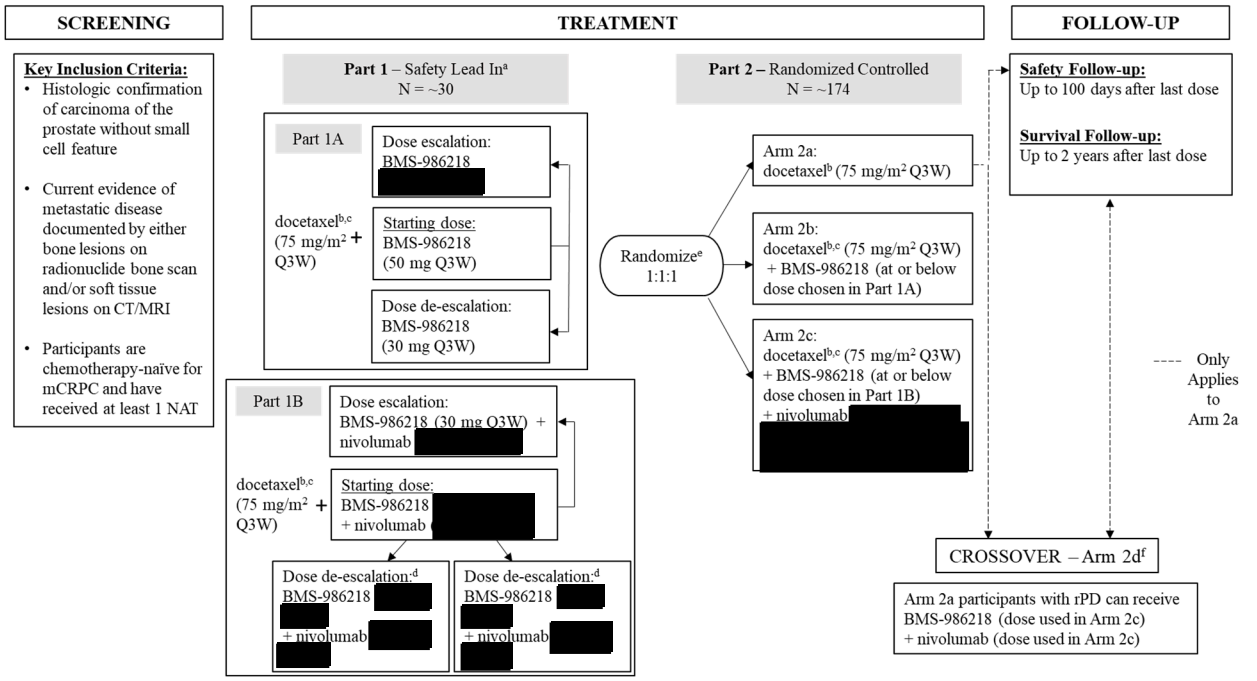
Overall Design:

This multi-center, randomized, controlled, open-label, Phase 2 study evaluates docetaxel alone, in combination with BMS-986218, or in combination with BMS-986218 plus nivolumab in men who have mCRPC that progressed after NAT and have not received chemotherapy for mCRPC.

The study will be carried out in 2 parts: Part 1, a safety lead-in portion, and Part 2, a randomized, controlled portion. All participants will complete up to 3 study periods: screening (up to 28 days), treatment (up to 2 calendar years from first dose of study treatment regardless of treatment delays [21 days/cycle]), and follow-up. The Follow-up Period includes Safety Follow-up (comprising 3 visits over about 100 days) and Survival Follow-up (up to 2 years from the last dose of study treatment) periods. The maximum duration of study participation will be approximately 4 years (up to 28 days of screening, treatment of up to 2 years, and follow-up of up to 2 years). Images will be submitted to a central imaging vendor and will undergo Blinded Independent Central Review (BICR). Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA022009 Imaging Manual provided by the central imaging vendor.

The study design schematic is presented in Figure 1 below.

Figure 1: Study Design Schema



Abbreviations: CT, computed tomography; DLT, dose-limiting toxicity; I-O, immuno-oncology; mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging; N, number of participants; NAT, novel antiandrogen therapy; Q3W, every 3 weeks; rPD, radiographic progressive disease; Y/N, yes/no.

[a] The DLT evaluation period will be 42 days (6 weeks) starting on Cycle 1 Day 1 for Part 1A and Part 1B.

[b] Administer docetaxel for a maximum of 10 cycles.

[c] For participants who are also receiving BMS-986218 or BMS-986218 and nivolumab, treatment with these I-O agents may continue beyond 10 cycles, up to 2 years (until disease progression, unacceptable toxicity, or withdrawal of consent).

[d] In Part 1B, BMS-986218 or nivolumab may be dose reduced based on safety data.

[e] In Part 2, randomization to 1 of 3 treatment arms will be stratified by measurable disease (Y/N).

[f] See Crossover (Arm 2d) text below for details regarding optional crossover treatment for participants randomized to Part 2 Arm 2a, including maximum duration of treatments.

Physical examinations, vital sign measurements, 12-lead electrocardiograms, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for adverse events (AEs) throughout the study. Blood will be collected according to the protocol for pharmacokinetic (PK) analysis.

Screening Period

The screening period will be up to 28 days. Informed consent will be obtained prior to any study-specific procedures. All participants (Part 1 and Part 2) being screened will be evaluated based on inclusion and exclusion criteria and will be enrolled using an Interactive Response Technology (IRT) system.

Participants for Part 2 will be randomized to 1 of 3 treatment arms and will be stratified according to measurable disease status which will be assessed by investigator based on the tumor assessment performed during screening (Prostate Cancer Working Group 3 [PCWG3]).

Tumor tissue must be obtained and submitted to central laboratory prior to treatment assignment (Part 1) or randomization (Part 2) for participants with any soft tissue lesion that is suspected to represent metastatic disease based on local review of imaging and is considered accessible for biopsy by an interventional radiologist (or other appropriate specialist). Lymph nodes must measure at least 1 cm in diameter along the short axis in order to be considered for biopsy.

For participants who meet the above criteria, a pre-treatment, on-treatment, and on-progression biopsy are required if medically feasible (tumor sites that can be biopsied with acceptable clinical risk). Baseline tumor tissue is not mandatory for participants with bone metastasis only.

Participants who have met all eligibility criteria will be enrolled to receive treatment in Part 1 or Part 2 as applicable.

Treatment Period

The treatment period for BMS-986218 and/or nivolumab will last for up to 2 calendar years from first dose of study treatment and up to a maximum of 10 doses for docetaxel regardless of treatment delays (21 days/cycle). In addition to dosing visits on Day 1 of each cycle, there are also non-dosing visits on Days 8 and 15 in Cycles 1 and 4 and Day 15 in Cycle 2 f[redacted] biomarkers assessments.

Part 1A will evaluate the safety and tolerability of BMS-986218 in combination with docetaxel. The dose-limiting toxicity (DLT) evaluation period will be 42 days (6 weeks) starting on Cycle 1 Day 1 for Part 1A and Part 1B. The DLT evaluation during this safety lead in, including potential decision to escalate or to de-escalate the BMS-986218 dose level, will be guided by the Bayesian Optimal Interval (BOIN) design framework with a target DLT rate of 30%. In Part 1B, there is also a potential to de-escalate the nivolumab dose level [redacted]. The target DLT in Part 1A was selected based on an observed DLT rate of 2/6 = 33% for BMS-986218 monotherapy [redacted] in CA022001, estimated by the basic linear ranking model (BLRM) design and the maximum tolerated dose not reached with 2 dose levels higher being evaluated. For Part 1B, the observed DLT rate was 1/9 = 11% following treatment with nivolumab [redacted] + BMS-986218 [redacted] in the same study (CA022001). In addition, in Study CA2099KD in participants treated with docetaxel with nivolumab, there was a 14.3% reported frequency of treatment discontinuations due to Grade 3-4 treatment-related adverse events (TRAEs), with the most frequent TRAEs (any grade) leading to discontinuation being pneumonitis (7.1%), fatigue (6.0%), peripheral neuropathy (6.0%), and pneumonia (3.6%).

The Part 1A decisions for escalation, de-escalation, or continuing evaluating at the same dose level, will be guided by the BOIN escalation design (Table 2). Approximately 12 DLT-evaluable participants are expected to be treated, depending on the number of dose levels and the number of observed DLTs. Dose escalation/de-escalation decisions or decision to continue enrollment at the current dose will be made by the Sponsor in collaboration with investigators and take into consideration all available safety and, if available, PK and pharmacodynamic data. Participants

will enroll in cohorts of 3 to 4 initially. After the first 3 to 6 participants are evaluated, additional cohorts of 3 to 6 participants may be enrolled, as needed, with no more than 12 participants at a specific dose level. Once at least 6 participants have cleared the DLT observation period at a tolerable dose level in Part 1A, participants will be enrolled in Part 1B to assess safety and tolerability of the combination of BMS-986218 + docetaxel + nivolumab, starting at a lower BMS-986218 dose level than in Part 1A. Additional participants may be enrolled in Part 1A at this dose or a higher dose in order to continue to assess safety in this combination.

Table 2: Safety Lead-in Evaluation Guidance Based on BOIN Design

Actions Based on Number of DLTs Observed	Number of DLT-evaluable Participants Treated at Current Dose									
	3	**4**	**5**	**6**[a]	**7**	**8**	**9**	**10**	**11**	**12**
Escalate Dose[b] if # of DLTs ≤	0	0	1	1	1	1	2	2	2	2
Stay[c] if # of DLTs =	1	1	NA	2	2	2	3	3	3	3,4
De-escalate[d] if # of DLTs ≥	2	2	2	3	3	3	4	4	4	5
De-escalate and Eliminate[e] from Evaluation if # of DLTs ≥	3	3	4	4	5	5	5	6	6	7

Abbreviations: BOIN, Bayesian Optimal Interval; DLT, dose-limiting toxicity; NA, not applicable (for decision).

[a] A minimum of 6 DLT-evaluable participants will be required to meet acceptable DLT criteria for a dose level to be selected for Part 2.

[b] "Escalate" indicates that a higher dose level may be evaluated.

[c] "Stay" indicates that more participants need to be treated to determine tolerability.

[d] "De-escalate" indicates that a lower dose level needs to be evaluated.

[e] Such dose level is excessively non-tolerable and re-escalation is not allowed after de-escalation. A lower dose level will be evaluated.

Treatment in Part 1B may be initiated in a staggered manner relative to the BMS-986218 + docetaxel escalation (Part 1A). Specifically, Part 1B can be initiated upon the evaluation of a sufficient number of participants at a dose level in Part 1A who have cleared the DLT requirements (eg, 6 evaluable participants with 0 or 1 DLT), after which dose evaluation in Part 1A and Part 1B may proceed in parallel. At no point will the dose of BMS-986218 administered in combination with nivolumab and docetaxel in Part 1B exceed the highest dose determined to be tolerated in Part 1A.

Part 1B will also use a BOIN design framework for the evaluation of BMS-986218 tolerability in combination with docetaxel and nivolumab. Approximately 12 to 18 DLT-evaluable participants are expected to be treated if 2 or more dose-level combinations are evaluated in this part. Initially, 3 to 4 participants will be treated at the starting dose and subsequent decisions will be based on

the BOIN design framework as shown in Table 2 above, similar to Part 1A. If needed, based on the number of DLTs, additional participants in groups of 3 to 6 participants may be enrolled at the same dose level, or otherwise a lower dose level may be evaluated.

If de-escalation is necessary based on the number of toxicities, a lower combination dose level will be evaluated. The specific dose level to be administered in combination will be determined based on the nature of the DLTs and will be either: 1) a lower dose of BMS-986218 in combination with the same dose levels of nivolumab and docetaxel or 2) a lower dose level of nivolumab [redacted] in combination with the same dose levels of BMS-986218 and docetaxel.

Once a tolerable dose has been determined for BMS-986218 in combination with docetaxel in Part 1A and for BMS-986218 in combination with docetaxel + nivolumab in Part 1B in at least 6 evaluable participants, the randomized Part 2 of the study will open for enrollment. In Part 2, randomization 1:1:1 to 1 of 3 treatment arms will be stratified according to the following baseline factor:

- Measurable disease (Y/N): Measurable disease status will be assessed by investigator based on the tumor assessment performed during screening (Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1])

Crossover (Arm 2d): Participants treated in Arm 2a who demonstrate radiographic progressive disease (rPD) while on treatment (during active treatment with docetaxel) or after treatment (while in Safety or Survival Follow-up), may be eligible to crossover to optional Arm 2d and receive treatment of BMS-986218 in combination with nivolumab [redacted] at the dose level chosen in Arm 2c). Further docetaxel treatment will not be administered on Arm 2d.

In order to qualify for crossover, radiographic progression per PCWG3 must be confirmed by BICR and the participant must meet all inclusion criteria and exclusion criteria specified in the protocol (with the exception that prior treatment with docetaxel is allowed.) The BMS medical monitor must approve crossover to Arm 2d.

In Arm 2d, BMS-986218 in combination with nivolumab (dose chosen in Arm 2c [redacted]) is administered until disease progression, unacceptable toxicity, or withdrawal of consent, and may continue for a maximum of 2 calendar years from Cycle 1 Day 1 (Arm 2a) regardless of treatment delays (for participants who crossover during active treatment with docetaxel), or until the study ends, whichever occurs first. For participants who crossover after treatment (while in Safety or Survival Follow-up), BMS-986218 in combination with nivolumab may continue for up to 1 calendar year from the start of crossover treatment, or for a maximum of 2 calendar years from Cycle 1 Day 1 (Arm 2a) regardless of treatment delays (whichever is longer), or until the study ends, whichever occurs first.

Follow-up Period

The Follow-up Period includes Safety Follow-up (comprising 3 visits over about 100 days) and Survival Follow-up (up to 2 years from the last dose of study treatment) periods.

Safety Follow-up: Upon completion of study intervention or early termination, all participants will enter a safety follow-up period. All participants will be evaluated for any new AEs for at least 100 days after the last dose of study intervention. Participants who have discontinued treatment without having BICR-assessed disease progression will continue to have radiologic and clinical tumor assessments after treatment discontinuation for up to 2 years after end of treatment or until rPD, whichever occurs first.

Survival Follow-up: In parallel with the safety follow-up period, participants will enter the survival follow-up period. Participants will be followed by phone contact or clinic visit every 12 weeks (± 2 weeks) from the last dose of study intervention for a period of 2 years or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first.

Number of Participants:

Approximately 12 participants may be treated in the safety lead-in Part 1A and approximately 12 to 18 participants in Part 1B, with a possible total of 30 DLT-evaluable participants, if 2 or more dose levels are evaluated.

In addition, approximately 174 participants are expected to be randomized across 3 treatment arms in Part 2 of the study, to account for 21% dropout rate prior to radiographic progression across the 3 arms.

Study Population:

Main Inclusion Criteria

- Male participants, must be ≥ 18 years of age or local age of majority at the time of signing the informed consent.
- Histologic confirmation of carcinoma of the prostate without small cell features. Diagnosis must be stated in a pathology report and confirmed by the investigator.
- Current evidence of metastatic disease documented by either bone lesions on radionuclide bone scan and/or soft tissue lesions on computed tomography (CT)/magnetic resonance imaging (MRI). Metastases may be in regional lymph nodes (N1 per American Joint Committee on Cancer [AJCC] staging criteria, 8th edition) and/or distant metastases (M1 per AJCC staging criteria, 8th edition).
  - Participants whose disease spread is limited to regional pelvic lymph nodes (N1) measuring at least 2 cm in short axis will be considered eligible.
- Documented prostate cancer progression by 1 of the following Prostate Cancer Working Group 3 (PCWG3) criteria while castrate, within 6 months prior to screening, and without initiating a new intervening systemic prostate cancer therapy (other than gonadotropin-releasing hormone [GnRH] agonist/antagonist) prior to screening:
  - Prostate-specific antigen (PSA) progression defined by a minimum of 2 rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value at the screening visit should be ≥ 2 µg/L (2 ng/mL).
  - Radiographic disease progression in soft tissue based on PCWG3 criteria.
  - Radiographic disease progression in bone.

- Participants are chemotherapy-naïve for mCRPC and have received at least 1 second generation hormonal manipulations (also known as novel antiandrogen therapies [NATs], including but not limited to abiraterone acetate, enzalutamide, apalutamide, and darolutamide) in the recurrent non-metastatic setting and/or the metastatic setting. Participants must have progressed during treatment on an NAT or have documented intolerance to the drug (ie, unacceptable toxicity despite comprehensive supportive therapy). Prior docetaxel for metastatic castration-sensitive prostate cancer is allowed if ≥ 12 months have elapsed from last dose of docetaxel. Prior therapy with a poly ADP ribose polymerase (PARP) inhibitor (eg, olaparib, rucaparib) is also allowed. Prior radium 223 and ^{177}Lu-prostate-specific membrane antigen(PSMA)-617 treatment for prostate cancer is allowed.
- Participants with a soft tissue lesion that is suspected to represent metastatic disease based on local review of imaging and is considered accessible for biopsy by an interventional radiologist (or other appropriate specialist), must provide tumor sample from a newly-obtained ("fresh") biopsy (obtained during screening, if there are tumor sites that can be biopsied with acceptable clinical risk). Lymph nodes must measure at least 1 cm in diameter along the short axis in order to be considered for biopsy. If the only site amenable to biopsy is also the only site of measurable disease, the investigator should prioritize maintaining a measurable target lesion (by RECIST v1.1) if there is a concern that the biopsy might impact tumor assessment.

  A formalin-fixed paraffin-embedded tissue block (preferred) or a minimum of 20 unstained slides* of tumor tissue from core biopsy, punch biopsy, excisional biopsy or surgical specimen obtained during screening or prior to treatment assignment (Part 1)/randomization (Part 2) must be sent to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable.

  *If despite best efforts, a minimum of 20 slides is not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with Sponsor or designee.

Main Exclusion Criteria

- Prior treatment for biochemically recurrent or metastatic prostate cancer with an anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4), anti-programmed death-(ligand-)1 (anti-PD-[L]1), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. The prior use of such agents in the neoadjuvant setting is allowed.
- Prior radiation therapy within 2 weeks prior to start of study treatment. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.

Intervention Groups and Duration:

Participants who are assigned/randomized to a study intervention with nivolumab will receive nivolumab at a dose of [redacted] over an approximately 30-minute infusion each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment, or the study ends, whichever occurs first. If needed, flush the intravenous line with an appropriate amount of diluent (eg, 0.9% sodium chloride) to ensure that the complete

dose is administered over approximately 30 minutes. Begin study treatment within 3 calendar days of treatment assignment (Part 1) or randomization (Part 2).

When study interventions BMS-986218 and docetaxel are to be administered on the same day, BMS-986218 should be administered first. Flush the intravenous line with an appropriate amount of diluent (eg, 0.9% sodium chloride) to ensure that the complete dose is administered over approximately 30 minutes. After the BMS-986218 infusion, there is a 30-minute delay before the start of the docetaxel infusion to monitor the participant for signs of possible infusion reactions and differentiate any such reaction from one related to the subsequent docetaxel infusion. Dosing of docetaxel will continue for a maximum of 10 cycles Q3W (± 3 days), until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. A minimum of 3 to 4 cycles of docetaxel is recommended. Prednisone 5 mg twice daily will be administered with docetaxel in accordance with package insert/Summary of Product Characteristics (SmPC) guidelines. However, daily prednisone may be dose reduced or omitted at the discretion of the investigator if it negatively affects glycemic control or other comorbid conditions. Premedication with dexamethasone will also be given for docetaxel (see below).

Dosing calculations of docetaxel should be based on the body weight assessed at baseline using Mosteller body surface area formula: the square root of (weight [kg] × height [cm]/3600). It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

When study interventions nivolumab, BMS-986218 and docetaxel (or nivolumab and BMS-986218 for crossover participants in Arm 2d), are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the BMS-986218 infusion. The second infusion will always be BMS-986218 and will start after the infusion line has been flushed, filters changed, and participant has been observed to ensure no infusion reaction has occurred. Then, follow the instructions above to administer docetaxel (docetaxel will not be administered for participants who crossover into Arm 2d).

There will be no intra-subject dose escalations or reductions of nivolumab or BMS-986218 allowed. For Q3W dosing cycles, participants may be dosed no less than 19 days from the previous dose.

Premedication

Premedications for BMS-986218 and nivolumab are not recommended. For docetaxel, given the concurrent use of prednisone (5 mg twice daily), the recommended premedication regimen is oral dexamethasone 8 mg (or equivalent dose of another corticosteroid) to be administered at 12, 3, and 1 hour(s) before the docetaxel infusion; however, other corticosteroids and/or schedules and routes of administration are also acceptable according to local standards. Antiemetic premedication will be administered according to local standards.

Study Intervention:

Study Intervention for CA022009		
Medication	**Potency**	**IMP/Non-IMP/AxMP**
Docetaxel	Various Strengths	Non-IMP
BMS-986218	200 mg/vial	IMP
Nivolumab	100 mg/vial	IMP

Abbreviations: AxMP, auxiliary medicinal product; IMP, investigational medicinal product; Non-IMP, non-investigational medicinal product.

Statistical Methods

Sample Size Justification for Safety Lead-in Portion (Part 1)

Escalation/de-escalation decisions will be guided by the BOIN design. Though the exact number treated at a dose level will depend on the number of participants with a DLT, approximately 12 DLT-evaluable participants may be treated in Part 1A to assess the tolerability of BMS-986218 in combination with docetaxel (see Figure 1 for study design schema). Similarly, in Part 1B, approximately 12 to 18 participants may be treated with BMS-986218 in combination with docetaxel and nivolumab. With a maximum of 12 DLT-evaluable participants at a dose level, there will be above 80% probability to observe at least 1 occurrence of a safety event if the event rate in the population is 13%. Similarly, with 6 or 9 DLT-evaluable participants at a dose level, there will be above 80% probability to observe at least 1 occurrence of the safety event if the event rate in the population is 24% or 17%, respectively. A minimum of 6 DLT-evaluable participants and no more than 12 DLT-evaluable participants will be evaluated at a dose level in Part 1A or Part 1B to ensure tolerability prior to initiating enrollment in Part 2 at these dose levels. Therefore, a total of approximately 30 DLT-evaluable participants may be evaluated during the safety lead in, including at least 6 participants (with 0 or 1 DLT) at each of the BMS-986218 + docetaxel and BMS-986218 + nivolumab + docetaxel combination doses that will be evaluated in Part 2.

Sample Size Justification for Randomized, Controlled Portion (Part 2)

The sample size of the study is calculated to have sufficient power for the primary efficacy endpoint of radiographic progression-free survival (rPFS) to compare Arm 2c to Arm 2a and Arm 2b to Arm 2a. Assuming that Arm 2a median rPFS is 6 months and a constant hazard ratio (HR) of 0.55 for the Arm 2c to Arm 2a comparison (for target median rPFS = 10.9 months), a total of 78 rPFS events will need to be observed across these 2 arms, in order to have 91.3% power to show a difference at the 20% 2-sided alpha level, in this population, based on 58 participants per arm. Based on hierarchical testing of Arm 2b vs Arm 2a, assuming there was statistical significance in the Arm 2c vs Arm 2a comparison, and a constant HR of 0.62 for the Arm 2b to Arm 2a comparison, a total of 79 rPFS events will need to be observed across these 2 arms, with 58 participants per arm in order to have 80% power to show a difference at the 20% 2-sided alpha

level. These calculations assume 18 months for accrual and a minimum of 10 months follow up. A total of 174 participants will need to be randomized assuming about 21% dropout rate across arms (5% in control arm, 9% in the BMS-986218 + docetaxel arm, and 7% in the BMS-986218 + nivolumab + docetaxel arm).

The actual time of the final analysis will be based on the number of events observed, which will be monitored separately among Arm 2c and Arm 2a and among Arm 2b and Arm 2a during the study conduct.

Primary Endpoints

The primary endpoint for Part 1 is to assess safety based on incidence of AEs, serious adverse events (SAEs), AEs meeting protocol-defined DLT criteria, TRAEs, AEs leading to discontinuation, and deaths. In addition, the selected tolerable dose levels of BMS-986218 in combination with docetaxel (Part 1A) and BMS-986218 in combination with docetaxel and nivolumab (Part 1B) will be determined using the DLT rate within the 6-week DLT window among DLT-evaluable participants in Part 1A and in Part 1B. The incidence of DLTs will be calculated for DLT-evaluable participants and compared to the actions recommended by the BOIN design to guide the dose escalation/stay/de-escalation decision for the BMS-986218 + docetaxel treatment and for the BMS-986218 + nivolumab + docetaxel treatment.

The primary endpoint for Part 2 is rPFS of BMS-986218 + docetaxel and BMS-986218 + nivolumab + docetaxel combination therapies compared to rPFS of docetaxel monotherapy control, in the randomized population. rPFS is defined as the time from randomization to the date of first documented radiographic progression per BICR using PCWG3 or death due to any cause, whichever occurs first. Participants who do not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any evaluable on-study tumor assessments and did not die will be censored at randomization date.

Interim Analysis

There is no plan for an official interim analysis of efficacy in Part 2 with any adjustment of the type 1 error rate.

Safety Monitoring in Part 1:

BMS has developed a multi-layered process to ensure safety monitoring through close collaboration of study site investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led Safety Management Team. This collaborative process plus a Data Monitoring Committee (DMC) for Part 2, constitutes the safety monitoring plan for the study.

To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and analyses. Because this is an open-label study, WWPS representatives, the BMS medical monitor, and the investigators will have access to individual participants safety data necessary for safety evaluation.

Data Monitoring Committee: Yes

A DMC will be used for Part 2 of this study to provide oversight of the safety. In addition, during the randomized Part 2 of the study, a continuous safety monitoring framework will be implemented by the Sponsor to monitor for DLT adverse events.

The DMC charter will describe the procedures related to DMC operations in greater detail.

Other Committee: Yes

A Blinded Independent Central Review (BICR) will also be used for this study to review CT and bone scans, including the primary study objective.

Brief Summary:

CA022009 is a Phase 2, open-label, controlled, randomized, global study assessing the efficacy and safety of combining BMS-986218, or BMS-986218 plus nivolumab, with standard of care docetaxel in men who have metastatic castration-resistant prostate cancer (mCRPC) that progressed after a second-generation hormonal manipulation, also known as novel antiandrogen therapy (NAT), and have not received chemotherapy for mCRPC. The study will have a safety lead-in portion (Part 1) and a randomized controlled portion (Part 2). Part 2 of the study aims to demonstrate that addition of BMS-986218, or BMS-986218 plus nivolumab, to docetaxel improves clinical efficacy as assessed by radiographic progression-free survival (rPFS). Study details include:

Study Duration: The maximum duration for a participant on study is 4 years (up to 2 years on treatment and up to 2 years on follow-up).

Study Intervention: Each dosing cycle will last 21 days. Study intervention is administered on Day 1 of each cycle until disease progression or a maximum of 2 years.

Study Visit Frequency: In each dosing cycle of 21 days, the participant will attend a dosing visit every 3 weeks (Q3W). In Cycle 1 and Cycle 4, participants will attend a non-dosing visit on Days 8 and 15, and in Cycle 2, participants will attend a non-dosing visit on Day 15. Tumor assessments during the treatment period will be every 9 weeks (from first dose) for the first 27 weeks and then every 12 weeks thereafter.

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (CA022009)

Procedure	Screening Visit (Days -28 to -1)	Notes: [a] All windows are based on calendar days
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed. Must be obtained prior to performing any screening procedures. Study allows for re-enrollment of a participant that has discontinued the study as a pre-treatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT.
Contact IRT	X	Register in Interactive Response system to obtain participant number.
Inclusion/Exclusion Criteria	X	Must be confirmed prior to treatment assignment (Part 1) or randomization (Part 2) in IRT.
Medical History	X	All medical history relevant to disease under study. Medical history will also include COVID-19 vaccines, toxicities of prior treatments, and known allergies.
Body Imaging/Bone Scan	X	Technetium-99m bone scan, contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease, within 28 days prior to treatment assignment (Part 1) or randomization (Part 2). If a participant has a contraindication for CT intravenous contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained. Section 9.1.1 for further details. Please refer to Appendix 5 for PCWG3 guidelines for tumor assessments.
Brain Imaging	X	MRI of the brain without and with contrast is required for participants with known or suspected brain metastases, unless participant has completed an imaging study of the brain, within 28 days prior to treatment assignment (Part 1) or randomization (Part 2). CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.

Table 2-1: Screening Procedural Outline (CA022009)

Procedure	Screening Visit (Days -28 to -1)	Notes: [a] All windows are based on calendar days
Prior Medications/Radiation/Surgery for Cancer	X	Details and dates of prior therapy, including all hormonal therapies, as well as prior cancer surgeries.
Safety Assessments		
Physical Examination (PE)	X	If the screening PE is performed within 72 hours prior to dosing on Day 1, then a single exam may count as both the screening and predose evaluation.
Physical Measurements	X	Includes height, weight, and BMI.
Vital Signs	X	Includes body temperature, respiratory rate, oxygen saturation and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
ECOG Performance Status	X	Refer to Appendix 6.
Assessment of Signs and Symptoms	X	Within 14 days prior to treatment assignment (Part 1) or randomization (Part 2).
Prior/Concomitant Medication Use	X	Within 14 days prior to treatment assignment (Part 1) or randomization (Part 2). Vaccine use within 30 days prior to Cycle 1 Day 1.
Electrocardiogram (ECG)	X	Single ECG should be recorded after the participant has been supine for at least 5 minutes, within 14 days prior to randomization/treatment assignment.
Laboratory Tests		
Clinical Laboratory Assessments	X	Must be performed within 14 days prior to treatment assignment (Part 1) or randomization (Part 2). Refer to Section 9.4.4 for list of laboratory tests to conduct. The following must be performed up to 28 days prior to first dose: PSA and testosterone (See Section 6.1, Inclusion Criteria)

Table 2-1: Screening Procedural Outline (CA022009)

Procedure	Screening Visit (Days -28 to -1)	Notes: [a] All windows are based on calendar days
Serology	X	Viral testing to be completed within 28 days prior to treatment assignment (Part 1) or randomization (Part 2). Refer to Section 9.4.4 for list of laboratory tests to conduct. Includes hepatitis B/C, (HBsAg, HCV antibody or HCV RNA), and HIV-1 and HIV-2 antibody (if mandated locally; refer to Appendix 7).
Biomarker Assessments		See Section 9.8 for sampling schedule.
SARS-CoV-2 Serology	X	Serum collected to be used for possible measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG [see Section 9.8]). Results will not be used to determine eligibility.
Pre-treatment Plasma and Serum	X	See Section 9.8 for specification on samples and Table 9.8-1 for sampling schedule.

Table 2-1: Screening Procedural Outline (CA022009)

Procedure	Screening Visit (Days -28 to -1)	Notes: [a] All windows are based on calendar days
Collection of Tumor Tissue	X (See Notes)	• Participants with any soft tissue lesion that is suspected to represent metastatic disease based on local review of imaging and is considered accessible for biopsy by an interventional radiologist (or other appropriate specialist), must provide tumor sample from a newly-obtained ("fresh") biopsy (obtained during screening, if there are tumor sites that can be biopsied with acceptable clinical risk). Lymph nodes must measure at least 1 cm in diameter along the short axis in order to be considered for biopsy. If the only site amenable to biopsy is also the only site of measurable disease, the investigator should prioritize maintaining a measurable target lesion (by RECIST v1.1) if there is a concern that the biopsy might impact tumor assessment. – A FFPE tissue block (preferred) or a minimum of 20 unstained slides* of tumor tissue from core biopsy, punch biopsy, excisional biopsy or surgical specimen obtained during screening or prior to treatment assignment (Part 1)/randomization (Part 2) must be sent to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable. *If despite best efforts, a minimum of 20 slides is not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with Sponsor or designee. Please refer to Section 9.8.4 for additional details on tumor tissue requirements. – Consent for pre-treatment, on-treatment, and on-progression tumor biopsy samples are required for enrollment for participants who meet the above criteria. • For participants with bone-only disease, inaccessible soft tissue lesions, or if the biopsy procedure would pose an unacceptable clinical risk for the participant, submission of tumor tissue obtained from a fresh biopsy is not required.

Table 2-1: Screening Procedural Outline (CA022009)

Procedure	Screening Visit (Days -28 to -1)	Notes: [a] All windows are based on calendar days
Adverse Event Reporting		
Monitor for Non-Serious Adverse Events	X	• The collection of non-serious AEs (with the exception of non-serious AEs related to SARS-CoV-2 infection) should begin at initiation of study treatment and continue during the treatment period, and for a minimum of 100 days following discontinuation of study treatment. • All SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing. AEs are graded per NCI CTCAE v5.
Monitor for Serious Adverse Events	X	All SAEs must be collected from time of consent until 100 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.
Study Intervention		
Randomize (Part 2 only)	X	Within 3 days of Cycle 1 Day 1.
Contact IRT	X	For Part 1 and Part 2, register in IRT system to obtain participant number prior to starting any screening procedures. After completing all screening procedures, utilize IRT to either screen fail or obtain treatment assignment information, as applicable. Treatment assignment can occur up to 3 days prior to first dose. See Section 7.2 (Method of Study Intervention Assignment).

Abbreviations: AE, adverse event; BMI, body mass index; COVID-19, coronavirus disease 2019; CRF, case report form; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin-embedded; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IRT, Interactive Response Technology; MRI, magnetic resonance imaging; NCI CTCAE v5, National Cancer Institute Common Terminology Criteria for Adverse Events version 5; PCWG3, Prostate Cancer Working Group 3; PE, physical examination; PSA, prostate-specific antigen; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RNA, ribonucleic acid; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Some of the assessments referred to in this section may not be captured as data in the CRF. 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 be institutional or local regulations.

Table 2-2: On Study Treatment Procedural Outline (CA022009)

Procedure	Cycle 1 (21 Days)	Cycle 2 and Beyond (each cycle = 21 days)	EOT or Early Termination	Notes[a]
	Day 1[b]	Day 1[b] (± 3 days)		
Eligibility Assessments				
Inclusion/Exclusion Criteria	X			Confirm eligibility prior to treatment assignment/randomization in IRT.
Medical History	X			Update any additional medical history prior to participant receiving study drug (does not apply for participants who crossover to Arm 2d).
Safety Assessments				
Physical Examination (PE)	X			If the screening PE is performed within 72 hours prior to dosing on Day 1, then a single exam may count as both the screening and predose evaluation.
Targeted Physical Examination		X	X	Includes weight and BMI. If there are any new or worsening clinically significant changes since the last examination, report changes on the appropriate non-serious or serious AE CRF page.
ECOG Performance Status	X	X	X	Record on days participant is being dosed and at EOT or early termination (refer to Appendix 6).

Table 2-2: On Study Treatment Procedural Outline (CA022009)

Procedure	Cycle 1 (21 Days)	Cycle 2 and Beyond (each cycle = 21 days)	EOT or Early Termination	Notes[a]
	Day 1[b]	Day 1[b] (± 3 days)		
Vital Signs	Collected at each visit		X	Vital signs will be obtained within 30 (± 5) minutes before the start of the first infusion, and then prior to each additional infusion (if applicable), and at EOT or early termination. Includes body temperature, respiratory rate, oxygen saturation, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Assessment of Signs and Symptoms	X	X		
Electrocardiogram (ECGs)	X	X	X	An ECG should be recorded prior to dosing after the participant has been supine for at least 5 minutes.
Concomitant Medication Use	Collected at each visit		X	Record at each visit.
Adverse Event Reporting[c]				
Monitor for Serious Adverse Events	Continuously		X	All SAEs must be collected from the date of participant's written consent until 100 days post discontinuation of dosing or participant's participation in the study if the last scheduled visit occurs at a later time.

Table 2-2: On Study Treatment Procedural Outline (CA022009)

Procedure	Cycle 1 (21 Days)	Cycle 2 and Beyond (each cycle = 21 days)	EOT or Early Termination	Notes[a]
	Day 1[b]	Day 1[b] (± 3 days)		
Monitor for Non-serious Adverse Events	Continuously		X	Non-serious AEs will be collected starting with the first dose of study medication and through 100 days following the last dose of study treatment. All AEs (SAEs or non-serious AEs), including those associated with SARS-CoV-2 infection, must be collected continuously during the treatment period.
Laboratory Tests				See Section 9.4.4.
Clinical Laboratory Assessments	X	X	X	Perform on site/local laboratory testing. There will be a minus-72-hour window for collection of laboratory tests on Day 1 of each cycle. See Section 9.4.4 and Table 9.4.4-1. For the first treatment visit, labs need not be repeated if they were performed within 72 hours and the results are available and have been reviewed for eligibility.
Thyroid Function Test	X	X	X	If thyroid function test is abnormal, free T3 and free T4 should be collected. See Section 9.4.4 and Table 9.4.4-1.
Urinalysis	X	X	X	See Section 9.4.4 and Table 9.4.4-1.

Table 2-2: On Study Treatment Procedural Outline (CA022009)

Procedure	Cycle 1 (21 Days)	Cycle 2 and Beyond (each cycle = 21 days)	EOT or Early Termination	Notes[a]
	Day 1[b]	Day 1[b] (±3 days)		
PSA	X	X	X	Perform on Day 1 of every cycle. Participants who discontinue study treatment without PSA progression or radiographic progression will continue to have PSA performed at Follow-up 1, Follow-up 2, and Follow-up 3, and every 12 weeks thereafter. PSA collection will continue until PSA progression, radiographic progression, or end of study treatment, whichever occurs last. Additional PSA collection outside of this schedule is allowed to confirm PSA progression as needed, during prolonged dose delays, or if clinically indicated.
[redacted]				
Biomarker Assessments				
Biomarker Sample Collections for Blood/Serum/Plasma and Pharmacodynamic Sampling	See Table 9.8-1[d]			See biomarker collection table in Section 9.8 for timing of collections. Crossover participants in Arm 2d will not have any biomarkers samples drawn with the exception of anti-SARS-CoV-2 serology.
Tumor Biopsy		(See Notes)		On-study tumor biopsy should be taken between Cycle 2 Day 15 and Cycle 3 Day 1 (prior to dosing; if there is a delay in dosing Cycle 3, biopsy can be taken up until Cycle 2 Day 28 as long as it is prior to the Cycle 3 dose), for participants with any soft tissue lesion that is suspected to represent metastatic disease based on local review of imaging and is considered

Table 2-2: On Study Treatment Procedural Outline (CA022009)

Procedure	Cycle 1 (21 Days)	Cycle 2 and Beyond (each cycle = 21 days)	EOT or Early Termination	Notes[a]
	Day 1[b]	Day 1[b] (±3 days)		
				accessible for biopsy by an interventional radiologist (or other appropriate specialist). Lymph nodes must measure at least 1 cm in diameter along the short axis in order to be considered for biopsy. A biopsy should also be performed if medically feasible at the time of progression for participants on treatment for more than 6 cycles, for all study parts. If the only site amenable to biopsy is also the only site of measurable disease, the investigator should prioritize maintaining a measurable target lesion (by RECIST v1.1) if there is a concern that the biopsy might impact tumor assessment. Bone lesion biopsies are unacceptable for submission. Note: For participants who have toxicities related to study therapy (ie, cytopenia) that may put them at increased risk from the biopsy, the on-study biopsy is not required. Crossover participants in Arm 2d will not have any tumor biopsies performed. Refer to Section 9.8.4 for more details.
SARS-CoV-2 Serology	X (See Notes)		X	Serum collected approximately every 6 months during study treatment to be used for possible measurements of anti-SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG). Serum should also be collected approximately 4 weeks after a documented or suspected SARS-COV-2 infection (see Section 9.8).

Table 2-2: On Study Treatment Procedural Outline (CA022009)

Procedure	Cycle 1 (21 Days)	Cycle 2 and Beyond (each cycle = 21 days)	EOT or Early Termination	Notes[a]
	Day 1[b]	Day 1[b] (±3 days)		
Efficacy Assessments				
Body Imaging/Bone Scan	X (See Notes)			Technetium-99m Bone Scans, Contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease. If a participant has a contraindication for CT intravenous contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained. Tumor assessments should occur every 9 weeks (± 7 days) from first dose, regardless of treatment schedule or dose delays for first 27 weeks. Thereafter, switch to every 12 weeks (± 7 days). If progression is not documented prior to discontinuation of study treatment, tumor assessments should continue every 9 weeks (± 7 days) for the first 27 weeks from the first dose, and thereafter, switch to every 12 weeks (± 7 days). Imaging must continue until radiographic progression per PCWG3 assessed by investigator and confirmed by BICR, or study treatment is discontinued, whichever occurs later. In case subsequent therapy has begun, imaging must continue until radiographic progression per PCWG3 is confirmed by BICR. See Section 9.1.1 for further details.

Table 2-2: On Study Treatment Procedural Outline (CA022009)

Procedure	Cycle 1 (21 Days)	Cycle 2 and Beyond (each cycle = 21 days)	EOT or Early Termination	Notes[a]
	Day 1[b]	Day 1[b] (±3 days)		
Brain Imaging	X (See Notes)			Participants with a history of brain metastasis or symptoms should have a surveillance MRI study per standard of care (approximately every 12 weeks, or sooner if clinically indicated and at the discretion of the investigator). CT of the brain without and with contrast can be performed if MRI is contraindicated. Imaging must continue until radiographic progression per PCWG3 is assessed by the investigator and confirmed by BICR or study treatment is discontinued, whichever occurs later. See Section 9.1.1 for further details.
Clinical Outcomes Assessments (Randomized Part 2 only)				
EORTC QLQ-C30	X	X		Participants will complete the EORTC QLQ-C30 at each cycle prior to any study-related study procedures using electronic data capture methods.
FACIT GP5	Complete weekly			Participants will complete the FACIT GP5 on a weekly basis for the first 12 weeks of treatment only. If data completion occurs on the same day as a scheduled clinic visit, then data collection should be prior to any other study procedures using electronic data capture methods.

Table 2-2: On Study Treatment Procedural Outline (CA022009)

Procedure	Cycle 1 (21 Days)	Cycle 2 and Beyond (each cycle = 21 days)	EOT or Early Termination	Notes[a]
	Day 1[b]	Day 1[b] (±3 days)		
Study Intervention				
Administer docetaxel (all Parts/Arms except Arm 2d)	X	X		Participants must receive the first dose of study medication within 3 calendar days from vial allocation. Administer docetaxel for a maximum of 10 cycles. If participants are also receiving BMS-986218 or BMS-986218 and nivolumab, treatment with these I-O agents may continue beyond 10 cycles, up to 2 years (until disease progression, unacceptable toxicity, or withdrawal of consent). Prednisone 5 mg twice daily will be administered with docetaxel in accordance with package insert/SmPC guidelines. Daily prednisone may be dose reduced or omitted at the discretion of the investigator if it negatively affects glycemic control or other comorbid conditions. Premedication with dexamethasone will also be given for docetaxel.
Administer nivolumab (Part 1B, Arm 2c, and Arm 2d)	X	X		Participants must receive the first dose of study medication within 3 calendar days from vial allocation. Nivolumab to be supplied by BMS; vials assigned by IRT should be used.
Administer BMS-986218 (Part 1A, Part 1B, Arm 2b, Arm 2c, and Arm 2d)	X	X		Participants must receive the first dose of study medication within 3 calendar days from vial allocation. BMS-986218 to be supplied by BMS; vials assigned by IRT should be used.

Abbreviations: AE, adverse event; BICR, blinded independent central review; BMI, body mass index; BMS, Bristol-Myers Squibb; CRF, case report form; CT, computed tomography; DLT, dose-limiting toxicity; DM, Data Management; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT, end of treatment; FACIT GP5, Functional Assessment of Chronic Illness Therapy General Physical Item 5; I-O, immuno-oncology; IRT, Interactive Response Technology; MRI, magnetic resonance imaging; PCWG3, Prostate Cancer Working Group 3; PE, physical examination; PK, pharmacokinetic; PSA, prostate-specific antigen; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SmPC, Summary of Product Characteristics; T3, triiodothyronine; T4, thyroxine.

[a] Some of the assessments referred to in this section may not be captured as data in the CRF. 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.

[b] If a dose is delayed, the procedures schedule for that same time point must also be delayed to coincide with when that time point's dosing actually occurs, with the exception of tumor assessments which must occur as scheduled.

[c] For Part 1A and Part 1B, the DLT evaluation period will be 42 days (6 weeks) starting on Cycle 1 Day 1.

[redacted]

Table 2-3: Long-term Follow-up Procedural Outline (CA022009)

Procedure	Safety Follow-up 1 30 days (±7 days)[a]	Safety Follow-up 2 60 days (±7 days)[a]	Safety Follow-up 3 100 days (±7 days)[a]	Survival Follow-up (Every 12 weeks, ± 2 weeks)[b]	Notes[c]
Safety Assessments					
Targeted Physical Examination	X	X	X		Includes weight, BMI, heart rate, BP, temperature, and oxygen saturation. BP and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Vital Signs	X	X	X		Record at each visit.
Concomitant Medication Use	X	X	X		Record at each visit.
Subsequent Cancer Therapy	X	X	X	X	Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy). Continuation of systemic ADT with GnRH antagonist/agonist does not need to be documented.

Table 2-3: Long-term Follow-up Procedural Outline (CA022009)

Procedure	Safety Follow-up 1 30 days (±7 days)[a]	Safety Follow-up 2 60 days (±7 days)[a]	Safety Follow-up 3 100 days (±7 days)[a]	Survival Follow-up (Every 12 weeks, ± 2 weeks)[b]	Notes[c]
Serious Adverse Events Assessment and Adverse Events Assessment	X	X	X	X*	Per NCI CTCAE v5. Record at each visit. All SAEs and non-serious AEs should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment. Participants will be followed for all SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3), or for suspected cases, until SARS-CoV-2 infection is ruled-out. *Beyond 100 days from the last dose of study therapy, participants will be followed for drug-related AEs/SAEs until resolution, return to baseline, deemed irreversible, or until the participant is lost to follow-up or withdraws study consent. See Section 9.2 (Adverse Events).

Table 2-3: Long-term Follow-up Procedural Outline (CA022009)

Procedure	Safety Follow-up 1 30 days (±7 days)[a]	Safety Follow-up 2 60 days (±7 days)[a]	Safety Follow-up 3 100 days (±7 days)[a]	Survival Follow-up (Every 12 weeks, ± 2 weeks)[b]	Notes[c]
Laboratory Tests					See Section 9.4.4.
Clinical Laboratory Assessments	X	X	X		Includes blood and urine samples.
PSA	X	X	X	X	Participants who discontinue study treatment without PSA progression or radiographic progression will continue to have PSA performed at follow-up visits and every 12 weeks thereafter. PSA collection will continue until PSA progression, radiographic progression, or end of study treatment, whichever occurs last. Additional PSA collection outside of this schedule is allowed to confirm PSA progression as needed, or if clinically indicated.
PK and Immunogenicity Assessments					
PK and Immunogenicity Collections	See Table 9.5-1 (Part 1A and Arm 2b) and Table 9.5-2 (Part 1B and Arm 2c)				See PK/Immunogenicity collection table in Section 9.5 for timing of collections.
Efficacy Assessments					
Survival Status	X	X	X	X	During Safety Follow-up (Follow-up Visits 1, 2, and 3) and every 12 weeks ± 2 weeks (clinic visit or by telephone) during Survival Follow-up. Include documentation of subsequent cancer therapy (ie, systemic therapy, tumor-directed surgery, or radiation therapy).

Table 2-3: Long-term Follow-up Procedural Outline (CA022009)

Procedure	Safety Follow-up 1 30 days (±7 days)[a]	Safety Follow-up 2 60 days (±7 days)[a]	Safety Follow-up 3 100 days (±7 days)[a]	Survival Follow-up (Every 12 weeks, ± 2 weeks)[b]	Notes[c]
Body Imaging/Bone Scan	X (See Notes)				Technetium-99m Bone Scans, Contrast enhanced CT of the chest, abdomen, pelvis, and all other known and/or suspected sites of disease. If a participant has a contraindication for CT intravenous contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained. Tumor assessments should occur every 9 weeks (± 7 days) from first dose, regardless of treatment schedule or dose delays for first 27 weeks. Thereafter switch to every 12 weeks (± 7 days). If progression is not documented prior to discontinuation of study treatment, tumor assessments should continue every 9 weeks (± 7 days) for the first 27 weeks from the first dose, and thereafter, switch to every 12 weeks (± 7 days). Imaging must continue until radiographic progression per PCWG3 assessed by investigator and confirmed by BICR, or study treatment is discontinued, whichever occurs later. In case subsequent therapy has begun, imaging must continue until radiographic progression per PCWG3 is confirmed by BICR. See Section 9.1.1 for further details.

Table 2-3: Long-term Follow-up Procedural Outline (CA022009)

Procedure	Safety Follow-up 1 30 days (±7 days)[a]	Safety Follow-up 2 60 days (±7 days)[a]	Safety Follow-up 3 100 days (±7 days)[a]	Survival Follow-up (Every 12 weeks, ± 2 weeks)[b]	Notes[c]
Brain Imaging	X (See Notes)				If progression is not documented prior to discontinuation of study treatment, participants with a history of brain metastasis or symptoms should have a surveillance MRI study per standard of care (approximately every 12 weeks, or sooner if clinically indicated). CT of the brain without and with contrast can be performed if MRI is contraindicated. See Section 9.1.1 for further details.

Abbreviations: ADT, androgen deprivation therapy; AE, adverse event; BICR, blinded independent central review; BMI, body mass index; BMS, Bristol-Myers Squibb; BP, blood pressure; CRF, case report form; CT, computed tomography; GnRH, gonadotropin-releasing hormone; MRI, magnetic resonance imaging; NCI CTCAE v5, National Cancer Institute Common Terminology Criteria for Adverse Events version 5; PCWG3, Prostate Cancer Working Group 3; PK, pharmacokinetic; PSA, prostate-specific antigen; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Participants must be followed for at least 100 days after last dose of study treatment. Follow-up Visit 1 must occur 30 days from the last dose (± 7 days) or can be performed on the date of discontinuation if that date is greater than 30 days after last dose. Follow-up Visit 2 occurs approximately 60 days (± 7 days) from last dose of study medication. Follow-up Visit 3 occurs approximately 100 days (± 7 days) from last dose of study medication.

[b] Survival Follow-up visits to occur every 12 weeks (± 2 weeks) from the last dose of study intervention (for up to 2 years) and will be performed in parallel to safety follow-up. Participants who crossover to Arm 2d after discontinuing docetaxel treatment and while in follow-up should only be followed for a maximum of 1 year from the last dose of crossover treatment. Survival visits may be conducted in clinic or by telephone. BMS may request that survival data be collected on all treated participants outside of the 3 month specified window. At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact.

[c] Some of the assessments referred to in this section may not be captured as data in the CRF. 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 regulation.

In the event that multiple procedures are required at a single time point, the following is a list of procedures from highest to low priority:

- Pharmacokinetic (PK) Sampling
- Safety (electrocardiogram [ECG])
- Safety (clinical labs)

3 INTRODUCTION

CA022009 is a Phase 2, open-label, randomized, controlled global study assessing the efficacy and safety of combining BMS-986218, or BMS-986218 plus nivolumab, with standard of care docetaxel in men who have metastatic castration-resistant prostate cancer (mCRPC) that progressed after a second-generation hormonal manipulation, also known as novel antiandrogen therapy (NAT), and have not received chemotherapy for mCRPC. The study will have a safety lead-in portion (Part 1) and a randomized controlled portion (Part 2). Participants in Part 2 who are randomized to the docetaxel arm (Arm 2a) and experience radiographic disease progression may qualify to receive BMS-986218 and nivolumab (crossover, Arm 2d) provided they continue to meet eligibility criteria and after consultation with the Medical Monitor. Part 2 of the study aims to demonstrate that addition of BMS-986218, or BMS-986218 plus nivolumab, to docetaxel improves clinical efficacy as assessed by radiographic progression-free survival (rPFS).

BMS-986218 is a fully human immunoglobulin G1 (hIgG1) monoclonal antibody (mAb) against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), an inhibitory receptor expressed on activated effector T-cells and regulatory T-cells (Tregs). BMS-986218 belongs to a class of agents referred to by the Sponsor as "next-generation" anti-CTLA-4 agents, which share the ligand-blocking poperties of ipilumumab, but have other modifications to improve efficacy and/or decrease toxicity. BMS-986218 shares the same amino acid sequence as ipilimumab but is produced in cells deficient for alpha-(1,6)-fucosyltransferase, the enzyme that mediates fucosylation of N-linked carbohydrates in the antibody (Ab) fragment crystallizable (Fc) region. Therefore, BMS-986218 is a non-fucosylated (NF) version of ipilimumab with an increased affinity for Fcγ receptors (FcγRs). Compared to ipilimumab, 2 additional FcγR-dependent mechanisms may augment BMS-986218 anti-tumor activity: depletion of tumor-infiltrating Tregs and enhanced stimulation of T-cells by antigen-presenting cells (APCs).

BMS-986288 is another non-fucosylated next-generation anti-CTLA-4 that shares the FcγR-dependent mechanisms of BMS-986218. BMS-986288 is identical to BMS-986218 except for [redacted]. These amino acids form a masking peptide with a protease-cleavable linker that is selectively cleaved in the tumor microenvironment. The "Probody" design could therefore decrease toxicity due to antibody binding to target outside of the tumor. Based on emerging data evaluating this concept, BMS-986288 may be incorporated into the CA022-009 study design via future protocol amendment.

A detailed description of the chemistry, pharmacology, efficacy, and safety of the study treatments is provided in the respective Investigator's Brochures (IBs) and package inserts.

3.1 Study Rationale

In 2004, 2 Phase 3 studies (TAX 327 and SWOG 99-16) demonstrated that docetaxel-based chemotherapy regimens improved survival in participants with mCRPC that progressed after castration therapy.[1,2] More recently, most patients have also received treatment with at least 1 NAT prior to use of docetaxel for mCRPC. The target population for this study is participants with mCRPC that progressed after an NAT and have not received chemotherapy for mCRPC. Treatment with chemotherapy in this population has a modest benefit with regard to overall survival (OS)

and does not produce long-term disease control. Several lines of evidence support the hypothesis that addition of next-generation anti-CTLA-4 agents, with or without nivolumab, will improve outcomes compared to docetaxel alone.

3.2 Background

3.2.1 Indication Background

Prostate cancer is a leading cause of cancer mortality in men worldwide,[3] with an estimated incidence of 1,276,106 new cases and 358,989 deaths globally[4] and 191,930 new cases and 33,330 deaths in the United States (US) in 2020.[5] Prostate cancer is the most frequently diagnosed cancer and second most frequent cause of cancer deaths in US males. In the US, prostate cancer accounted for almost 1 in 5 new diagnoses of cancer in men in 2018. In Europe, prostate cancer was the most common primary site in men in 2018 (21.8% of the total), with 450,000 new cases and 107,000 deaths.[6]

In 1941, Huggins and Hodges first noted the beneficial effects of castration via orchiectomy or injection of estrogens in patients with metastatic prostate cancer.[7] Over time, androgen deprivation therapy (ADT) achieved through either orchiectomy or gonadotropin-releasing hormone (GnRH) therapy, which blocks gonadal androgen production, became the cornerstone of treatment for patients with metastatic disease, as well as for some patients with localized or locally advanced prostate cancers. ADT results in disease remission in 90% of metastatic prostate cancer patients, evidenced by a decline in levels of prostate-specific antigen (PSA).[8] Nevertheless, most patients with metastatic disease progress to a state of castration-resistant prostate cancer (CRPC) at a median of 18 to 24 months of conventional castration therapies.[9] Despite castrate levels of testosterone in the periphery, it has long been speculated that local sources of biological active androgen remain in prostate tumors. Moreover, genetic and molecular evidence suggested that androgen receptor (AR) gene amplification and mutations may promote AR reactivation in CRPC. These concepts supported the development of a new generation of androgen axis blockers to be utilized in combination with conventional ADT.[10]

Since 2012, 4 NATs have gained approval for use in various prostate cancer disease states. Abiraterone, which blocks extra gonadal androgen production, first gained approval in the mCRPC setting and subsequently in patients with metastatic castration-sensitive prostate cancer (mCSPC). Enzalutamide, apalutamide, and darolutamide are all direct AR antagonists. Based on improvements in median overall survival (mOS), enzalutamide is approved for use in mCRPC, mCSPC, and non-metastatic castration-resistant prostate cancer (nmCRPC), a distinct clinical state in which patients demonstrate PSA progression while on ADT, despite having never demonstrated metastatic disease on conventional imaging.[11,12,13,14] Apalutamide is approved to treat mCSPC and nmCRPC, and darolumatide is approved to treat nmCRPC.[15,16,17]

Docetaxel became the first chemotherapeutic agent to show an OS benefit in mCRPC in 2 randomized controlled clinical trials (TAX 327 and SWOG 99-16), and was approved in combination with prednisone for this indication in the US in 2004.[1,2] In the landmark TAX 327

Phase 3 trial, 1006 participants with mCRPC were randomized to receive daily prednisone and either mitoxantrone 12 mg/m^2 every 3 weeks (Q3W), docetaxel 75 mg/m^2 Q3W, or docetaxel 30 mg/m^2 every week (QW) for 5 of every 6 weeks.[1] Participants who received docetaxel Q3W had a median survival of 19.2 months, compared to 16.3 months in the mitoxantrone Q3W and 17.8 months in the docetaxel QW arms. The hazard ratio (HR) for the docetaxel Q3W arm was 0.76 (95% confidence interval [CI], 0.62 to 0.94; P = 0.009). Cabazitaxel is another taxane-based chemotherapy that was approved by the Food and Drug Administration (FDA) in 2010, in patients with mCRPC previously treated with docetaxel.[18] In the FIRSTANA trial, which studied cabazitaxel vs docetaxel as first line (1L) therapy in chemotherapy-naïve mCRPC, different dosages of cabazitaxel did not show superiority over docetaxel.[19]

Two radiopharmaceuticals have demonstrated an improvement in mOS in mCRPC: 1) the bone targeting alpha-emitting radionuclide radium-223 chloride was approved in men with symptomatic bone metastases but no visceral disease, based on data from the ALSYMPCA trial, which showed an mOS benefit (HR, 0.7; 14.9 vs 11.3 months; P < 0.001),[20] and 2) ^{177}Lu-prostate-specific membrane antigen(PSMA)-617, which demonstrated an improvement in rPFS and mOS in the VISION study leading to a Breakthrough Therapy designation by the FDA in 2021.[21]

Genomic evaluation over the past few years has identified that loss of function in genes involved in deoxyribonucleic acid (DNA) homologous recombination repair (HRR) occurs in nearly 20% of mCRPC patients.[22] Based on the validated concept that defects in HHR genes can sensitize tumor cells to poly ADP ribose polymerase (PARP) inhibitors, multiple PARP inhibitors have been evaluated in mCRPC. The randomized Phase 3 PROfound trial compared olaparib with second-generation hormonal therapy in 387 men with mCRPC harboring alterations in genes with roles in HRR and had experienced progression on a prior systemic therapy for metastatic disease with a NAT, with one prior chemotherapy agent also permitted but not required. The olaparib-treated men had longer OS (17.3 vs 14 months). These data supported the approval in 2020 of olaparib for adults with mCRPC who have disease progression following treatment with a NAT and have a germline or somatic pathogenic variant in an HRR gene.[23]

Sipuleucel-T was the first immunotherapy to receive FDA approval in men with asymptomatic mCRPC based on the Phase 3 IMPACT trial, which showed a median survival of 25.8 months vs 21.7 months (placebo arm).[24] Sipuleucel-T did not improve time to objective progression or meaningfully increase PSA response rate (2.6% vs 1.3%).

While the availability of these treatment options allows for tailoring therapy to patient characteristics such as presence or absence of symptoms, prior treatments, patient preferences, and life expectancy, none of these therapies result in durable clinical responses. Despite high initial response rates, remissions following second-generation hormone therapies are temporary due to the development of resistance mechanisms. At this time, with judicious sequencing and use of available new therapies, patients with established mCRPC have a life expectancy in the range of 12 to 35 months. Thus, mCRPC remains a disease with a lethal outcome with the urgent need for treatment options that will provide durable disease control and long-term survival. Immune

checkpoint blockade provides clearly-established durable benefit in other indications and has also been evaluated in prostate cancer with encouraging signs in some patients.

3.2.1.1 CTLA-4 Blockade in Prostate Cancer

The first-in-human (FIH) study of ipilimumab was in prostate cancer: an investigation of a single 3 mg/kg dose of ipilimumab in 14 participants with CRPC.[25] Ipilimumab as a single dose had acceptable PK and safety profiles, but only 2 of the 14 participants experienced PSA declines of > 50%. Results have since been reported for 6 other clinical studies of ipilimumab in mCRPC.[26] Together, these 7 trials encompassed 240 participants across multiple settings of advanced CRPC, roughly 20% of whom had progressed on or relapsed after docetaxel. These studies utilized multiple doses (ranging from 0.5 to 10 mg/kg as either monotherapy or in combination studies) and schedules (ranging from a single dose of ipilimumab to recurring doses every 3 weeks for 4 cycles) and demonstrated the clinical activity of ipilimumab 3, 5, and 10 mg/kg, defined as PSA response, in the treatment of mCRPC (Table 3.2.1.1-1) whether used as monotherapy, with ADT or with other interventions such as radiotherapy, or other immunotherapeutics with different mechanisms of action.[26] In 3 studies that included ipilimumab monotherapy at 3 mg/kg in mCRPC, PSA responses were observed in 6 of 46 evaluable participants (13.6%). In 1 study that included ipilimumab monotherapy at 10 mg/kg, PSA responses were observed in 4 of 16 participants (25%).

Table 3.2.1.1-1: Phase 1/2 Studies with Ipilimumab in Prostate Cancer

Protocol	Population	Combination	Subjects Treated/Target	PSA Response	PSA Response Rate (%)
MDX010-21 (CA184017)	Docetaxel failure and docetaxel eligible	Monotherapy and single-dose radiation combination	3 mg/kg: 8/6	2	13/70 evaluable (18.6%)
			5 mg/kg: 6/6 10 mg/kg:16/16 3 mg/kg + RT: 6/6	1 4 2	
			10 mg/kg + RT: 34/34	4	
MDX010-17 (CA184119)	Docetaxel eligible	GVAX (CellGenesys)	< 3 mg/kg: 6/6		5/28 (18%)
			3 mg/kg: 19/19	3	
			5 mg/kg: 3/3	2	
CTEP 7207[a] (CA184066)	Docetaxel failure and docetaxel eligible	Prostavac (fixed dose)	1 mg/kg: 3/3		5/28 (7%)
			3 mg/kg: 6/6 5 mg/kg: 6/6 10 mg/kg: 13/16	1 3 1	
CTEP 6032 (CA184067)	Docetaxel eligible	GM-CSF (on Days 1-14)	< 3 mg/kg: 15/15 3 mg/kg: 9/9 5 mg/kg: 5/6 10 mg/kg: 1/16	3	3/30 (10%)
MDX010-01 (CA184009)	Metastatic HRPC	Monotherapy	3 mg/kg: 14/14	2	2/14 (14%)
MDX010-07 (CA184019)	Docetaxel eligible	Docetaxel	3 mg/kg alone: 24/20 3 mg/kg + docetaxel: 20/20	2 1	3/42 evaluable (7%)
		HRPC (subtotal)	190/225	31	16%
MDX010-06 (CA184118)	Unresectable PC (< 90 days prior hormonal Rx)	3 months androgen ablative therapy	3 mg/kg: 50/108	11	11/50 (22%)
		Total Subjects	240/333	44	17%

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; HRPC, hormone-refractory prostate cancer; PC, prostate cancer; PSA, prostate-specific antigen; RT, radiation therapy.

[a] Ongoing accrual

Two Phase 3 studies (CA184043 and CA184095) carried out subsequently have failed to show a clear-cut survival advantage for ipilimumab (10 mg/kg) over placebo.[27,28] CA184043 was a double-blind, randomized Phase 3 study comparing ipilimumab plus radiotherapy to placebo plus radiotherapy in participants with mCRPC who had received prior treatment with docetaxel for their disease.[27] It did not meet its primary endpoint of demonstrating a statistically significant prolongation of survival for the ipilimumab group compared with the placebo group. However, ipilimumab was associated with reductions in PSA concentration (13.1% [95% CI·9.5 to 17.5] for ipilimumab and 5.2% [3.0 to 8.4] for placebo) and an improvement in progression-free survival (PFS) compared with placebo (median 4.0 [95% CI 3.6 to 4.3] vs 3.1 [2.9 to 3.4] months; HR 0.70, 95% CI 0.61 to 0.82; $p < 0.0001$). PFS was a composite endpoint based on confirmed PSA progression, confirmed radiological progression, clinical deterioration, or death. During an additional exploratory assessment at approximately 2.4 years after the primary analysis, 721/799 participants had died. Survival analysis showed crossing of the curves at 7 to 8 months, followed by persistent separation of the curves beyond that point, favoring the ipilimumab arm. Given the lack of proportional hazards, a piecewise hazard model showed that the hazard ratio (HR) changed over time: the HR was 1.49 (95% CI 1.12 to 1.99) for 0 to 5 months, 0.66 (0.51 to 0.86) for 5 to 12 months, and 0.66 (0.52 to 0.84) beyond 12 months. OS rates were higher in the ipilimumab versus placebo arms at 2 years (25.2% vs 16.6%), 3 years (15.3% vs 7.9%), 4 years (10.1% vs 3.3%), and 5 years (7.9% vs 2.7%). Disease progression was the most frequent cause of death in both arms. In 7 participants (1.8%) in the ipilimumab arm and 1 (0.3%) in the placebo arm, the primary cause of death was reported as study drug toxicity. No long-term safety signals were identified.[29]

Similarly, Study CA184095 a double-blind, randomized Phase 3 study in participants with asymptomatic or minimally symptomatic, chemotherapy-naïve, mCRPC with no known visceral metastases did not meet its primary endpoint based on intent-to-treat analysis (HR 1.11; 95.87% CI: 0.88, 1.39; P value = 0.3667) for OS. However, treatment with ipilimumab was associated with longer median PFS (defined as time to confirmed PSA or radiological progression, clinical deterioration, or death) in the ipilimumab group (5.6 months) versus the placebo group (3.8 months, HR, 0.67; 95.87% CI, 0.55 to 0.81), longer median time to non-hormonal cytotoxic chemotherapy (HR, 0.65; 95.87% CI, 0.52 to 0.83) and to docetaxel therapy (HR, 0.70; 95% CI, 0.55 to 0.88) in the ipilimumab arm versus placebo. In addition, a higher PSA response rate was observed with ipilimumab (23%; 95% CI, 19% to 27%) compared to placebo (8%; 95% CI, 5% to 13%).

3.2.1.2 Programmed Death-1 (PD-1)/Programmed Death-ligand 1(PD-L1) Blockade in Prostate Cancer

In primary prostate tumors, programmed death-ligand 1 (PD-L1) expression is rare, suggesting that it is not a driver of primary immune resistance in primary prostate cancer. In mCRPC, PD-L1 positivity increased with 31.6% of cases showing PD-L1-specific immunoreactivity.[30] Nivolumab monotherapy was evaluated in a cohort of 17 participants with mCRPC.[31] All participants with mCRPC were treated with nivolumab 10 mg/kg, and no objective responses were observed. One out of 10 participants evaluable for PSA response demonstrated a PSA reduction ≥ 50% from

baseline. Other anti-PD-(L)1 inhibitors have also demonstrated limited clinical activity in mCRPC. Atezolizumab monotherapy was evaluated in a Phase 1 study, including 35 participants with mCRPC. All 35 evaluable participants received atezolizumab after ≥ 1 prior line of therapy; 62.9% of participants had received ≥ 3 prior lines. One participant had a confirmed partial response (PR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and 1 participant had a PR per immune-related response criteria. The confirmed 50% PSA response rate was 8.6% (3 participants). The Phase 2 KEYNOTE-199 study included 3 cohorts of participants with mCRPC previously treated with docetaxel and one or more targeted endocrine therapies. Cohorts 1 and 2 enrolled participants with RECIST-measurable PD-L1-positive and PD-L1-negative disease, respectively. Cohort 3 enrolled participants with bone-predominant disease, regardless of PD-L1 expression. All participants received pembrolizumab 200 mg every 3 weeks for up to 35 cycles. 258 participants were enrolled: 133 in Cohort 1, 66 in Cohort 2, and 59 in Cohort 3. Objective response rate was 5% in Cohort 1 and 3% in Cohort 2. Disease control rate was 10% in Cohort 1, 9% in Cohort 2, and 22% in Cohort 3. Median OS was 9.5 months in Cohort 1, 7.9 months in Cohort 2, and 14.1 months in Cohort 3.[32]

Since single-agent PD-(L)1 inhibitors have limited anti-tumor activity in mCRPC, these agents have also been evaluated in combination with standard of care docetaxel chemotherapy. In COU-AA-302, Arm B treated 84 participants with chemotherapy-naive mCRPC with ongoing androgen deprivation therapy and ≤ 2 prior NATs. Participants received nivolumab [redacted] + docetaxel 75 mg/m^2 Q3W + prednisone 5 mg twice a day for ≤ 10 cycles, followed by nivolumab [redacted] until disease progression/unacceptable toxicity (up to 2 years). The median number of docetaxel cycles was 8; the median number of nivolumab doses was 11. Median follow-up was 15.2 months. There was 1 (2.2%) complete objective response and 17 (37.8%) partial responses in 45 participants with measurable disease. Median rPFS was 9 months overall, 12 months in the 30 participants who had not received prior NAT, and 8.5 months in the 54 participants previously treated with NAT. Based on the pivotal Phase 3 studies in an era prior to NAT development, median PFS with docetaxel would be expected to be 6 to 7 months. Moreover, clinical benefit of docetaxel treatment may be reduced in patients following NAT exposure.[33] Thus, the observed PFS compares favorably and led to the ongoing randomized controlled Phase 3 study CheckMate 7DX to determine if the addition of nivolumab improves rPFS and OS compared to docetaxel alone.[34]

KEYNOTE-365 Cohort B examined the safety and efficacy of pembrolizumab + docetaxel and prednisone in participants with mCRPC, all previously treated with NAT: 104 participants were treated with median time from enrollment to data cutoff of 32.4 months.[35] ORR in participants with measurable disease was 23% and median rPFS was 8.5 months, similar to the subset of participants in CheckMate 9KD previously treated with NAT. These data led to the ongoing KEYNOTE-921 Phase 3 study evaluating pembrolizumab in combination with docetaxel in mCRPC.

3.2.1.3 Role for Dual Checkpoint Blockade Inhibition: (anti-CTLA-4 and anti-PD-1) in Prostate Cancer

While PD-L1 expression is low in prostate tumors, pre-clinical data has indicated that it may be up-regulated on tumor cells as an adaptive resistance mechanism to CTLA-4 blockade. In a clinical trial, an increased frequency of CD4 and CD8 T-cell infiltration was observed in tumor tissues from participants with localized prostate cancer who were treated with ADT plus 2 doses of anti-CTLA-4 antibody (ipilimumab). Treatment with ipilimumab also led to increased expression of PD-L1.[36]

Accordingly, utilizing a combination checkpoint blockade approach with anti-CTLA-4 and anti-programmed death-1 (anti-PD-1) agents may be necessary to boost anti-tumor activity for maximum clinical benefit in prostate cancer. Combination of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg Q3W for up to 4 doses, followed by nivolumab 480 mg every 4 weeks has been evaluated in Cohorts B and C of CheckMate 650.[37] A safety and efficacy analysis (database lock date 27-Nov-2018) was conducted in all treated participants with at least 24 weeks of follow-up in Cohort B (participants with no prior chemotherapy treatment, n = 45) and Cohort C (participants who progressed after prior cytotoxic chemotherapy, n = 45). Among participants with baseline measurable disease, ORR was 25% in Cohort B and 10% in Cohort C.

Among participants with measurable disease, 44 participants had tumor samples that underwent whole exome sequencing for homologous recombination deficiency (HRD) and tumor mutational burden (TMB) testing (TMB “high” and “low” represent above and below the median of 74.5 mutations per participant). In participants with TMB above versus below the median, the objective response rate was 50.0% versus 5.3%, PSA response rate was 30.0% versus 5.9%, median rPFS was 7.4 versus 2.4 months, and median OS was 19.0 versus 10.1 months. Confirmed/unconfirmed PSA decline ≥ 50% in participants with baseline and ≥ 1 post-baseline PSA result were 17.6% Cohort B and 10% in Cohort C. Grade 3-4 treatment-related adverse events (TRAEs) occurred in 42% and 53% of participants in Cohorts B and C, respectively; TRAEs leading to discontinuation occurred in 15 participants (33.3%; Grade 3–4) in Cohort 1 and 16 (35.6%; Grade 3–4) in Cohort 2. Two treatment related deaths occurred in each cohort. Ongoing cohorts are exploring different dosing schedules of nivolumab in combination with ipilimumab to identify a dose combination which reduces toxicity and increases the potential clinical benefit from dual checkpoint inhibition.

3.2.2 BMS-986218 and BMS-986288 Mechanism of Action

BMS-986218 is a fully human immunoglobulin G1 (hIgG1) mAb against CTLA-4, an inhibitory receptor expressed on activated effector T-cells and Tregs. BMS-986218 shares the same amino acid sequence and ligand-blocking properties as ipilimumab but is produced in cells deficient for alpha-(1,6)-fucosyltransferase (Fut8), the enzyme that mediates fucosylation of the Ab carbohydrate side chain at N-linked glycopeptides. Therefore, BMS-986218 is an NF version of ipilimumab, which has increased affinity for FcγRs.

In comparison to ipilimumab which induces activation of effector CD4+ and CD8+ T-cells by blocking the inhibitory function of CTLA-4, BMS-986218 may increase the anti-tumor immune

response through 2 additional mechanisms: by depleting tumor-infiltrating Tregs and enhancing stimulation of T-cells by antigen-presenting cells (APCs). Increasing the affinity of the antibody (Ab) for FcγR increases the Ab-dependent cellular cytotoxicity of target-expressing cells engaged by the Ab. Antibody engagement of CTLA-4 has been shown to mediate specific depletion of immune suppressive Tregs at the tumor site in mouse tumor models.[38,39] The preferential depletion of Tregs is likely due to several factors, such as higher expression of CTLA-4 on tumor Tregs compared to Tregs in peripheral lymphoid organs, higher expression of CTLA-4 on tumor Tregs compared to effector CD4 and CD8 T-cells, and higher FcγR (CD16-2) expression in tumors compared to peripheral lymphoid organs. Additionally, Fc-FcγR co-engagement by anti-CTLA-4 can contribute to tumoricidal activity independent of Tregs, as evidenced by studies in mouse models in which Tregs are first depleted by other techniques. The mechanism involves enhanced T-cell receptor signaling at the immunological synapse with APCs, likely through co-engagement of T-cells by the antigen-binding fragment with simultaneous engagement of the Fc to FcγR expressed on APCs.[40]

BMS-986288 is another next-generation anti-CTLA-4 that is identical to BMS-986218 except for [redacted]. These amino acids form a masking peptide with a protease-cleavable linker. Proteases predominantly present in the tumor microenvironment cleave proteolytic sites in the masking peptide linker, selectively activating the mAb in the tumor microenvironment. The premise of this Probody technology is to create an mAb that is administered in a form that has a significantly reduced ability to bind to cognate antigen while in circulation or normal, healthy tissue. The Probody prodrug design could therefore widen the therapeutic window by decreasing toxicities due to antibody binding to sites outside of the tumor. Based on emerging data evaluating this concept, the addition of BMS-986288 may be incorporated into CA022-009 via future protocol amendment.

3.2.3 Nivolumab Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death-ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab (OPDIVO™) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (Jun-2015), and Japan (Jul-2014).

3.2.4 Docetaxel Mechanism of Action

Docetaxel is an anti-neoplastic chemotherapeutic agent which acts by disrupting the microtubular network that is essential for mitotic and interphase cellular functions. See the current prescribing information for docetaxel (Summary of Product Characteristics [SmPC], US Prescribing Information [USPI], or country-specific label) for more information.[41,42]

3.2.5 BMS-986218 and BMS-986288 Clinical Activity

Study CA022001 is an ongoing BMS study which is evaluating the safety, tolerability, and preliminary efficacy of intravenous (IV) doses of BMS-986218, administered as monotherapy and in combination with nivolumab in participants with advanced solid tumors.

BMS-986218 monotherapy has been administered [redacted] In addition, BMS-986218 monotherapy has also been administered [redacted]. BMS-986218 has also been administered in combination with nivolumab [redacted] at doses of BMS-986218 [redacted]. The maximum tolerated dose (MTD) of BMS-986218 as a monotherapy or in combination with nivolumab has not been reached, and dose escalation is currently ongoing. Overall, the safety profile of BMS-986218 as a single agent and in combination with nivolumab is clinically manageable. Efficacy for this ongoing study has not yet been evaluated.

Study CA043-001 is an ongoing BMS study which is evaluating whether BMS-986288 by itself and in combination with nivolumab is safe and tolerable in the treatment of select advanced solid tumors. Based on clinical data, the use of BMS-986288 will be added to the CA022-009 protocol via future amendment, if the Sponsor seeks to test BMS-986288 in the present study.

Additional details on the safety of BMS-986218 and BMS-986288 are summarized in their respective investigator brochures.[43,44]

3.2.6 Nivolumab Clinical Activity

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy in several tumor types, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), small cell lung cancer (SCLC), gastric cancer, squamous cell carcinoma of the head and neck (SCCHN), urothelial cancer, hepatocellular carcinoma (HCC), and colorectal cancer (CRC). In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in patients with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or recurrent or metastatic SCCHN. Details of the clinical activity in these various malignancies are provided in the USPI and SmPC.

3.2.7 Docetaxel Clinical Activity

The safety and efficacy of docetaxel in combination with prednisone or prednisolone in participants with mCRPC were evaluated in a randomized Phase 3 study (TAX 327). A total of 1006 participants were randomized to 3 different treatment arms: 1) docetaxel Q3W for 10 cycles, 2) mitoxantrone Q3W for 10 cycles, and 3) docetaxel weekly for the first 5 weeks in a 6-week

cycle for 5 cycles. All regimens were administered in combination with prednisone or prednisolone twice daily, continuously. The primary endpoint of the study was OS. When given with prednisone, treatment with docetaxel Q3W led to improved rates of response in terms of pain, serum PSA level, and quality of life, as compared with mitoxantrone plus prednisone.[1] Participants who received docetaxel Q3W demonstrated significantly longer OS compared to those treated with mitoxantrone. The median survival was 16.5 months in the mitoxantrone group and 18.9 months in the group given docetaxel Q3W. Respectively, for the mitoxantrone and docetaxel Q3W groups, 32% and 45% ($P < 0.001$) had at least a 50% decrease in the serum PSA level, 22% and 35% ($P = 0.01$) had predefined reductions in pain, and 13% and 22% ($P = 0.009$) had improvements in the quality of life.

3.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably anticipated adverse events (AEs) of BMS-986218 may be found in the Investigator's Brochure.[43]

Extensive details on the safety profile of nivolumab are available in the Investigator's Brochure, and will not be repeated herein.[45]

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

A pattern of immune-mediated adverse events (IMAEs) has been defined, for which management algorithms have been developed; these are provided in Appendix 8. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

3.3.1 Risk Assessment

Study CA022009 is designed to start out with a safety lead-in portion (Part 1) prior to moving on to the randomized controlled portion (Part 2). The study visits allow for close monitoring of participants' safety throughout the clinical trial (see Section 2, Schedule of Activities), and participants are encouraged to contact the investigator if an intercurrent illness develops between study visits. To minimize therapy-related risk to participants enrolled in the present study, the following safety measures will be employed throughout the conduct of the study:

- Rigorous continuous safety monitoring by BMS to ensure participants' safety including regular and systematic review of safety data, close follow-up of reported safety events, and intensive site and study investigator training/education on the implementation of the toxicity management algorithms. A BMS Safety Management Team (SMT) will review and evaluate all emerging data across the program for potential safety signal assessment in a timely manner.

BMS Worldwide Patient Safety (WWPS) is an internal group that operates independently from the clinical team to monitor safety across all BMS protocols (Section 5.1.4.1).

- An independent Data Monitoring Committee (DMC) will evaluate the safety for the randomization phase (Section 5.1.4). This evaluation will be based on all available data with particular attention to AEs or other safety trends in this or any other clinical study of the study intervention whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury.
- Risks will be further minimized by adherence to inclusion and exclusion selection criteria (Section 6), avoidance of prohibited medication (Section 7.7), close safety monitoring (Section 9.2 and Section 9.4), and dose adjustment guidelines (Section 7.4). These will also be clearly discussed and highlighted during site visits.
- Study treatment administration will occur at infusion centers with medical monitoring and the capability to manage infusion reactions or anaphylaxis. The protocol provides a treatment algorithm for infusion reactions. In addition to conventional safety measures for infusion of biologic agents, all participants will undergo observation and assessment for signs of infusion reaction for 30 minutes post infusion after all infusions of BMS-986218.

Selected important clinically significant risks for BMS-986218, nivolumab and docetaxel are presented in Table 3.3.1-1.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BMS-986218		
Overall Safety Profile	The safety profile of BMS-986218 is based on the data from Study CA022001, the Phase 1/2a first-in-human (FIH) clinical study for this drug product. Both as a monotherapy and in combination with nivolumab, its observed toxicity profile thus far is similar to that observed with ipilimumab, which is anticipated based on the mechanism of action. Reference Safety Information in IB.[43]	See Section 7.4.1 and Table 7.4.1-1 for dose modification criteria and AE criteria for delay, resume and discontinuation of nivolumab and BMS-986218.
Diarrhea Pneumonitis	These events were commonly reported and are considered important identified risks. Reference Safety Information in IB.[43]	Recommended management algorithms are included in Appendix 8.
Study Interventions: BMS-986218 and Nivolumab		
Increased Toxicity Combining Multiple Checkpoint Inhibitors,	The paradigm of combining of ipilimumab and nivolumab with	The toxicity profile with the combination was consistent with

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
(anti-CTLA-4 [ipilimumab] and anti-PD-1 [nivolumab]), with Chemotherapy	chemotherapy was established by the Phase 3 CheckMate 9LA study, an open-label, multi-center, randomized Phase 3 trial evaluating ipilimumab plus nivolumab combined with platinum doublet chemotherapy compared to chemotherapy alone as 1L treatment for patients with metastatic NSCLC. The addition of ipilimumab and nivolumab increased toxicity: Grade 3 or 4 TRAEs were reported in 48% of patients who received ipilimumab and nivolumab with chemotherapy and in 38% of patients who received chemotherapy only.	that of the treatment components and was acceptable based on improved clinical activity, leading to approval of the combination as 1L treatment for adult patients with metastatic or recurrent non-small cell lung cancer with no epidermal growth factor receptor (EGFR) or ALK genomic tumor aberrations.
IMAEs	The frequency and types of immune-mediated adverse reactions are similar across multiple types of tumors. Unanticipated side effect events may also occur. Reference Safety Information in IB.[45]	Recommended management algorithms are included in Appendix 8.
Diarrhea Colitis Pneumonitis	These events were commonly reported and are considered important identified risks. Reference Safety Information in IB.	Recommended management algorithms are included in Appendix 8.
Study Intervention: Docetaxel		
Well-characterized AE Profile as a Cytotoxic Chemotherapy: Pancytopenia, Fluid Retention, Peripheral Neuropathies, Diarrhea, Nausea, and Vomiting	The safety and tolerability of docetaxel in combination with pembrolizumab in patients with mCRPC appeared to be acceptable. Grade 3 to 5 treatment-related AEs (TRAEs) occurred in 27 (38%) of patients, including 2 deaths from TRAEs (pneumonitis). The most commonly reported Grade ≥ 3 TRAEs were febrile neutropenia (12%), decreased neutrophil count (6%), colitis (4%), and pneumonitis (4%). Most immune-mediated AEs (IMAEs) were low grade with the most common being infusion-related reactions (11%) and colitis (10%). Of the 104 treated participants, treatment-related adverse events (TRAEs) occurred	See Section 7.4.2 and Table 7.4.2-1 for dose modification criteria and AE criteria for delay, resume and discontinuation of docetaxel.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	in 100 participants (96.2%); the most frequent (≥ 30%) were diarrhea (41.3%), fatigue (41.3%), and alopecia (40.4%). Grade 3-5 TRAEs occurred in 46 participants (44.2%). Five participants (4.8%) died of AEs; 2 were treatment-related pneumonitis.[35] Docetaxel was also tested in combination with nivolumab in Arm B of the ongoing Phase 2 CA2099KD study (NCT03338790). Of 84 treated patients with a median age of 71 years (range: 53 to 88 years), 47.6% of patients experienced Grade 3-4 TRAEs, most commonly neutropenia (16.7%). TRAEs led to discontinuation in 29.8% of patients. The most common immune-related AEs were GI (35.7%) or skin-related (26.2%). There were 3 treatment-related deaths (1 pneumonitis related to nivolumab; 2 pneumonias related to docetaxel).[34]	
Study Procedures		
Biopsies	The biopsies pose limited risk to the participant and include discomfort, pain, and bleeding.	Section 9.8 gives guidance on lesions that are appropriate for a research biopsy and when no appropriate lesion is identified participants are still able participate. Because of the need for development of predictive biomarkers for participants treated with BMS-986218 in future studies, the limited risk of a research biopsy in selected (low-risk) participants is considered appropriate in a Phase 2 research setting.
Blood Sampling	The amount of blood sampling poses limited risk to the participant and includes discomfort, pain, and bleeding.	The amount of total blood is reduced to the minimal quantity required to address the need of safety monitoring, standard of care, PK/anti-drug antibodies (ADAs), and biomarker needs and is below the recommended daily limits for each treatment day.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
SARS-CoV-2 Infection	The global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial participants in general.	Whether BMS-986218 in combination with docetaxel or docetaxel plus nivolumab administration increases the risk for contracting SARS-CoV-2 infection or increases the severity or duration of symptoms is currently unknown. This unknown risk must be considered when enrolling a participant. No additional safety monitoring or routine screening tests will be required due to the SARS-CoV-2 pandemic. Participants with recent or acute infections will be excluded or delay start of treatment as defined in Section 6.2. If a participant has a confirmed SARS-CoV-2 infection while on study treatment, dose delay or interruption of study treatment is required as described in Section 7.4. An exploratory analysis of the impact of SARS-CoV-2 serologic status on participants receiving BMS-986218 in combination with docetaxel or docetaxel plus nivolumab may be performed. The study has been designed with study visits that allow for close monitoring of participants' safety throughout the clinical trial (Section 9.4), and participants are encouraged to contact the investigator if an intercurrent illness develops between study visits. Testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice. Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving BMS-986218

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		in combination with docetaxel or docetaxel plus nivolumab is unknown.

Abbreviations: 1L, first line; ADA, anti-drug antibody; AE, adverse event; ALK, anaplastic lymphoma kinase; COVID-19, coronavirus disease 2019; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; FIH, first-in-human; GI, gastrointestinal; IB, Investigator's Brochure; IMAE, immune-mediated adverse event; mCRPC, metastatic castration-resistant prostate cancer; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PK, pharmacokinetic; SARS-CoV-2, severe acute respiratory syndrome coronavirus disease 2; TRAE, treatment-related adverse event.

3.3.2 Benefit Assessment

Although multiple new agents have been approved for mCRPC over the last decade, benefits remain modest and the median survival of patients with mCRPC is unsatisfactory at approximately 12 to 35 months.[11,18,20,46,47,48] Participants with mCRPC who received docetaxel Q3W had a median survival of 19.2 months, compared to 16.3 months in the mitoxantrone Q3W and 17.8 months in the docetaxel QW arms. The hazard ratio (HR) for the docetaxel Q3W arm was 0.76 (95% CI, 0.62 to 0.94; P = 0.009). Furthermore, OS may be shorter in patients who received prior treatment with NAT.[49,50] It is clear that there is an urgent need for new therapeutic options that offer further improvement in cancer control and OS. Ipilimumab has demonstrated anti-tumor activity in mCPRC when administered to patients who have not yet received chemotherapy or in patients previously treated with docetaxel, and the activity may be augmented by combination with nivolumab. The additional mechanisms of anti-tumor activity provided by BMS-986218 compared to ipilumumab could provide greater benefit. Moreover, two Phase 2 studies, KEYNOTE-365 and CheckMate 9KD have suggested that addition of PD-1 blockade to docetaxel improves mPFS compared to historical data, providing further support for combining chemotherapy and immunotherapy in mCRPC.[35,34]

3.3.3 Overall Benefit/Risk Conclusion

In conclusion, treatment with BMS-986218 and nivolumab in combination with docetaxel in men with mCRPC is expected to be tolerable, and toxicities of the treatment are expected to be manageable and reversible upon dose reduction, treatment interruption, or discontinuation. IMAE-related toxicities may require use of immunosuppressive agents. For management algorithms for AEs related to immuno-oncology (I-O) agents, refer to Appendix 8. Together, the potential for 1) CTLA-4 blockade to induce long-term disease control and improve survival in a subset of patients as a monotherapy,[29] 2) better response to CTLA-4 blockade when combined with nivolumab,[37] 3) longer term disease control when immunotherapy is added to chemotherapy,[34,35] and 4) better anti-tumor activity and less relative toxicity with BMS-986218 compared to ipilimumab all support the likelihood of substantial benefit to patients when treated

with the combination of docetaxel with BMS-986218 or BMS-986218 plus nivolumab. The overall risk-benefit of the combination is deemed acceptable.

Lastly, due to the Probody design, BMS-986288 may have a better benefit/risk profile than BMS-986218. If emerging data from Study CA043-001 support its potential, the Sponsor may elect to incorporate BMS-986288 into the CA022-009 study design via future protocol amendment.

Detailed information about the known and expected benefits and risks and reasonably anticipated AEs of BMS-986218, BMS-986288, and nivolumab may be found in their respective IBs.[43,45,45] Similar information is provided for docetaxel in the associated Patient Information Leaflet, USPI, country-specific label, Development Safety Update Report, or SmPC.[41,42]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	**Primary**
• To assess the safety, tolerability, and DLTs of docetaxel in combination with BMS-986218 or in combination with BMS-986218 plus nivolumab in participants with mCRPC (**Part 1**)	• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, TRAEs, AEs leading to discontinuation, and deaths
• To compare the rPFS in mCRPC participants treated with docetaxel and either docetaxel in combination with BMS-986218 or docetaxel in combination with BMS-986218 and nivolumab (**Part 2**)	• rPFS for randomized participants is the time between randomization date and the first date of documented radiographic progression, or death due to any cause, whichever occurs first. The radiographic progression will be assessed by blinded independent central review (BICR) per PCWG3
Secondary	**Secondary**
• To assess the antitumor activity of the combination of docetaxel with BMS-986218 or BMS-986218 and nivolumab in mCRPC participants, based on ORR, TTR, and DOR (**Part 2**)	• Objective response rate per PCWG3 (ORR-PCWG3) is the proportion of participants who have a confirmed complete or partial best overall response (BOR) per PCWG3 among randomized participants who have measurable disease at baseline. The BOR is defined as the best response designation, as determined by the BICR, recorded between the date of randomization and the date of objectively documented radiographic progression, or last tumor measurement, whichever occurs first • Time to response per PCWG3 (TTR-PCWG3) is the time from randomization date to the date of the first documented CR or PR per PCWG3, as determined by BICR • Duration of response per PCWG3 (DOR-PCWG3) is the time between the date of first response (CR/PR per PCWG3) to the date of first documented radiographic progression per PCWG3 (as determined by BICR), or death due to any cause
• To assess PSA response rate (PSA-RR) and time to PSA progression (TTP-PSA; limited to participants with measurable PSA [defined as ≥ 2 ng/ml] at baseline) (**Part 2**)	• PSA-RR is the proportion of randomized participants with a 50% or greater decrease in PSA from baseline to any post-baseline PSA result. A second consecutive value obtained 3 or more weeks later is required to confirm the PSA response • TTP-PSA is the time between randomization date to the date of PSA progression per PCWG3 in randomized participants
• To assess overall survival (OS) (**Part 2**)	• OS for all randomized participants is the time between randomization date and the date of death from any cause
• To characterize safety of BMS-986218 in combination with docetaxel, and with nivolumab and docetaxel in Part 2	• Overall safety and tolerability will be measured by the incidence of AEs, TRAEs, SAEs, AEs leading to discontinuation, and deaths

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Exploratory	**Exploratory**
• To characterize the PK of BMS-986218 when administered in combination with docetaxel only or in combination with docetaxel and nivolumab	• Summary of PK parameters of BMS-986218
• To characterize the immunogenicity of BMS-986218 when administered in combination with docetaxel only or in combination with docetaxel and nivolumab	• Summary of ADA incidence to BMS-986218
• To characterize the PK of nivolumab when administered in combination with docetaxel and BMS-986218	• Summary of PK parameters of nivolumab
• To characterize the immunogenicity of nivolumab when administered in combination with docetaxel and BMS-986218	• Summary of ADA incidence to nivolumab
• To estimate the time to initiation of subsequent systemic therapy (TT-SST)	• TT-SST is the time from treatment assignment (Part 1) or randomization date (Part 2) to the start of subsequent systemic therapy, including hormonal therapy (excluding continued ADT with GnRH agonist/antagonist), chemotherapy, immunotherapy, or investigational therapy
• To investigate the time to first symptomatic skeletal events (TT-SSEs)	• TT-SSE is the time between treatment assignment (Part 1) or randomization (Part 2) and the date of first symptomatic fracture, radiation or surgery to bone, or spinal cord compression
• To evaluate the change in health-related quality of life domains (**Part 2 only**)	• Change in baseline mean scores (total, subscale and symptoms scores) as assessed by EORTC QLQ-C30
• To evaluate the change in perceptions of bothersomeness in treatment-related symptoms (**Part 2 only**)	• Proportion of participants endorsing each response category of the single item FACIT GP5 at baseline and post-baseline administration
• To explore measures of clinical activity in participants in Part 1	• Based on ORR, TTR and DOR
• To explore measures of clinical activity in participants receiving the crossover treatment (Arm 2d in **Part 2**), based on ORR and PSA-RR	• ORR and PSA-RR based on clinical activity after initiation of crossover treatment
• To explore the time to and duration of PSA response	• Time to PSA response (TTR-PSA) is defined for PSA responders as the time from treatment assignment (Part 1) or randomization date (Part 2) to the date of the first PSA response. Duration of PSA response (DOR-PSA) is defined for PSA responders as the time between the date of first confirmed PSA response and the date of PSA progression

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To explore pharmacodynamic biomarkers in blood (cytokines, circulating immune subsets) and tumor (immune cell subsets in tumor microenvironment) and explore the association between baseline and other markers with response following Part 1 and Part 2 treatment	• Summary measures for key baseline blood and tumor biomarkers and change (or % change) from baseline and measure of association of anti-tumor response and pharmacodynamic markers
• To assess the impact of SARS-CoV-2 serologic status on participants with mCRPC who are receiving study intervention(s)	• Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG), from serum samples collected at baseline and specified timepoints
• To explore the potential association of ctDNA (HRD, DDR and TMB) in peripheral blood with anti-tumor activity prior to treatment and following administration of docetaxel alone or in combination with BMS-986218 or BMS-986218 plus nivolumab	• Summary measures of anti-tumor activity by pre-treatment level of ctDNA, measure of association of anti-tumor activity and change (or % change) from baseline with ctDNA

Abbreviations: ADA, anti-drug antibody; ADT, androgen deprivation therapy; AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CR, complete response; ctDNA, circulating tumor DNA; DNA, deoxyribonucleic acid; DDR, DNA damage repair; DLT, dose-limiting toxicity; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACIT GP5, Functional Assessment of Chronic Illness Therapy General Physical Item 5; GnRH, gonadotropin-releasing hormone; HRD, homologous recombination deficiency; IgG, immunoglobulin G; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; PK, pharmacokinetic; PR, partial response; PSA, prostate-specific antigen; PSA-RR, PSA response rate; rPFS, radiographic progression-free survival; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMB, tumor mutational burden; TRAE, treatment-related adverse event; TTP-PSA, time to PSA progression; TTR, time to response; TTR-PSA, time to PSA response; TT-SSE, time to first symptomatic skeletal event; TT-SST, time to initiation of subsequent systemic therapy.

5 STUDY DESIGN

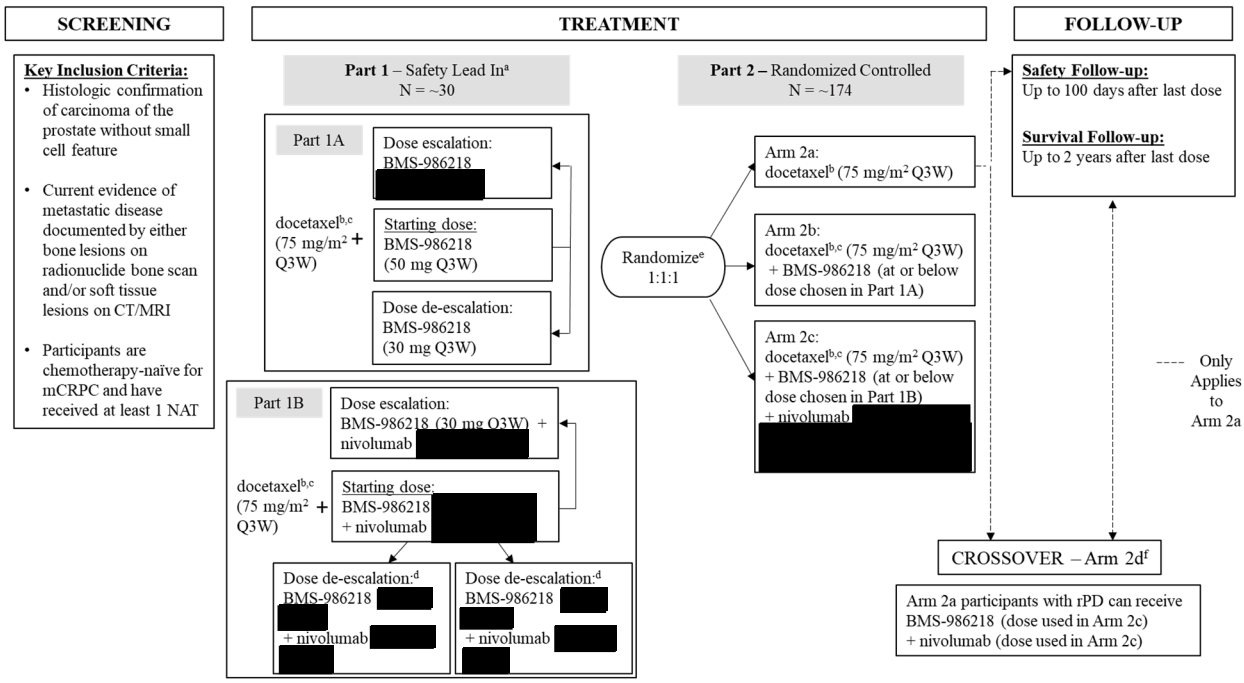
5.1 Overall Design

This multi-center, randomized, controlled, open-label, Phase 2 study evaluates docetaxel alone, in combination with BMS-986218, or in combination with BMS-986218 plus nivolumab in men who have mCRPC that progressed after NAT and have not received chemotherapy for mCRPC.

The study will be carried out in 2 parts: Part 1, a safety lead-in portion, and Part 2, a randomized, controlled portion. All participants will complete up to 3 study periods: screening (up to 28 days), treatment (up to 2 calendar years from first dose of study treatment regardless of treatment delays [21 days/cycle]), and follow-up. The Follow-up Period includes Safety Follow-up (comprising 3 visits over about 100 days) and Survival Follow-up (up to 2 years from the last dose of study treatment) periods. The maximum duration of study participation will be approximately 4 years (up to 28 days of screening, treatment of up to 2 years, and follow-up of up to 2 years). Images will be submitted to a central imaging vendor and will undergo Blinded Independent Central Review (BICR). Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA022009 Imaging Manual provided by the central imaging vendor.

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

Figure 5.1-1: Study Design Schema



Abbreviations: CT, computed tomography; DLT, dose-limiting toxicity; I-O, immuno-oncology; mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging; N, number of participants; NAT, novel antiandrogen therapy; Q3W, every 3 weeks; rPD, radiographic progressive disease; Y/N, yes/no.

[a] The DLT evaluation period will be 42 days (6 weeks) starting on Cycle 1 Day 1 for Part 1A and Part 1B.

[b] Administer docetaxel for a maximum of 10 cycles.

[c] For participants who are also receiving BMS-986218 or BMS-986218 and nivolumab, treatment with these I-O agents may continue beyond 10 cycles, up to 2 years (until disease progression, unacceptable toxicity, or withdrawal of consent).

[d] In Part 1B, BMS-986218 or nivolumab may be dose reduced based on safety data.

[e] In Part 2, randomization to 1 of 3 treatment arms will be stratified by measurable disease (Y/N).

[f] See Section 5.1.2 for details regarding optional crossover treatment (Arm 2d) for participants randomized to Part 2 Arm 2a, including maximum duration of treatments.

Physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory evaluations will be performed at selected times throughout the dosing interval (see Section 2, Schedule of Activities). Participants will be closely monitored for AEs throughout the study. Blood will be collected according to Section 9.5 for PK analysis.

5.1.1 Screening Period

The screening period will be up to 28 days. Informed consent will be obtained prior to any study-specific procedures. All participants (Part 1 and Part 2) being screened will be evaluated based on inclusion and exclusion criteria (Section 6.1 and Section 6.2) and will be enrolled using an Interactive Response Technology (IRT) system (Section 7.2).

Participants for Part 2 will be randomized to 1 of 3 treatment arms and will be stratified according to measurable disease status which will be assessed by investigator based on the tumor assessment performed during screening (Prostate Cancer Working Group 3 [PCWG3]; refer to Appendix 5).

Tumor tissue must be obtained and submitted to central laboratory prior to treatment assignment (Part 1) or randomization (Part 2) for participants with any soft tissue lesion that is suspected to represent metastatic disease based on local review of imaging and is considered accessible for biopsy by an interventional radiologist (or other appropriate specialist). Lymph nodes must measure at least 1 cm in diameter along the short axis in order to be considered for biopsy. See Section 6.1 (Inclusion Criteria) and Section 9.8 (Biomarkers) for specifications.

For participants who meet the above criteria, a pre-treatment, on-treatment, and on-progression biopsy are required if medically feasible (tumor sites that can be biopsied with acceptable clinical risk). Baseline tumor tissue is not mandatory for participants with bone metastasis only.

Participants who have met all eligibility criteria will be enrolled to receive treatment in Part 1 or Part 2 as applicable.

5.1.2 Treatment Period

The treatment period for BMS-986218 and/or nivolumab will last for up to 2 calendar years from first dose of study treatment and up to a maximum of 10 doses for docetaxel regardless of treatment delays (21 days/cycle). In addition to dosing visits on Day 1 of each cycle, there are also non-dosing visits on Days 8 and 15 in Cycles 1 and 4 and Day 15 in Cycle 2 f[redacted] biomarkers assessments (see Section 9.5 and Section 9.8).

Part 1A will evaluate the safety and tolerability of BMS-986218 in combination with docetaxel. The dose-limiting toxicity (DLT) evaluation period will be 42 days (6 weeks) starting on Cycle 1 Day 1 for Part 1A and Part 1B. The DLT evaluation during this safety lead-in, including potential decision to escalate or to de-escalate the BMS-986218 dose level, will be guided by the Bayesian Optimal Interval (BOIN) design framework (refer to Appendix 9) with a target DLT rate of 30%.[51] In Part 1B, there is also a potential to de-escalate the nivolumab dose level [redacted]. The target DLT in Part 1A was selected based on an observed DLT rate of 2/6 = 33% for BMS-986218 monotherapy at the [redacted] dosing in CA022001, estimated by the basic linear ranking model (BLRM) design and the MTD not reached with 2 dose levels higher being evaluated. For Part 1B, the observed DLT rate was 1/9 = 11% following treatment with nivolumab [redacted] + BMS-986218 [redacted] in the same study (CA022001). In addition, in Study CA2099KD in participants treated with docetaxel with nivolumab, there was a 14.3% reported frequency of treatment discontinuations due to Grade 3-4 TRAEs, with the most frequent TRAEs (any grade) leading to discontinuation being pneumonitis (7.1%), fatigue (6.0%), peripheral neuropathy (6.0%), and pneumonia (3.6%).

The Part 1A decisions for escalation, de-escalation, or continuing evaluating at the same dose level, will be guided by the BOIN escalation design (Table 5.1.2-1). Approximately 12 DLT-evaluable participants are expected to be treated, depending on the number of dose levels and the number of observed DLTs. Dose escalation/de-escalation decisions or decision to continue enrollment at the current dose will be made by the Sponsor in collaboration with investigators and take into

consideration all available safety and, if available, PK and pharmacodynamic data. Participants will enroll in cohorts of 3 to 4 initially. After the first 3 to 6 participants are evaluated, additional cohorts of 3 to 6 participants may be enrolled, as needed, with no more than 12 participants at a specific dose level. Once at least 6 participants have cleared the DLT observation period at a tolerable dose level in Part 1A, participants will be enrolled in Part 1B to assess safety and tolerability of the combination of BMS-986218 + docetaxel + nivolumab, starting at a lower BMS-986218 dose level than in Part 1A. Additional participants may be enrolled in Part 1A at this dose or a higher dose in order to continue to assess safety in this combination.

Table 5.1.2-1: Safety Lead-in Evaluation Guidance Based on BOIN Design

Actions Based on Number of DLTs Observed	Number of DLT-evaluable Participants Treated at Current Dose									
	3	**4**	**5**	**6**[a]	**7**	**8**	**9**	**10**	**11**	**12**
Escalate Dose[b] if # of DLTs ≤	0	0	1	1	1	1	2	2	2	2
Stay[c] if # of DLTs =	1	1	NA	2	2	2	3	3	3	3,4
De-escalate[d] if # of DLTs ≥	2	2	2	3	3	3	4	4	4	5
De-escalate and Eliminate[e] from Evaluation if # of DLTs ≥	3	3	4	4	5	5	5	6	6	7

Abbreviations: BOIN, Bayesian Optimal Interval; DLT, dose-limiting toxicity; NA, not applicable (for decision).

[a] A minimum of 6 DLT-evaluable participants will be required to meet acceptable DLT criteria for a dose level to be selected for Part 2.

[b] "Escalate" indicates that a higher dose level may be evaluated.

[c] "Stay" indicates that more participants need to be treated to determine tolerability.

[d] "De-escalate" indicates that a lower dose level needs to be evaluated.

[e] Such dose level is excessively non-tolerable and re-escalation is not allowed after de-escalation. A lower dose level will be evaluated.

Treatment in Part 1B may be initiated in a staggered manner relative to the BMS-986218 + docetaxel escalation (Part 1A). Specifically, Part 1B can be initiated upon the evaluation of a sufficient number of participants at a dose level in Part 1A who have cleared the DLT requirements (eg, 6 evaluable participants with 0 or 1 DLT), after which dose evaluation in Part 1A and Part 1B may proceed in parallel. At no point will the dose of BMS-986218 administered in combination with nivolumab and docetaxel in Part 1B exceed the highest dose determined to be tolerated in Part 1A.

Part 1B will also use a BOIN design framework for the evaluation of BMS-986218 tolerability in combination with docetaxel and nivolumab. Approximately 12 to 18 DLT-evaluable participants are expected to be treated if 2 or more dose-level combinations are evaluated in this part. Initially, 3 to 4 participants will be treated at the starting dose and subsequent decisions will be based on the BOIN design framework as shown in Table 5.1.2-1 above, similar to Part 1A. If needed, based

on the number of DLTs, additional participants in groups of 3 to 6 participants may be enrolled at the same dose level, or otherwise a lower dose level may be evaluated.

If de-escalation is necessary based on the number of toxicities, a lower combination dose level will be evaluated. The specific dose level to be administered in combination will be determined based on the nature of the DLTs and will be either: 1) a lower dose of BMS-986218 in combination with the same dose levels of nivolumab and docetaxel or 2) a lower dose level of nivolumab [redacted] in combination with the same dose levels of BMS-986218 and docetaxel.

Once a tolerable dose has been determined for BMS-986218 in combination with docetaxel in Part 1A and for BMS-986218 in combination with docetaxel + nivolumab in Part 1B in at least 6 evaluable participants, the randomized Part 2 of the study will open for enrollment. In Part 2, randomization 1:1:1 to 1 of 3 treatment arms will be stratified according to the following baseline factor:

- Measurable disease (Y/N): Measurable disease status will be assessed by investigator based on the tumor assessment performed during screening (RECIST v1.1).

Optional Crossover Treatment (Arm 2d) for Participants Randomized to Part 2 Arm 2a:

Participants treated in Arm 2a who demonstrate radiographic progressive disease (rPD) while on treatment (during active treatment with docetaxel) or after treatment (while in Safety or Survival Follow-up) may be eligible to crossover to optional Arm 2d and receive treatment of BMS-986218 in combination with nivolumab (Q3W at the dose level chosen in Arm 2c). Further docetaxel treatment will not be administered in Arm 2d.

In order to qualify for crossover, radiographic progression per PCWG3 must be confirmed by BICR and the participant must meet all inclusion criteria and exclusion criteria specified in Section 6.1 and Section 6.2 (with the exception that prior treatment with docetaxel is allowed). The BMS medical monitor must approve crossover to Arm 2d.

At least a 3-week period from the last dose of docetaxel is required prior to the first dose of crossover treatment. Participants who are receiving treatment in Arm 2d should restart the Schedule of Activities (Section 2, Table 2-2) at Cycle 1 Day 1. The imaging tumor assessments performed at progression while on Arm 2a may serve as the new baseline by which to assess response during crossover and will be submitted to BICR.

The following assessments will not be repeated for crossover participants:

- Crossover participants in Arm 2d will not have any biomarkers samples drawn or tumor biopsies performed with the exception of anti-severe acute respiratory syndrome coronavirus 2 (anti-SARS-CoV-2) serology, which should follow Table 9.8-1.

In Arm 2d, BMS-986218 in combination with nivolumab (dose chosen in Arm 2c Q3W) is administered until disease progression, unacceptable toxicity, or withdrawal of consent, and may continue for a maximum of 2 calendar years from Cycle 1 Day 1 (Arm 2a) regardless of treatment delays (for participants who crossover during active treatment with docetaxel) or until the study

ends, whichever occurs first. For participants who crossover after treatment (while in Safety or Survival Follow-up), BMS-986218 in combination with nivolumab may continue for up to 1 calendar year from the start of crossover treatment, or for a maximum of 2 calendar years from Cycle 1 Day 1 (Arm 2a) regardless of treatment delays (whichever is longer), or until the study ends, whichever occurs first. Treatment for crossover participants beyond radiographic progression per PCWG3 criteria is permitted if the participant has investigator-assessed clinical benefit and is tolerating the treatment, as specified in Section 8.1.2.

Upon discontinuation of crossover treatment, participants will enter or re-enter the Follow-Up Period (Safety Follow-up and Survival Follow-up). Participants who crossover during the treatment portion (during active treatment with docetaxel) of the study should proceed with follow-up guidelines in Section 5.1.3 and Table 2-3.

Participants who crossover after discontinuing docetaxel treatment and while in follow-up should only be followed for a maximum of 1 year from the last dose of crossover treatment.

For participants re-entering the Follow-up Period, the following guidelines apply:

- The 3 Safety Follow-up visits will be conducted (30, 60, and 100 days ± 7 days [see Table 2-3]).
- Survival Follow-up visits to occur every 12 weeks (± 2 weeks) from the last dose of crossover intervention and will be performed in parallel to safety follow-up (for a maximum of 1 year from the last dose of crossover treatment) or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. Survival visits may be conducted in clinic or by telephone (see Table 2-3).
- Participants who have discontinued treatment without having BICR-assessed disease progression (during the crossover) will continue to have radiologic and clinical tumor assessments after crossover treatment discontinuation for up to a maximum of 1 calendar year or until rPD, whichever occurs first.

5.1.3 Follow-up Period

The Follow-up Period includes Safety Follow-up (comprising 3 visits over about 100 days) and Survival Follow-up (up to 2 years from the last dose of study treatment) periods.

Participants in Arm 2d who crossover after discontinuing docetaxel treatment and while in follow-up should only be followed for a maximum of 1 year from the last dose of crossover treatment.

5.1.3.1 Safety Follow-up

Upon completion of study intervention or early termination, all participants will enter a safety follow-up period. All participants will be evaluated for any new AEs for at least 100 days after the last dose of study intervention. Participants who have discontinued treatment without having BICR-assessed disease progression will continue to have radiologic and clinical tumor assessments after treatment discontinuation for up to 2 years after end of treatment (EOT) or until rPD, whichever occurs first.

Participants in Arm 2d who crossover after discontinuing docetaxel treatment and who re-enter the follow-up period will repeat the 100-day Safety Follow-up visits (Day 30, 60, and 100). Participants who have discontinued treatment without having BICR-assessed disease progression (during the crossover), will continue to have radiologic and clinical tumor assessments after crossover treatment discontinuation for up to a maximum of 1 calendar year or until rPD, whichever occurs first.

5.1.3.2 Survival Follow-up

In parallel with the safety follow-up period, participants will enter the survival follow-up period. Participants will be followed by phone contact or clinic visit every 12 weeks (± 2 weeks) from the last dose of study intervention for a period of 2 years or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first.

Participants in Arm 2d who crossover after discontinuing docetaxel treatment and who re-enter the Survival Follow-up period, the visits will occur every 12 weeks (± 2 weeks) from the last dose of crossover intervention and will be performed in parallel to Safety Follow-up (for a maximum of 1 year from the last dose of crossover treatment) or until death, loss to follow-up, withdrawal of consent, or conclusion of the study, whichever comes first. Survival visits may be conducted in clinic or by telephone.

The Sponsor may decide to terminate the Survival Follow-up period once all participants have completed the Safety Follow-up period.

5.1.4 Data Monitoring Committee and Other Committees

5.1.4.1 Safety Monitoring for Part 1

BMS has developed a multi-layered process to ensure safety monitoring through close collaboration of study site investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led Safety Management Team (SMT). This collaborative process plus a DMC for Part 2, constitutes the safety monitoring plan for the study.

To support safety oversight, BMS has established ongoing processes for collection, review, analysis, and submission of individual AE reports and analyses. Because this is an open-label study, WWPS representatives, the BMS medical monitor, and the investigators will have access to individual participants safety data necessary for safety evaluation.

BMS WWPS is an internal group that operates independently from the clinical team to monitor safety across all BMS protocols. Within BMS, an SMT is established for investigational therapies under clinical development, and a member of WWPS chairs this team. In addition, signal detection is performed at least monthly and ad hoc throughout the study by the SMT, composed, at a minimum, of the WWPS medical safety assessment physician (Chair of the SMT), the Clinical Development Lead and/or Medical Affairs Lead, Global Regulatory Lead, and Pharmacovigilance Scientist. Furthermore, the SMT routinely monitors for actual or potential issues related to participant safety that could result in a change in the medical risk-benefit balance associated with the use of study treatment(s).

5.1.4.2 Data Monitoring Committee

A DMC will be used for Part 2 of this study. The DMC charter will describe the procedures related to the committee operations in greater detail.

The independent DMC will be utilized to provide general oversight and safety evaluations during the randomized portion (Part 2) of the study. In addition, during the randomized Part 2 of the study, a continuous safety monitoring framework will be implemented by the Sponsor to monitor for adverse events (see Section 10.4.5.1).

The independent DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of participants enrolled in this study. The independent DMC will be charged with assessing such actions in light of an acceptable benefit-risk profile for nivolumab, BMS-986218, and docetaxel. The independent DMC will act in an advisory capacity to BMS and will monitor participant safety data of the study. BMS will have responsibility for the overall conduct of the study, including managing the communication of study data. BMS will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required. The DMC charter will describe the procedures related to the committee operations in greater detail. The DMC will meet on a regular basis, which will be defined in the charter, and on an ad hoc basis as necessary throughout study conduct

Decisions related to the continuation or any changes to study conduct based on safety, toxicity, and benefit-risk will be solely the responsibility of BMS and will take account of the totality of the data available and in consideration of any DMC recommendations.

5.1.4.3 Blinded Independent Central Review

A Blinded Independent Central Review (BICR) will also be used for this study to review computed tomography (CT) and bone scans, including the primary study objective. A BICR is recommended by regulatory agencies in situations where clinical site image interpretation is variable and results of image measurements are important for eligibility determination, safety, and/or efficacy endpoints. Specifically, BICR review of scans may mitigate bias regarding endpoint assessment due to the subjectivity involved in lesion measurement and interpretation of rPFS. Sites must submit all images to BICR on a continuing basis. Treatment decisions for the individual participants will be based on investigator assessment and not the BICR results.

Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA022009 Imaging Manual provided by the central imaging vendor.

5.2 Number of Participants

Approximately 12 participants may be treated in the safety lead-in Part 1A and approximately 12 to 18 participants in Part 1B, with a possible total of 30 DLT-evaluable participants, if 2 or more dose levels are evaluated. In addition, approximately 174 participants are expected to be

randomized across 3 treatment arms in Part 2 of the study, to account for 21% dropout rate prior to radiographic progression across the 3 arms.

5.3 End of Study Definition

The start of the trial is defined as the first participant first visit.

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

Study completion is defined as the final date on which data for the primary endpoint were or are expected to be collected, if this is not the same.

A participant is considered to have completed the study if he/she has completed the last visit or the last procedure shown in the Schedule of Activities.

5.4 Scientific Rationale for Study Design

BMS-986218 is being investigated in males with mCRPC, either in combination with docetaxel or in combination with docetaxel and nivolumab. The study design (Figure 5.1-1) includes the following:

- A 28-day screening period
- A treatment period that can last up to 2 calendar years for BMS-986218 (Q3W) and/or nivolumab [redacted], and up to a maximum of 10 doses for docetaxel (Q3W)
- Safety lead-in portion (Part 1; includes Part 1A and Part 1B)
- Randomized controlled portion (Part 2)
- Safety follow-up (100 days over 3 visits)
- Survival follow-up (up to 2 years after last dose)
- Optional crossover for participants in Arm 2a who demonstrate rPD

5.4.1 Rationale for Population

Men with mCRPC who have progressed after NAT(s) and have not received chemotherapy for mCRPC will be included in this study. Although many patients without symptoms are not treated with chemotherapy, the survival benefit reported with docetaxel applies to those with or without symptoms. National Comprehensive Cancer Network (NCCN) guidelines recommend docetaxel (category 1) as the preferred first line (1L) chemotherapy in men with symptomatic mCRPC and in patients with signs of rapid progression or visceral metastases despite lack of symptoms.[52] Docetaxel also has a category 1 recommendation in mCRPC following enzalutamide/abiraterone therapy. Clinical data from a number of small retrospective cohort studies suggests that once participants with mCRPC progress on NAT therapy, response rates to abiraterone after enzalutamide and conversely enzalutamide after abiraterone are low and no robust clinical criteria exist to select one drug rather than the other.[49] Given that abiraterone and enzalutamide are the preferred 1L option for men with asymptomatic, chemotherapy-naïve mCRPC and the recent approvals of NATs in mCSPC and nmCRPC settings, it is expected that most patients will have received one NAT prior to consideration of docetaxel for treatment of mCRPC. Therefore, the

current study will include chemotherapy-naïve mCRPC participants who have been previously treated with NAT.

5.4.2 Rationale for Docetaxel and BMS-986218 or BMS-986218 plus Nivolumab

Docetaxel, a second-generation semisynthetic taxane analog, became the first chemotherapeutic agent to show an OS benefit in mCRPC in 2 randomized controlled clinical trials (TAX 327 and SWOG 99-16), and was approved in combination with prednisone for this indication in the US in 2004.[1,2] In addition to inducing direct tumor cell cytotoxicity, it is hypothesized that chemotherapy may modify the immune response to tumors by influencing multiple mechanisms, including inducing immunogenic cell death, stimulating release of tumor antigens, and/or depleting immuno-suppressive Tregs.

CTLA-4 blockade has demonstrated clinical activity against mCPRC, but it is not yet a standard treatment. Two Phase 3 studies demonstrated that ipilimumab (10 mg/kg) improved PFS when administered either prior (CA184095) or following (CA184043) chemotherapy, but failed to show a statistically significant survival benefit.[28,29] After longer follow-up, retrospective analysis of CA184043, which specifically compared radiotherapy to radiotherapy plus ipilimumab, showed ipilimumab significantly improved landmark OS at 2, 3, 4, and 5 years. PD-(L)1 directed therapy has not shown meaningful clinical activity against mCRPC in monotherapy studies. Prostate cancer tumor cells have been shown to have low expression of PD-L1, but its expression is up-regulated in response to inflammatory cytokines, induced by CTLA-4.[36] PD-1 blockade therefore may augment clinical activity when administered in combinations. In support, ~25% of participants with mCRPC, that were not previously treated with chemotherapy, demonstrated an objective response to ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg). Moreover, addition of nivolumab or pembrolizumab to docetaxel is associated with a longer-than-expected PFS compared with historical studies of docetaxel alone, serving as the rationale for 2 ongoing Phase 3 studies comparing docetaxel to docetaxel plus PD-1 blockade.[1,2,34,35] The additional mechanisms of anti-tumor activity of BMS-986218 compared to ipilimumab, which may improve its anti-tumor activity relative to toxicity, and its use in combinations with other immune-modulating agents, have the potential to meaningfully improve outcomes in mCRPC.

5.4.2.1 Rationale for Docetaxel and BMS-986288 or BMS-986288 plus Nivolumab

BMS-986288 is not evaluated in the current CA022-009 study design but may be introduced via future protocol amendment. BMS-986288 is a non-fucosylated anti-CTLA-4 agent identical to BMS-986218, but with an additional Probody element (see Section 3.2.2). BMS-986288 has the same enhanced Fc engagement as BMS-986218, and the Probody aspect may further improve the benefit/risk profile, as compared to BMS-986218, by enabling selective CTLA-4 blockade in the tumor microenvironment. If emerging clinical data support improved clinical utility, the Sponsor may amend CA022-009 to test docetaxel and BMS-986288 or docetaxel and BMS-986288 plus nivolumab.

5.4.3 Rationale for Two Year Duration of Treatment

The optimal duration of immunotherapy is an important question and continues to be investigated. Clinical trials across different tumor types in the nivolumab and ipilimumab development program indicate that most of the responses occur early, with a median time to response of 2 to 4 months, and emerging data suggests that benefit can be maintained in the absence of continued treatment. A retrospective pooled analysis of two melanoma studies suggest the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment.[53] Furthermore, a limited duration of ipilimumab, including only 4 induction doses, resulted in long term survival in patients with metastatic melanoma, with a sustained plateau in survival starting around 2 years after the start of treatment.[54]

Accumulating data suggest that 2 years of PD-1 checkpoint inhibitor treatment may be sufficient for long term benefit. CA209003, a dose-escalation cohort expansion trial evaluating the safety and clinical activity of nivolumab in patients with previously treated advanced solid tumors (including 129 patients with NSCLC), specified a maximum treatment duration of 2 years. Among 16 patients with non-small cell lung cancer (NSCLC) who discontinued nivolumab after completing 2 years of treatment, 12 patients were alive >5 years and remained progression-free without any subsequent therapy. In the CA209003 NSCLC cohort, the OS curve begins to plateau after 2 years, with an OS rate of 25% at 2 years and 18% at 3 years.[55] These survival outcomes are similar to Phase 3 studies in previously treated NSCLC, in which nivolumab treatment was continued until progression or unacceptable toxicity (2 year OS rates of 23% and 29%, and 3 year OS rates of 16%-18% for squamous and non-squamous NSCLC respectively).[56]

Taken together, these data suggest that treatment beyond 2 years is unlikely to confer additional clinically meaningful benefit and that the risk of progression after discontinuing treatment at 2 years is low.

In contrast, a shorter duration of nivolumab of only 1 year was associated with increased risk of progression in previously treated patients with NSCLC, suggesting that treatment beyond 1 year is likely needed. In CA209153, patients with previously treated advanced NSCLC who completed 1 year of nivolumab therapy were randomized to either continue or stop treatment, with the option of retreatment upon progression. Among 163 patients still on treatment at 1 year and without progression, those who were randomized to continue nivolumab had significant improvement in PFS compared to those who were randomized to stop treatment, with median PFS (post-randomization) not reached vs 10.3 months, respectively; hazard ratio (HR)=0.42 (95% CI, 0.25 to 0.71). With a median follow-up of 14.9 months post-randomization, there also was a trend for patients on continued treatment to live longer (OS HR = 0.63 [95% CI: 0.33, 1.20]). Of note, the PFS curves in both groups plateau approximately 1 year after randomization (ie, 2 years after treatment initiation), suggesting that there may be minimal benefit in extending treatment beyond a total of 2 years.[57]

Collectively, these data suggest that there is minimal if any benefit derived from continuing I-O treatment beyond two years in advanced tumors. Even though immunotherapy is well tolerated, patients will be at risk for additional toxicity with longer-term treatment. Therefore, in this study,

BMS-986218 and nivolumab will be given for a maximum of 2 years from the start of study treatment.

5.4.4 Rationale for Treatment Beyond Progression

Immunotherapeutic agents produce atypical clinical response patterns that are not usually observed with conventional chemotherapy. Accumulating clinical evidence indicates that some participants treated with immune system stimulating agents may develop disease progression by the conventional response criteria before demonstrating clinical objective responses and/or stable disease (SD). Two distinct non-conventional patterns have been reported: 1) a reduction in target tumor burden despite the appearance of new lesion(s), and 2) a transient increase in target tumor burden in an initial phase, followed by subsequent tumor shrinkage. These phenomena were observed in the BMS Phase 2 study (CA209003) of nivolumab in patients with solid tumors. Two hypotheses potentially explain these phenomena. First, enhanced inflammation within tumors could lead to an increase in tumor size, which would appear as enlarged index lesions and as newly-visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease, leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, it is important to avoid premature discontinuation of the study treatment that might induce a non-conventional response pattern in some patients.

5.4.5 Rationale for Open-label Design

This study will use an open-label design to ensure that immune-related toxicities in participants receiving immunotherapy are promptly identified and managed. Scans will be submitted to an imaging core laboratory for review by BICR. BICR review of scans may mitigate bias regarding endpoint assessment due to the subjectivity involved in lesion measurement and interpretation of rPFS. Treatment decisions for the study will be based on investigator assessment and not the BICR results.

5.5 Justification for Dose

5.5.1 BMS-986218

CA022009 is the first study combining BMS-986218 or BMS-986218 plus nivolumab with chemotherapy. Study CA022001 is an ongoing Phase 1/2a, FIH study that has evaluated BMS-986218 as monotherapy and in combination with nivolumab in multiple solid tumor

[redacted]

preliminary as the study remains ongoing.

As a monotherapy, the MTD for BMS-986218 has not yet been defined and the most common AEs are consistent with those observed with ipilimumab. Preliminary analysis supports

[redacted]

[redacted] Similar data was collected from CA184169, which evaluated ipilimumab at 3 mg/kg and 10 mg/kg in participants with melanoma, enabling estimation of activity equivalency for BMS-986218 based on [redacted]

The proposed starting dose of BMS-986218 (50 mg Q3W, [redacted]) in combination with docetaxel is at least 2 dose levels below the maximum administered dose (MAD) of [redacted] in the CA022001 study (study is ongoing and may continue to dose escalate). Based on preliminary analysis, median duration of treatment [redacted] ipilimumab, where clinical anti-tumor activity in mCRPC was demonstrated. In the CA022009 study, BMS-986218 will be administered at [redacted] dose of 50 mg Q3W [redacted] will be based on the totality of the data available at that time including safety data as well as efficacy and biomarker data from the CA022001 study BMS-986218 monotherapy treatments and the present study.

Flat dose nivolumab [redacted] has been established to be tolerable in combination with docetaxel (see Section 5.5.2) and the tolerability of BMS-986218 in combination with docetaxel will be tested in Part 1A prior to initiating BMS-986218 + nivolumab + docetaxel therapy in Part 1B. In Part 1B, BMS-986218 will be initiated at a dose no higher [redacted] and at least 1 dose level below that, which was demonstrated to be tolerable in at least 6 participants in Part 1A. In CA022001, [redacted] in combination with flat dose nivolumab [redacted] has been administered to 15 participants with acceptable tolerability. Median duration of treatment based on a [redacted] in combination with nivolumab [redacted]. No participants remain on study treatment. [redacted]

[redacted] BMS-986218 dose evaluation in combination with [redacted] remains ongoing on the CA022001 study at doses above the proposed starting dose for Part 1B of the CA022009 study. A decision to dose escalate (to BMS-986218 30 mg Q3W) will be based on the totality of the data available at that time including safety data as well as efficacy and biomarker data from the CA022001 study evaluating BMS-986218 with nivolumab and the present study. The MAD of BMS-986218 dose in Part 1B will not exceed that given in Part 1A and may be lower. Similarly, the dose selected of BMS-986218 for Part 2 Arm 2c may be lower than that selected for Arm 2b. Lastly, the dose of BMS-986218 in combination with flat dose nivolumab and docetaxel will not exceed the equivalent of dose demonstrated to be tolerable in combination with nivolumab in the on-going CA022001 study.

5.5.2 Nivolumab

The nivolumab dose [redacted] was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types.

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, CRC and urothelial carcinoma and has been safely administered at doses [redacted]. Nivolumab monotherapy was originally approved as a body-weight based dose [redacted], and was updated to [redacted] or [redacted] in multiple indications.[58,59] Nivolumab [redacted] has recently been approved in malignant pleural mesothelioma as monotherapy, metastatic non-small cell lung cancer in combination with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy, and in gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma, in combination with fluoropyrimidine- and platinum-containing chemotherapy. Less frequent [redacted] and [redacted] dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens. Nivolumab [redacted] was accordingly administered in the CheckMate 9KD [redacted] which is administered every 3 weeks for the treatment of mCRPC.

The benefit-risk profiles of nivolumab [redacted] are predicted to be comparable to [redacted]. This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and exposure-response relationships across indications. Population PK (PPK) analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no clinically meaningful differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including [redacted]. The simulated average serum concentration at steady state [Cavgss] following administration of nivolumab [redacted] and [redacted] are predicted to be similar to those following administration of nivolumab [redacted] and nivolumab [redacted] administered to patients over a wide body weight range (34-180 kg) across tumor types.

Additional details on nivolumab posologies and risk-benefit can be found in the Investigator's Brochure.

5.5.3 Rationale for Duration of Treatment with Docetaxel

The duration of treatment for docetaxel should be based on the assessment of benefit and toxicities. In a pivotal trial establishing the survival advantage of docetaxel chemotherapy, participants received up to 10 cycles of treatment.[1] Administering more than 10 cycles of docetaxel has not demonstrated any further improvement in survival and is associated with more adverse effects.[60,61] Therefore, in the present study, docetaxel will be administered for a maximum of 10 cycles, or until disease progression, unacceptable toxicity, withdrawal of participant consent, or the end of the study, whichever occurs sooner. Please consult the current prescribing information for docetaxel for further details concerning administration.

5.6 Clinical Pharmacology Summary of BMS-986218

Preliminary PK analysis from the ongoing study CA022001 was based on available data as of 05-Jan-2021. Preliminary PK analysis showed the maximum observed concentration (Cmax) and the area under the concentration-time curve in 1 dosing interval (AUC[TAU]) of BMS-986218 in serum [redacted] as monotherapy treatment. [redacted] Full details on the clinical pharmacology aspects of BMS-986218 can be found in the Investigator's Brochure.

5.7 Clinical Pharmacology Summary of Nivolumab

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for both single-agent nivolumab and nivolumab with ipilimumab.

Nivolumab as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of 24.5% (47.6%) resulting in a geometric mean steady-state clearance (CLss) (CV%) of 8.2 mL/h (53.9%) in patients with metastatic tumors; the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was 3.7-fold. The exposure to nivolumab increases dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

Nivolumab with ipilimumab: When nivolumab 1 mg/kg was administered in combination with ipilimumab 3 mg/kg, the CL of nivolumab was increased by 29%, and the CL of ipilimumab was unchanged compared to nivolumab administered alone. When nivolumab 3 mg/kg was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab and ipilimumab were

unchanged. These results are unlikely to be clinically relevant given the flat dose-response observed between nivolumab and efficacy and safety.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m^2), or severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with HCC and in patients with other tumors with mild hepatic impairment (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) and in HCC patients with moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). No clinically important differences in the clearance of nivolumab were found between patients with mild/moderate hepatic impairment.

Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator's Brochure and product label.

Nivolumab [redacted] is approved in malignant pleural mesothelioma as monotherapy, metastatic non-small cell lung cancer in combination with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy, and in gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma, in combination with fluoropyrimidine- and platinum-containing chemotherapy. Nivolumab [redacted] dosing will be the starting dose used in this study (in Part 1B).

6 STUDY POPULATION

This study permits the re-enrollment of a participant that has discontinued the study as a pretreatment failure. If re-enrolled, the participant must be re-consented and meet all inclusion/exclusion criteria.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent form (ICF) 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 patient care.

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

2) Type of Participant and Target Disease Characteristics

a) Histologic confirmation of carcinoma of the prostate without small cell features. Diagnosis must be stated in a pathology report and confirmed by the investigator.

b) Current evidence of metastatic disease documented by either bone lesions on radionuclide bone scan and/or soft tissue lesions on CT/magnetic resonance imaging (MRI). Metastases may be in regional lymph nodes (N1 per American Joint Committee on Cancer [AJCC] staging criteria, 8th edition) and/or distant metastases (M1 per AJCC staging criteria, 8th edition).[62]

   i) Participants whose disease spread is limited to regional pelvic lymph nodes (N1) measuring at least 2 cm in short axis will be considered eligible.

c) Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.

d) Ongoing androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) agonist/antagonist or bilateral orchiectomy (ie, surgical or medical castration) confirmed by testosterone level ≤ 1.73 nmol/L (50 ng/dL) at the screening visit. Castrate levels of testosterone must be maintained by surgical or medical means (GnRH agonist/antagonist) throughout the conduct of the study. For participants who have not had an orchiectomy but maintained castrate levels of testosterone without ongoing medical therapy, GnRH agonist/antagonist must be reinitiated at least 4 weeks prior to first dose of study treatment and continued throughout the study on a standard dosing schedule.

e) Documented prostate cancer progression by 1 of the following Prostate Cancer Working Group 3 (PCWG3) criteria while castrate, within 6 months prior to screening, and without initiating a new intervening systemic prostate cancer therapy (other than GnRH agonist/antagonist) prior to screening:

   i) Prostate-specific antigen (PSA) progression defined by a minimum of 2 rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value at the screening visit should be ≥ 2 µg/L (2 ng/mL).

   ii) Radiographic disease progression in soft tissue based on PCWG3 criteria.

   iii) Radiographic disease progression in bone.

f) Participants are chemotherapy-naïve for mCRPC and have received at least 1 second-generation hormonal manipulations (also known as novel antiandrogen therapies [NAT], including but not limited to abiraterone acetate, enzalutamide, apalutamide, and darolutamide) in the recurrent non-metastatic setting and/or the metastatic setting. Participants must have progressed during treatment on an NAT or have documented intolerance to the drug (ie, unacceptable toxicity despite comprehensive supportive therapy). Prior docetaxel for metastatic castration-sensitive prostate cancer is allowed if ≥ 12 months have elapsed from last dose of docetaxel. Prior therapy with a PARP inhibitor (eg, olaparib, rucaparib) is also allowed. Prior radium 223 and ^{177}Lu-PSMA-617 treatment for prostate cancer is allowed.

g) Prior prostate cancer vaccine therapy (eg, sipuleucel-T), second-generation hormonal manipulations (eg, abiraterone acetate, enzalutamide, apalutamide, and darolutamide), antiandrogens (eg, flutamide), ketoconazole, and diethylstilbestrol or other estrogens are allowed if treatment was completed at least 28 days prior to start of study treatment. Note: bicalutamide or nilutamide must be discontinued at least 6 weeks prior to the start of study treatment.

h) Participants with a soft tissue lesion that is suspected to represent metastatic disease based on local review of imaging and is considered accessible for biopsy by an interventional radiologist (or other appropriate specialist), must provide tumor sample from a newly-obtained ("fresh") biopsy (obtained during screening, if there are tumor sites that can be biopsied with acceptable clinical risk). Lymph nodes must measure at least 1 cm in diameter along the short axis in order to be considered for biopsy. If the only site amenable to biopsy is also the only site of measurable disease, the investigator should prioritize maintaining a measurable target lesion (by RECIST v1.1) if there is a concern that the biopsy might impact tumor assessment.

A formalin-fixed paraffin-embedded (FFPE) tissue block (preferred) or a minimum of 20 unstained slides* of tumor tissue from core biopsy, punch biopsy, excisional biopsy or surgical specimen obtained during screening or prior to treatment assignment (Part 1)/randomization (Part 2) must be sent to the central laboratory. Fine needle aspirates or other cytology samples are not acceptable.

*If despite best efforts, a minimum of 20 slides is not obtainable, submission of fewer slides may be acceptable in some circumstances following discussion with Sponsor or designee.

Please refer to Section 9.8.4 for additional details on tumor tissue requirements.

3) Age of Participant

a) Participant must be male and ≥ 18 years of age or local age of majority at the time of signing the informed consent.

4) Reproductive Status

a) **Male Participants:** Males who are sexually active with women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception as defined in Appendix 4 and as described below.

i) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

ii) Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom during the intervention period and for at least 3 months after the last dose of study intervention.

iii) Female partners of males participating in the study should be advised to use highly effective methods of contraception during the intervention period and for at least 3 months after the last dose of study intervention in the male participant.

iv) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral), even if the participants have undergone a successful vasectomy, during the intervention period and for at least 3 months after the last dose of study intervention.

v) Male participants must refrain from donating sperm during the intervention period and for at least 3 months after the last dose of study intervention.

vi) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1) Medical Conditions

a) Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to treatment assignment in Part 1 or randomization in Part 2 (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before treatment assignment [Part 1] or randomization [Part 2] and the participant has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer, superficial bladder cancer, or other non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

b) Untreated central nervous system (CNS) metastases. Participants are eligible if CNS metastases have been treated and participants have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). In addition, participants must have been either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to treatment assignment (Part 1) or randomization (Part 2). Imaging performed within 28 days prior to treatment assignment (Part 1) or randomization (Part 2) must document radiographic stability of CNS lesions and be performed after completion of any CNS directed therapy.

c) Leptomeningeal metastases

d) Participants must have recovered from the effects of major surgery requiring general anesthesia or significant traumatic injury at least 14 days before start of study treatment.

e) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 or baseline before administration of study treatment. Participants with toxicities attributed to prior anti-cancer therapy that are not expected to resolve and result in long-lasting sequelae not anticipated to impact tolerance of study treatments (ie, hearing loss, Grade 2 erectile dysfunction etc.), are permitted to enroll as long as they meet all other eligibility criteria.

f) Participants who have ≥ Grade 2 peripheral neuropathy are excluded.

g) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

   i) Euthyroid participants with a history of Grave's disease (participants with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin [Ig] prior to the first dose of study treatment).

h) History of (non-infectious) pneumonitis or has current pneumonitis or a history of symptomatic chronic interstitial lung disease

i) Previous SARS-CoV-2 infection within 10 days for mild or asymptomatic infections or 20 days for severe/critical illness prior to Cycle 1 Day 1.

i) Acute symptoms must have resolved and based on investigator assessment in consultation with the medical monitor, there are no sequelae that would place the participant at a higher risk of receiving study treatment.

j) Altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent or completing quality of life questionnaire.

k) Active viral hepatitis, including the following:

i) Any positive test result for hepatitis B virus (HBV) indicating presence of virus, eg, hepatitis B surface antigen (HBsAg, Australia antigen) positive.

ii) Any positive test result for hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV-RNA).

(1) Participants with positive HCV antibody and an undetectable HCV RNA are eligible to enroll.

(2) Additional testing or substitute testing per institutional guidelines to rule out infection is permitted.

iii) History of resolved hepatitis A virus infection is not an exclusion criterion.

l) Known human immunodeficiency virus (HIV) positive with an AIDS defining opportunistic infection within the last year, or a current CD4 count < 350 cells/µL. Participants with HIV are eligible if:

i) They have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization/treatment assignment as clinically indicated while enrolled on study (see Section 7.7.2 for CYP3A4 restriction)

ii) They continue on ART as clinically indicated while enrolled on study

iii) CD4 counts and viral load are monitored per standard of care by a local health care provider.

NOTE: Testing for HIV must be performed at sites where mandated locally. HIV positive participants must be excluded where mandated locally (see Appendix 7).

m) Participants with serious or uncontrolled medical disorders that, in the opinion of the investigator, would impair the ability of the participant to receive protocol therapy or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea.

n) Psychiatric illness/social situations that would limit compliance with study requirements.

o) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of treatment assignment (Part 1) or randomization (Part 2). Inhaled or topical steroids (including ocular, intra-articular, and intranasal), and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

p) Participant has any condition, including, but not limited to, active or uncontrolled infection, the presence of laboratory abnormalities, history of congestive heart failure, unstable angina pectoris, or cardiac arrhythmia, which places the subject at unacceptable risk if he were to participate in the study.

q) Participants with superscan on Technetium-99m radionuclide bone scans are not eligible for the study. Superscan is defined as a bone scan which demonstrates markedly increased

skeletal radioisotope uptake relative to soft tissue in association with absence of faint renal activity (absent kidney sign).

2) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7 (Concomitant Therapy).

b) Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to first study treatment. Such medications are permitted if they are used as supportive care. Refer to Section 7.7.1 for prohibited therapies. As some herbal supplements may modulate CYP3A4, see Section 7.7.2 for CYP3A4 restrictions.

c) Treatment with any live/attenuated vaccine, including SARS-CoV-2 vaccine, within 30 days of first study treatment.

d) Previous SARS-CoV-2 vaccine within 14 days of Cycle 1 Day 1. For vaccines requiring more than 1 dose, the full series (eg, both doses of a 2-dose series) should be completed prior to Cycle 1 Day 1 when feasible and when a delay in Cycle 1 Day 1 would not put the study participant at risk.

e) Prior treatment for biochemically recurrent or metastatic prostate cancer with an anti-CTLA-4, anti-PD-(L)1, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. The prior use of such agents in the neoadjuvant setting is allowed.

f) Prior radiation therapy within 2 weeks prior to start of study treatment. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.

3) Physical and Laboratory Test Findings

a) White blood cells (WBCs) < 2000/µL

b) Neutrophils < 1500/µL

c) Platelets < 100×10^3/µL

d) Hemoglobin < 9.0 g/dL (blood transfusion within 2 weeks of screening labs is not allowed)

e) Serum creatinine > 1.5× upper limit of normal (ULN), unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockroft-Gault formula)

f) AST/ALT > 3.0× ULN OR AST and/or ALT > 1.5× ULN concomitant with alkaline phosphatase > 2.5× ULN in the absence of bone metastasis

g) Total bilirubin > 1.0× ULN (except participants with Gilbert's syndrome, if the T.bili is < 2× ULN and direct bilirubin is in the normal range)

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

b) History of hypersensitivity to docetaxel or polysorbate 80

c) History of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, hypothyroidism)

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)

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

c) Inability to comply with restrictions as listed in Section 6.3 (Lifestyle Restrictions).

d) Participation in another clinical trial concurrent with this study.

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

Participants receiving docetaxel should be advised to use appropriate sun protection due to the potential risk of photosensitivity which may cause sunburn with minimal sun exposure.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered in the study/included in the analysis population.

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, as applicable, 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 who has discontinued the study as a pretreatment failure (ie, participant has not been randomized/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 administration of study intervention is the value by which study inclusion will be assessed, because it represents the participant's most current clinical state.

Laboratory parameters and/or assessments that are included in Section 2 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.

Testing for asymptomatic SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction (RT-PCR) or viral antigen is not required. However, some participants may develop

suspected or confirmed symptomatic SARS-CoV-2 infection, or be discovered to have asymptomatic SARS-CoV-2 infection during the screening period. In such cases, participants may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive RT-PCR or viral antigen test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Acute symptoms (eg, cough, shortness of breath) have resolved and
- In the opinion of the investigator, there are no SARS-CoV-2 infection sequelae that may place the participant at a higher risk of receiving investigational treatment
- In the instance of a SARS-CoV-2 infection during screening, the screening period may be extended up to 4 additional weeks beyond the protocol-specified timeframe with MM approval.
- Any screening tests already performed which could potentially be affected by the SARS-CoV-2 infection or its complications on an individual basis and agreed upon with the MM (including but not limited to safety labs, SpO2, chest CT scan) should be repeated.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, procedure(s) or medical device intended to be administered to a study participant according to the study protocol.

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP) as indicated in Table 7.1-1 and Table 7.1-2.

An IP, also known as IMP 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 from 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-IPs/AxMPs.

7.1 Study Interventions Administered

The selection and timing of dose for each participant are as shown in Table 7.1-1 (Part 1) and Table 7.1-2 (Part 2).

Table 7.1-1: Study Interventions - Part 1

Part Name	Part 1A	Part 1B
Intervention Name	Docetaxel[a,b] + BMS-986218[c]	Docetaxel[a,b] + BMS-986218[c] + Nivolumab[c]
Type	Drug + Biologic	Drug + Biologic + Biologic
Dose Formulation	Solutions in a single-use vial	Solutions in a single-use vial
Unit Dose Strength(s)	Various strengths + 200 mg/vial	Various strengths + 200 mg/vial + 100 mg/vial
Dosage Level(s)	Docetaxel 75 mg/m^2 Q3W + BMS-986218 50 mg Q3W BMS-986218 may be [redacted] de-escalated (30 mg Q3W)	Docetaxel 75 mg/m^2 Q3W + BMS-986218 [redacted] BMS-986218 may be escalated (30 mg Q3W) [redacted] [redacted]
Route of Administration	IV infusions	IV infusions
Use	SOC + experimental	SOC + experimental (BMS-986218 + Nivolumab)
IMP and Non-IMP/AxMP	Non-IMP + IMP	Non-IMP + IMP + IMP
Sourcing	Provided locally by the trial site[d] + Provided centrally by the Sponsor	Provided locally by the trial site[d] + Provided centrally by the Sponsor (BMS-986218 + Nivolumab)
Packaging and Labeling	Study interventions will be provided in vials. Each vial will be labeled as required per country requirement.	Study interventions will be provided in vials. Each vial will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	1) Docetaxel or TAXOTERE 2) BMS-986218 or anti-CTLA-4-NF	1) Docetaxel or TAXOTERE 2) BMS-986218 or anti-CTLA-4-NF 3) Nivolumab or BMS-936558 or MDX1106 or ONO-4538

Abbreviations: AxMP, auxiliary medicinal product; CTLA-4-NF, cytotoxic T-lymphocyte-associated protein 4 non-fucosylated; IMP, investigational medicinal product; IV, intravenous; Q3W, every 3 weeks; SOC, standard of care; SmPC, Summary of Product Characteristics.

[a] Prednisone 5 mg twice daily will be administered with docetaxel in accordance with package insert/SmPC guidelines. Daily prednisone may be dose reduced or omitted at the discretion of the investigator if it negatively affects glycemic control or other comorbid conditions. Premedication with dexamethasone will also be given for docetaxel (for more details, see additional text in Section 7.1, below).

[b] A minimum of 3 to 4 cycles of docetaxel is recommended and up to 10 cycles is allowed per the package insert and SOC.

[c] The treatment period for BMS-986218 and/or nivolumab will last for up to 2 calendar years from first dose of study treatment.

[d] Sponsor may provide docetaxel in regions where it is not available through insurance or as part of SOC.

Table 7.1-2: Study Interventions - Part 2

Arm Name	Arm 2a[a]	Arm 2b	Arm 2c
Intervention Name	Docetaxel[b,c]	Docetaxel[b,c] + BMS-986218[d]	Docetaxel[b,c] + BMS-986218[d] + Nivolumab[d]
Type	Drug	Drug + Biologic	Drug + Biologic + Biologic
Dose Formulation	Solutions in a single-use vial	Solutions in a single-use vial	Solutions in a single-use vial
Unit Dose Strength(s)	Various strengths	Various strengths + 200 mg/vial	Various strengths + 200 mg/vial + 100 mg/vial
Dosage Level(s)	75 mg/m^2 Q3W	75 mg/m^2 Q3W + BMS-986218 at or below dose chosen in Part 1A Q3W	75 mg/m^2 Q3W + BMS-986218 at or below dose chosen in Part 1B Q3W + Nivolumab [redacted]
Route of Administration	IV infusion	IV infusions	IV infusions
Use	SOC	SOC + experimental	SOC + experimental (BMS-986218 + Nivolumab)
IMP and Non-IMP/AxMP	Non-IMP	Non-IMP + IMP	Non-IMP + IMP + IMP
Sourcing	Provided locally by the trial site[e] + Provided centrally by the Sponsor	Provided locally by the trial site[e] + Provided centrally by the Sponsor	Provided locally by the trial site[e] + Provided centrally by the Sponsor (BMS-986218 + Nivolumab)
Packaging and Labeling	Study interventions will be provided in vials. Each vial will be labeled as required per country requirement.	Study interventions will be provided in vials. Each vial will be labeled as required per country requirement.	Study interventions will be provided in vials. Each vial will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	1) Docetaxel or TAXOTERE	1) Docetaxel or TAXOTERE 2) BMS-986218 or anti-CTLA-4-NF	1) Docetaxel or TAXOTERE 2) BMS-986218 or anti-CTLA-4-NF 3) Nivolumab or BMS-936558 or MDX1106 or ONO-4538

Abbreviations: AxMP, auxiliary medicinal product; CTLA-4-NF, cytotoxic T-lymphocyte-associated protein 4 non-fucosylated; IMP, investigational medicinal product; IV, intravenous; Q3W, every 3 weeks; SOC, standard of care; SmPC, Summary of Product characteristics.

[a] Participants in Arm 2a who experience rPD can receive BMS-986218 (same dose as Arm 2c) + nivolumab (same dose as Arm 2c) as crossover treatment in Arm 2d (see column above for Arm 2c minus the docetaxel study intervention).

[b] Prednisone 5 mg twice daily will be administered with docetaxel in accordance with the package insert/SmPC guidelines. Daily prednisone may be dose reduced or omitted at the discretion of the investigator if it negatively affects glycemic control or other comorbid conditions. Premedication with dexamethasone will also be given for docetaxel (for more details, see additional text in Section 7.1, below).

[c] A minimum of 3 to 4 cycles of docetaxel is recommended and up to 10 cycles is allowed per the package insert and SOC.

[d] The treatment period for BMS-986218 and/or nivolumab will last for up to 2 calendar years from first dose of study treatment.

[e] Sponsor may provide docetaxel in regions where it is not available through insurance or as part of SOC.

Participants who are assigned/randomized to a study intervention with nivolumab will receive nivolumab at a dose of [redacted] over an approximately 30-minute infusion each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of 24 months of treatment, or the study ends, whichever occurs first. If needed, flush the intravenous line with an appropriate amount of diluent (eg, 0.9% sodium chloride) to ensure that the complete dose is administered over approximately 30 minutes. Begin study treatment within 3 calendar days of treatment assignment (Part 1) or randomization (Part 2).

When study interventions BMS-986218 and docetaxel are to be administered on the same day, BMS-986218 should be administered first. Flush the intravenous line with an appropriate amount of diluent (eg, 0.9% sodium chloride) to ensure that the complete dose is administered over approximately 30 minutes. After the BMS-986218 infusion, there is a 30-minute delay before the start of the docetaxel infusion to monitor the participant for signs of possible infusion reactions and differentiate any such reaction from one related to the subsequent docetaxel infusion. Dosing of docetaxel will continue for a maximum of 10 cycles Q3W (± 3 days), until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. A minimum of 3 to 4 cycles of docetaxel is recommended. Prednisone 5 mg twice daily will be administered with docetaxel in accordance with package insert/SmPC guidelines. However, daily prednisone may be dose reduced or omitted at the discretion of the investigator if it negatively affects glycemic control or other comorbid conditions. Premedication with dexamethasone will also be given for docetaxel (see below).

Dosing calculations of docetaxel should be based on the body weight assessed at baseline using Mosteller body surface area formula: the square root of (weight [kg] × height [cm]/3600). It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

When study interventions nivolumab, BMS-986218 and docetaxel (or nivolumab and BMS-986218 for crossover participants in Arm 2d), are to be administered on the same day, nivolumab is to be administered first. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line of nivolumab before starting the BMS-986218 infusion. The second

infusion will always be BMS-986218 and will start after the infusion line has been flushed, filters changed, and participant has been observed to ensure no infusion reaction has occurred. Then, follow the instructions above to administer docetaxel (docetaxel will not be administered for participants who crossover into Arm 2d).

There will be no intra-subject dose escalations or reductions of nivolumab or BMS-986218 allowed. For Q3W dosing cycles, participants may be dosed no less than 19 days from the previous dose.

Monitor participants carefully for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, manage participants according to Section 7.4.6.

Doses of study drug(s) may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Please refer to the current Investigator Brochure and/or Pharmacy Manual for further details regarding storage, preparation, and administration of nivolumab.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

For details regarding BMS-986218 storage, preparation and administration, please refer to the current Investigator's Brochure and/or Pharmacy Manual.

Use separate infusion bags and filters when administering the study interventions on the same day.

Premedication:

Premedications for BMS-986218 and nivolumab are not recommended. For docetaxel, given the concurrent use of prednisone (5 mg twice daily), the recommended premedication regimen is oral dexamethasone 8 mg (or equivalent dose of another corticosteroid) to be administered at 12, 3, and 1 hour(s) before the docetaxel infusion; however, other corticosteroids and/or schedules and routes of administration are also acceptable according to local standards. Antiemetic premedication will be administered according to local standards.

Participants should be carefully monitored for infusion reactions during BMS-986218, docetaxel, and nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.6 and Section 7.4.8.

7.2 Method of Study Intervention Assignment

Study using Interactive Response Technology (IRT): All participants will be centrally assigned to treatment (Part 1) or randomized (Part 2) using IRT. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT.

Study intervention will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

Participants in Part 2 will be randomized to receive 1 of 3 study interventions (Q3W) as follows: Arm 2a- docetaxel; Arm 2b- docetaxel and BMS-986218; Arm 2c- docetaxel, BMS-986218, and nivolumab. Randomization is done according to a computer-generated randomization scheme

prepared by a Randomization Coordinator within the Drug Supply Management Department of BMS Research and Development and will be stratified by presence of measurable disease (Y/N).

During the screening visit, the investigative site will call into the enrollment option of the IRT designated by BMS for assignment of 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 [redacted] (eg, [redacted]). The patient identification number (PID) will ultimately comprise the site number and participant number. For example, the first participant screened (ie, enrolled) at site number 1 will have a PID of [redacted] . Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to assign (Part 1) or randomize (Part 2) the participant into the open dose panel.

7.3 Blinding

This is an open-label study; participants in Part 1 will be assigned to treatment and participants in Part 2 will be randomized to treatment. It has been determined that blinding could negatively impact participant safety management, therefore blinding procedures are not applicable. The specific treatment to be taken by a participant will be assigned using IRT. The site will contact the Interactive Response System prior to the start of study intervention administration for each participant. The site will record the treatment assignment on the applicable case report form (CRF), if required.

Release of Treatment Assignment:

Access to randomized treatment codes will be restricted from BMS personnel (with exceptions noted below) prior to the final analysis. Access to the participants' individual treatment assignment as recorded on the CRF will be allowed in order to monitor and manage potential safety risks that may be specific to the treatment received.

Since this is an open-label study, blinding procedures are not applicable to global sites; however, the specific treatment to be taken by a participant will be assigned using an IRT. The site will contact the IRT prior to the start of study treatment administration for each participant. The site will record the treatment assignment on the applicable CRF.

In order to monitor safety, designated staff of BMS Research & Development (R&D) will have access to the treatment codes prior to the final database lock. Specific safety events may be tabulated by treatment (for Arm 2b and Arm 2c) in order to assess whether toxicity boundaries have been reached, based on the continuous safety monitoring plan. To prevent bias and to protect the data integrity of the study, efficacy data will not be summarized by treatment arm prior to the final database lock, unless otherwise specified. In order to plan the time of the final efficacy analysis, designated Sponsor representatives will periodically monitor the total number of events between Arm 2a and Arm 2c (or Arm 2a and Arm 2b) relative to the pre-specified events needed for the planned analysis. In addition, designated staff of BMS R&D, such as Clinical Pharmacology and Pharmacometrics scientist, or Informatics and Predictive Sciences representatives may have access to the treatment assignment prior to database lock to facilitate the analysis of PK, biomarker, and immunogenicity samples. A bioanalytical scientist in the

Bioanalytical Sciences department of BMS R&D (or a designee in the external central bioanalytical laboratory) will have access to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples for PK and immunogenicity.

7.4 Dosage Modification

Dosing for all drugs should initially be delayed if any criteria in Table 7.4.1-1 (for BMS-986218 and/or nivolumab) or Table 7.4.2-1 (for docetaxel) are met. That is, immunotherapy should also be delayed if criteria for delay of docetaxel are met and docetaxel should also be delayed if criteria for immunotherapy are met. Circumstances in which chemotherapy or immunotherapy can be independently resumed are discussed in Section 7.4.3.

7.4.1 Dose Modification Criteria for Nivolumab and/or BMS-986218

The criteria for dose delay, resumption, and discontinuation in Table 7.4.1-1 applies to nivolumab and/or BMS-986218.

In addition, delay nivolumab and BMS-986218 dosing for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

For participants who require delay of nivolumab and BMS-986218, re-evaluate weekly, or more frequently, if clinically indicated and resume dosing when criteria to resume treatment are met (see Section 7.4.3). Continue tumor assessments per protocol even if dosing is delayed.

There will be no dose modifications permitted for nivolumab or BMS-986218. Administration of either nivolumab and/or BMS-986218 is permitted when docetaxel is discontinued due to toxicity if the treating investigator determines that it is the best interest of the participant.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986218

Drug-related AE per CTCAE V5	Severity	Action Taken for BMS-986218 and/or Nivolumab	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Colitis and Diarrhea	Grade 2	Delay dose	Dosing may resume after AE returns to baseline
	Grade 3	Permanently discontinue BMS-986218	Nivolumab may be resumed when AE resolves to baseline. If Grade 3 diarrhea or colitis recurs while on nivolumab without BMS-986218 permanently discontinue
	Grade 4	Permanently discontinue	
Renal			
Serum Creatinine Increased	Grade 2 or 3	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 4	Permanently discontinue	
Pulmonary			
Pneumonitis	Grade 2	Delay dose	Dosing may resume after pneumonitis has resolved to ≤ Grade 1.
	Grade 3 or 4	Permanently discontinue	
Hepatic			
AST, ALT or T.bili[a] Increased	AST or ALT > 3× and ≤ 5× ULN or T.bili > 1.5× and ≤ 3× ULN, regardless of baseline value	Delay dose	Dosing may resume when laboratory values return to baseline. Exception: Permanently discontinue if the increase is associated with new clinical signs/symptoms of liver inflammation (eg, right upper quadrant tenderness, fatigue, nausea, vomiting, fever, rash, and/or eosinophilia).
	AST or ALT > 5× ULN or T.bili > 3× ULN, regardless of baseline value	Permanently discontinue	In most cases of AST or ALT > 5× ULN, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Medical Monitor/ designee must occur and approval from Medical Monitor prior to resuming therapy.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986218

Drug-related AE per CTCAE V5	Severity	Action Taken for BMS-986218 and/or Nivolumab	Clarifications, Exceptions, and Resume Criteria
	Concurrent AST or ALT > 3× ULN and T.bili > 2× ULN or INR > 1.5, regardless of baseline value	Permanently discontinue	
Endocrinopathy			
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Delay dose	Dosing may resume after adequately controlled with hormone replacement.
	Grade 3 or 4 adrenal insufficiency or adrenal crisis	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If adrenal insufficiency resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperglycemia	Hyperglycemia requiring initiation or change in daily management (Grade 2 or 3)	Delay dose	Dosing may resume if hyperglycemia resolves to Grade ≤ 1 or baseline value, or is adequately controlled with glucose-controlling agents.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If hyperglycemia resolves, or is adequately controlled with glucose-controlling agents, participant may not require discontinuation of study drug.
Hypophysitis/Hypopituitarism	Symptomatic Grade 1-3 that is also associated with corresponding abnormal lab	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic, or is adequately controlled with only physiologic hormone replacement.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986218

Drug-related AE per CTCAE V5	Severity	Action Taken for BMS-986218 and/or Nivolumab	Clarifications, Exceptions, and Resume Criteria
	and/or pituitary scan		
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement, participant may not require discontinuation of study drug.
Hyperthyroidism or Hypothyroidism	Grade 2 or 3	Delay dose	Dosing may resume if endocrinopathy resolves to be asymptomatic or is adequately controlled with only physiologic hormone replacement or other medical management.
	Grade 4	Delay dose or permanently discontinue	Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy. If endocrinopathy resolves or is adequately controlled with physiologic hormone replacement or other medical management, participant may not require discontinuation of study drug.
Skin			
Rash	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose	Dosing may resume when rash reduces to ≤ 10% body surface area. Exception: Permanently discontinue for Grade 3 rash that does not reduce to ≤ Grade 1 after 2-week treatment delay.
	Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS)	Delay dose	Dosing may resume if SJS, TEN, or DRESS is ruled out and rash reduces to ≤ 10% body surface area.
	Grade 4 rash or confirmed	Permanently discontinue	

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986218

Drug-related AE per CTCAE V5	Severity	Action Taken for BMS-986218 and/or Nivolumab	Clarifications, Exceptions, and Resume Criteria
	SJS,TEN, or DRESS		
Neurological			
Guillain-Barre Syndrome (GBS)	Any Grade	Permanently discontinue	
Myasthenia Gravis (MG)	Any Grade	Permanently discontinue	
Encephalitis	Any Grade encephalitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if encephalitis is not drug related, then dosing may resume when AE resolves.
	Any Grade drug-related encephalitis	Permanently discontinue	
Myelitis	Any Grade myelitis	Delay dose	After workup for differential diagnosis, (ie, infection, tumor-related), if myelitis is not drug related, then dosing may resume when AE resolves.
	Any Grade drug related myelitis	Permanently discontinue	
Neurological (other than GBS, MG, encephalitis, or myelitis)	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3 or 4	Permanently discontinue	
Myocarditis			
Myocarditis	Symptoms induced from mild to moderate activity or exertion	Delay dose	Dosing may resume after myocarditis has resolved. Mandatory discussion with and approval from the Medical Monitor needed prior to resuming therapy.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986218

Drug-related AE per CTCAE V5	Severity	Action Taken for BMS-986218 and/or Nivolumab	Clarifications, Exceptions, and Resume Criteria
	Severe or life threatening, with symptoms at rest or with minimal activity or exertion, and/or where intervention indicated.	Permanently discontinue	
Other Clinical AE			
Pancreatitis: Amylase or Lipase Increased	Grade 3 with symptoms	Delay dose	Note: Grade 3 increased amylase or lipase without signs or symptoms of pancreatitis does not require dose delay. Dosing may resume when participant becomes asymptomatic.
	Grade 4	Permanently discontinue	
Uveitis	Grade 2 uveitis	Delay dose	Dosing may resume if uveitis responds to topical therapy (eye drops) and after uveitis resolves to Grade ≤ 1 or baseline. If participant requires oral steroids for uveitis, then permanently discontinue study drug.
	Grade 3 or 4 uveitis	Permanently discontinue	
Other Drug-related AE (not listed above [non-laboratory AEs, see below for other laboratory drug-related AEs])	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value
	Grade 3 AE - First occurrence lasting ≤ 7 days	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986218

Drug-related AE per CTCAE V5	Severity	Action Taken for BMS-986218 and/or Nivolumab	Clarifications, Exceptions, and Resume Criteria
	Grade 3 AE- First occurrence lasting > 7 days	Permanently discontinue	
	Recurrence of Grade 3 AE of any duration	Permanently discontinue	Exception: Recurrent Grade 3 fatigue may resume treatment after resolution to Grade 2 or lower.
	Grade 4 or Life-threatening adverse reaction	Permanently discontinue	
Other Laboratory Abnormalities			
Other Drug-Related Lab Abnormality (not listed above) Not Attributed to Docetaxel	Grade 3	Delay dose	**Exceptions:** No delay required for: Grade 3 lymphopenia or Grade 3 anemia related to underlying disease that responds to red blood cell transfusion. Permanent Discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding. Grade ≥ 3 hemolysis.
	Grade 4	Permanently discontinue	**Exceptions:** The following events do not require discontinuation of study drug: • Grade 4 neutropenia ≤ 7 days • Grade 4 lymphopenia or leukopenia • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset

Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986218

Drug-related AE per CTCAE V5	Severity	Action Taken for BMS-986218 and/or Nivolumab	Clarifications, Exceptions, and Resume Criteria
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)			
Hypersensitivity Reaction or Infusion Reaction	Grade 3 or 4	Permanently discontinue except as described in Section 7.4.6	Refer to Section 7.4.6 on Treatment of Related Infusion Reactions
SARS-CoV-2 Infection Either Confirmed or Suspected		Delay dose	Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen), 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), 3) evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and 4) consultation with the BMS Medical Monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out as per institutional policy for testing of SARS-CoV-2 and other criteria to resume treatment are met.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMS, Bristol-Myers Squibb; CTCAE V5, Common Terminology Criteria for Adverse Events version 5; DRESS, drug reaction with eosinophilia and systemic symptoms; GBS, Guillain-Barre Syndrome; INR, international normalized ratio; MG, myasthenia gravis; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus disease 2; SJS, Steven-Johnson syndrome; T.bili, total bilirubin; TEN, toxic epidermal necrolysis; ULN, upper limit of normal.

[a] For participants with Gilbert's syndrome, direct bilirubin should be monitored and utilized in place of T.bili for toxicity assessments.

7.4.2 Dose Delay Criteria for Docetaxel

The criteria for dose delay, resumption, and discontinuation in Table 7.4.2-1 applies to docetaxel. In addition, delay docetaxel for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

For participants who require delay of docetaxel re-evaluate weekly, or more frequently, if clinically indicated and resume dosing when criteria to resume treatment are met (see Section 7.4.3). Continue tumor assessments per protocol even if dosing is delayed. Dose modifications of docetaxel are permissible (see Section 7.4.4).

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Docetaxel

Drug-related AE per CTCAE V5	Severity	Action Taken for docetaxel	Clarifications, Exceptions, and Resume Criteria
Hematological			
Neutropenia	Grade 2	Delay dose/reduce dose[a]	If not recovered on the day of administration, delay next infusion until neutrophil counts ≥ 1.5×10^9/L. • 1st episode: no dose reduction is required. • 2nd episode: consider dose reduction by 1 dose level.[a] Granulocyte colony-stimulating factor (G-CSF) may be administered at the discretion of the investigator and following local guidelines.
	Grade 3 or 4	Delay dose/reduce dose[a] or permanently discontinue	Delay next infusion until neutrophil counts ≥ 1.5×10^9/L. No dose reduction if isolated and duration ≤ 7 days and recovered by Day 22 to ≤ Grade 1. If duration > than 7 days or not recovered on Day 22 to ≤ Grade 1: • 1st episode: consider prophylactic G-CSF in subsequent cycles. • 2nd episode or 1st episode despite prophylactic G-CSF: Reduce dose by 1 dose level.[a] • 3rd episode or 2nd episode despite prophylactic G-CSF: permanently discontinue.
Febrile neutropenia or neutropenic infection	Grade 3 or 4	Delay dose/reduce dose[a] or permanently discontinue	Delay next infusion until neutrophil counts ≥ 1.5×10^9/L. • 1st episode: reduce the dose[a] and consider prophylactic G-CSF in subsequent cycles. • 2nd episode: permanently discontinue.
Thrombocytopenia	Grade 2	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline.
	Grade 3 or 4	Delay dose/reduce dose[a] or permanently discontinue	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. If Grade 3 without delay, no dose reduction required. If Grade 4, or Grade 3 with delay: • 1st episode: reduce dose by 1 dose level.[a] • 2nd episode: permanently discontinue. Permanent discontinuation for: Grade 3 thrombocytopenia > 7 days or associated with bleeding.

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Docetaxel

Drug-related AE per CTCAE V5	Severity	Action Taken for docetaxel	Clarifications, Exceptions, and Resume Criteria
Gastrointestinal			
Diarrhea	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline.
	Grade 3	Delay dose/reduce dose[a] or permanently discontinue	• 1st episode: reduce dose by 1 dose level.[a] • 2nd episode: permanently discontinue.
	Grade 4	Permanently discontinue	
Colitis or enterocolitis	Grade 2	Delay dose	Dosing may resume when AE resolves to baseline
	Grade 3 or 4	Delay dose/reduce dose[a] or permanently discontinue	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. • 1st episode: reduce dose by 1 dose level.[a] • 2nd episode: permanently discontinue.
Skin			
Rash	Grade 2 rash covering < 30% of body surface	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. Dosing may resume when rash reduces to ≤ 10% body surface area.
	Grade 2 rash covering > 30% body surface area or Grade 3 rash	Delay dose/reduce dose,[a] or permanently discontinue	Dosing may resume when AE resolves to Grade ≤ 1 or baseline. • 1st episode: reduce dose by 1 dose level.[a] • 2nd episode: permanently discontinue.
	Grade 4	Permanently discontinue	
Neurological			
Peripheral neuropathy	Grade 2	Reduce dose[a]	Reduce dose by 1 dose level.[a]

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Docetaxel

Drug-related AE per CTCAE V5	Severity	Action Taken for docetaxel	Clarifications, Exceptions, and Resume Criteria
	Grade 3 or 4	Permanently discontinue	
Hepatic			
Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin (T.bili)[b] increased with or without alkaline phosphatase increase	AST or ALT > 3× and ≤ 5× upper limit of normal (ULN) or T.bili > 1.5× and ≤ 3× ULN, regardless of baseline value or T.bili > ULN and/or AST/ALT > 1.5× ULN associated with alkaline phosphatase > 2.5× ULN (in the absence of bone metastasis)	Delay dose/reduce dose[a]	Dose reduction may be considered at the discretion of the investigator and following local guidelines.[a] Dosing may resume when laboratory values return to baseline.
	AST or ALT > 5× ULN or T.bili > 3× ULN, regardless of baseline value or concurrent AST or ALT > 3× ULN and T.bili > 2× ULN or INR > 1.5, regardless of baseline value	Permanently discontinue	

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Docetaxel

Drug-related AE per CTCAE V5	Severity	Action Taken for docetaxel	Clarifications, Exceptions, and Resume Criteria
Infusion Reactions (manifested by fever, chills, rigors, headache, rash, pruritus, arthralgia, hypotension, hypertension, bronchospasm, or other allergic-like reactions.)			
Hypersensitivity reaction or infusion reaction	Grade 3 or 4	Permanently discontinue	Refer to Section 7.4.8: Docetaxel-related Hypersensitivity Reactions.
Other Clinical AE			
Cystoid macular oedema (CMO) diagnosed by ophthalmologic examination	Any grade	Permanently discontinue	CMO has been reported in participants treated with docetaxel. Participants with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated.
Other drug-related AE (not listed above)	Grade 2 non-skin AE, except fatigue	Delay dose	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value.
	Grade 3	Delay dose/reduce dose[a] or permanently discontinue	Dosing may resume when AE resolves to Grade ≤ 1 or baseline value. • 1st episode: dose reduction may be considered at the discretion of the investigator.[a] • 2nd episode: permanently discontinue.
	Grade 4 or life-threatening adverse reaction	Permanently discontinue	
Other Laboratory Abnormalities			
Other drug-related lab abnormality (not listed above)	Grade 3	Delay dose/reduce dose[a]	Dose reduction may be considered at the discretion of the investigator and following local guidelines.[a] Exceptions: No delay required for: Grade 3 lymphopenia.
	Grade 4	Permanently discontinue	Exceptions: The following events do not require discontinuation of study drug: • Grade 4 lymphopenia or leukopenia. • Grade 4 isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are responding to supplementation/appropriate management within 72 hours of their onset.

Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Docetaxel

Drug-related AE per CTCAE V5	Severity	Action Taken for docetaxel	Clarifications, Exceptions, and Resume Criteria
SARS-CoV-2 Infection Either Confirmed or Suspected		Delay dose	Participants with SARS-CoV-2 infection (either confirmed or suspected) may resume treatment after 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result (eg, RT-PCR or viral antigen), 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), 3) evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and 4) consultation with the BMS Medical Monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out as per institutional policy for testing of SARS-CoV-2 and other criteria to resume treatment are met.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMO, cystoid macular oedema; CTCAE V5, Common Terminology Criteria for Adverse Events version 5; G-CSF, granulocyte colony-stimulating factor; INR, international normalized ratio; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus disease 2; T.bili, total bilirubin; ULN, upper limit of normal.

[a] See Section 7.4.4 for instructions on docetaxel dose reduction.

[b] For patients with Gilbert's syndrome, direct bilirubin should be monitored and utilized in place of T.bili for toxicity assessments.

7.4.3 Criteria to Resume Treatment

Dosing for all drugs should be delayed if any criteria in Table 7.4.1-1 (for BMS-986218 and/or nivolumab) or Table 7.4.2-1 (for docetaxel) are met. That is, immunotherapy should also be delayed if criteria for delay of docetaxel are met and docetaxel should also be delayed if criteria for immunotherapy are met. Participants may resume dosing when resuming criteria for BOTH immunotherapy and docetaxel are met. That is, immunotherapy and docetaxel will generally be administered together until completion of Cycle 10 or until one of the agents is permanently discontinued. The exception is immune-related toxicities that require prolonged immunotherapy delay (ie, toxicities treated with a prolonged corticosteroid taper). In such cases, dosing with docetaxel may resume prior to immunotherapy, when the criteria to resume dosing for docetaxel have been met. Immunotherapy dosing may be resumed later, after completion of the corticosteroid taper and when criteria to resume nivolumab or BMS-986218 dosing have been met.

Administration of either immunotherapy or docetaxel only is permitted, if the other study treatment(s) is (are) permanently discontinued due to toxicity, and the treating investigator assesses continued therapy to have a favorable likelihood of benefit compared to risk. For participants undergoing immunotherapy treatment with BMS-986218 and nivolumab, both agents should typically be administered or discontinued together. In circumstances where a toxicity is attributable to 1 immunotherapy agent (eg, infusion reaction), administration of only 1 immunotherapy agent is permitted after discussion with the BMS medical monitor or designee.

Participants with confirmed SARS-CoV-2 infection may resume treatment with BMS-986218 or BMS-986218 plus nivolumab, in combination with docetaxel after 1) at least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared, positive RT-PCR test result, or positive viral antigen test result, 2) resolution of acute symptoms (including at least 24 hours has passed since last fever without fever reducing medications), 3) evaluation by the Investigator with confirmation that there are no sequelae that would place the participant at a higher risk of receiving investigational treatment, and 4) consultation by the medical monitor. For suspected cases, treatment may also resume if SARS-CoV-2 infection is ruled-out and other criteria to resume treatment are met.

Prior to re-initiating on-study treatment in a participant with a dosing delay lasting 8 weeks due to SARS-CoV-2 infection, the medical monitor/designee must be consulted.

7.4.3.1 Criteria to Resume Treatment for Nivolumab and BMS-986218

Participants may resume treatment with study drug if they have completed AE management (ie, corticosteroid taper) or are on ≤ 10 mg prednisone or equivalent, and meet the requirements per Table 7.4.1-1.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 8 weeks, the Medical Monitor (or designee) must be consulted. Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies weekly or more frequently if clinically indicated during such dosing delays.

In circumstances where a toxicity is attributable to one immunotherapy agent (eg, infusion reaction), administration of only 1 immunotherapy agent is permitted after discussion with the BMS medical monitor or designee.

7.4.4 Docetaxel Dose Reduction and Criteria to Resume Treatment

The docetaxel dose can be reduced when necessary as described in Table 7.4.4-1. The dose which has been reduced for toxicity must not be re-escalated. Up to a maximum of 1 dose reduction will be allowed per participant. If a second dose reduction is required per the modifications above, the participant should discontinue study treatment. Participants who experience an event related to docetaxel necessitating discontinuation of chemotherapy may continue to receive other study treatments. See Section 7.4.2 for criteria on resuming docetaxel treatment after a dose delay.

Table 7.4.4-1: Dose Reductions for Docetaxel

Dose Level	Docetaxel
Starting dose	75 mg/m^2
First dose reduction	60 mg/m^2
Second dose reduction	Discontinue docetaxel

7.4.5 Dose-limiting Toxicities

For DLT evaluation, all AEs should be considered except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

DLTs will be defined as:

- Any treatment-related AEs for which a participant permanently discontinues a study treatment (other than daily prednisone) based on the criteria listed in Table 7.4.1-1 and Table 7.4.2-1 and that occurs during the first 2 cycles of treatment
- Any death not clearly due to the underlying disease or extraneous causes and that occurs during the first 2 cycles of treatment
- Greater than or equal to Grade 2 pneumonitis lasting greater than 5 days despite appropriate medical therapy and that occurs during the first 2 cycles of treatment
- Any neutropenic fever as well as Grade 4 neutropenia or thrombocytopenia for > 7 days that occurs during the first 2 cycles of treatment
- Any treatment-related AE that delays initiation of Cycle 2 or Cycle 3 of treatment by greater than 2 consecutive weeks
- Any Grade 3 or higher non-hematologic toxicity not specifically addressed elsewhere with the following exceptions:
  - Grade 3 or Grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 72 hours, and either resolve spontaneously or respond to conventional medical intervention

- Grade 3 nausea, vomiting, or diarrhea that lasts less than 72 hours and either resolves spontaneously or responds to conventional medical intervention
- Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
- Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical, or laboratory evidence of impaired end-organ perfusion)
- Grade 3 endocrinopathy that is well controlled by hormone replacement
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
- Grade 3 fatigue unless > 7 days
- Grade 3 infusion reaction that returns to Grade 1 in < 6 hours

Note: For participants who experience a DLT, further treatment will be based on Table 7.4.1-1 and Table 7.4.2-1 and the criteria to resume treatment in Section 7.4.3 and Section 7.4.4.

DLT Exception:

Infusion reactions attributed to docetaxel will not be considered DLTs.

AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.

7.4.6 Treatment of Related Infusion Reactions

Since nivolumab and BMS-986218 contain only human immunoglobulin protein sequences, they are 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, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Report all Grade 3 or 4 infusion reactions within 24 hours as an SAE if it meets the criteria.

Treatment recommendations are provided below based on CTCAE v5 grading definitions 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 acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab and/or BMS-986218 administrations.

For Grade 2 symptoms: (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDS], narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs**)**:

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/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 medication will be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg administered at least 30 minutes before nivolumab and/or BMS-986218 infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: Prolonged [eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention 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 1:1000 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. Monitor participant until the Investigator judges that the symptoms will not recur. Study drug will be permanently discontinued. Follow institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery of the symptoms.

In 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).

7.4.7 Management Algorithms for Immuno-oncology Agents

Immuno-oncology (I-O) agents are associated with IMAEs that can differ in severity and duration from AEs caused by other therapeutic classes. BMS-986218 and nivolumab are considered I-O agents in this protocol. Early recognition and management of IMAEs associated with I-O agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with ipilimumab and nivolumab to assist investigators in assessing and managing the following groups of IMAEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic

- Endocrinopathies
- Skin
- Neurological
- Myocarditis

The clinical nature of AEs noted with BMS-986218 will determine the role of the algorithms for use in toxicities related to its use in this study. The algorithms recommended for the management of IMAEs in this protocol can be found in Appendix 8.

7.4.8 Docetaxel-related Hypersensitivity Reactions

Participants should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require interruption of therapy. However, severe reactions (≥ Grade 3), such as severe hypotension, bronchospasm, or generalized rash/erythema require immediate discontinuation of docetaxel and appropriate therapy. Participants who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel. Participants who have previously experienced a hypersensitivity reaction to paclitaxel may be at risk to develop hypersensitivity reaction to docetaxel, including more severe hypersensitivity reaction. These participants should be closely monitored during initiation of docetaxel therapy.

7.5 Preparation/Handling/Storage/Accountability

The IP/AxMP must be stored in a secure area according to local regulations. It is the responsibility of the investigator, or designee where permitted, to ensure that IP/AxMP is only dispensed to study participants. The IP/AxMP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study intervention 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 intervention arise, the study intervention should not be dispensed, and BMS should be contacted immediately.

Study intervention not supplied by BMS will be stored in accordance with the package insert.

IP/AxMP documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure the 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).

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in Appendix 2.
- Further preparation/administration and handling instruction will be provided in the Pharmacy Manual

For study interventions not provided by BMS and obtained commercially by the site, storage should be in accordance with the product label.

7.6 Treatment Compliance

Not applicable.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

The following medications and treatments are prohibited during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids. Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted. Premedication with corticosteroids for docetaxel therapy is allowed as detailed in Section 7.1.
- Any concurrent systemic anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of mCRPC)
    - Approved bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are allowed
- Any non-palliative radiation therapy. Radiation therapy administered with palliative intent (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) is permitted.
- Megestrol acetate
- Any complementary medications (eg herbal supplements or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care.
- 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.
- Administration of investigational SARS-CoV-2 vaccines is not allowed during the study.

- Participants may receive authorized or approved SARS-CoV-2 vaccines while continuing on study treatment at the discretion of the Investigator.
    - Live COVID-19 vaccines should not be administered to a participant during the study, including during the treatment, safety follow-up period, and within 3 months following the last dose of IMP. In addition, the administration of a live COVID-19 vaccine is prohibited up to 30 days prior to the initiation of study treatment.
- Treatment of active SARS-CoV-2 infections or high risk exposures, including use of investigational therapies, is allowed and should be discussed with the medical monitor.

7.7.2 Other Restrictions and Precautions

Strong CYP3A4 inhibitors and inducers should be avoided during the treatment with docetaxel. Please refer to Appendix 10 for a list of common strong CYP3A4 inhibitors and inducers.

7.7.3 Permitted Therapy

Participants are permitted the use of the following treatments:

- In the absence of active autoimmune disease, ocular, intra-articular, intra-nasal, inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted.
- A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen).
- Participants receiving docetaxel may receive growth factors (including granulocyte colony-stimulating factor [G-CSF] and erythropoietin) at the discretion of the investigator and following local guidelines.

7.7.4 Palliative Radiation

Palliative local therapy, including palliative radiotherapy and palliative surgical resection, to symptomatic tumor lesions is permitted. Participants requiring palliative local therapy should be evaluated (by CT/MRI and bone scan if clinically indicated) for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the planned start of local therapy. If progression per PCWG3 is identified prior to the initiation of palliative local therapy, then participants must either discontinue study treatment or they must meet criteria to continue treatment beyond progression (Section 8.1.2) in order to resume study treatment after the completion of palliative local therapy. Participants in Arm 2a who meet progression criteria prior to palliative radiation may proceed to the crossover arm (Arm 2d) following radiation. Participants receiving palliative radiation of target lesions will no longer be evaluable for the determination of response subsequent to the date palliative radiation occurs. In cases where palliative radiotherapy is required, BMS-986218 and nivolumab dosing should be withheld for at least 1 week before (if radiation can be safely delayed based on the clinical scenario), during, and 1 week after radiotherapy. Participants should be closely monitored for any radiation-related toxicity during and after receiving radiotherapy, and such AEs should

resolve to baseline or less than or equal to Grade 1 prior to resuming BMS-986218 or nivolumab. For docetaxel resumption, local standard of care guidelines should be followed.

7.7.5 Surgery

Participants undergoing major surgery for any reason while on study should have BMS-986218, docetaxel, and/or nivolumab held for at least 4 weeks after surgery, and these study treatments should not be resumed until wound healing has occurred and it is considered safe to do so in the assessment of the investigator. Wound healing must be evaluated by the surgeon prior to resuming study treatment. Prior to resuming study treatment, surgically related AEs should resolve to Grade 1 or baseline, and participants must meet relevant eligibility criteria as determined by the BMS Medical Monitor (or designee) in discussion with the investigator.

7.7.6 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether or not they should receive contrast and if so, which contrast agent and dose is appropriate. Specific to MRI, participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis, therefore MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. This will be outlined in the imaging manual.

Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and standards set by the local Ethics Committee.

7.8 Continued Access to Study Intervention After the End of the Study

At the end of the study, BMS will not continue to provide BMS-supplied study intervention 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 intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986218 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 other health program. In all cases, BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation From Study Intervention

Participants MUST discontinue IP (and Non-IP/AxMP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention 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 the participant to provide this information

- Any clinical 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
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)
- Significant noncompliance with protocol (eg, procedures, assessments, medications, etc). The investigator should discuss such issues with the Medical Monitor.
- Radiographic progression of disease per PCWG3 criteria; however, participants who meet criteria for treatment beyond progression or who qualify for crossover into Arm 2d (from Arm 2a) may continue to receive study intervention.
- Clinical deterioration attributed to disease progression, without radiographic progression per PCWG3, that in the judgment of the investigator makes it unsafe for the participant to continue with study intervention.

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

All participants who discontinue study intervention should comply with protocol-specified follow-up procedures as outlined in Section 2. 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 (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study intervention 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 per local regulatory requirements in each region/country and entered on the appropriate CRF page.

For all participants, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration' in the source data and in the electronic case report form (eCRF). Tumor assessments for participants who discontinue study intervention without radiographic progression, confirmed by BICR (Section 5.1.4.3), should continue as per protocol until radiographic progression is determined by BICR.

8.1.1 Discontinuation from Nivolumab and/or BMS-986128

Nivolumab and/or BMS-986218 treatment must be permanently discontinued per criteria in Table 7.4.1-1 in Section 7.4.1. Discontinue nivolumab and/or BMS-986218 for 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 nivolumab dosing and/or BMS-986218.

Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation of study drug, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events 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 Medical Monitor (or designee).

8.1.2 Nivolumab and BMS-986218 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[63]

Participants treated with BMS-986218 or nivolumab will be permitted to continue with their assigned treatment beyond radiographic progression per PCWG3 criteria, assessed by the investigator up to a maximum of 24 months from date of first dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Participant provides written informed consent prior to receiving additional study treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

Treatment beyond progression may be administered during or after localized interventions (surgery/radiation therapy) after discussion with the Medical Monitor.

Continue radiographic assessment/scan(s) in accordance with the Section 2 Schedule of Activities for the duration of the treatment beyond progression and submit to the central imaging vendor. Balance the assessment of clinical benefit with clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued study treatment.

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. Further progression in bone is defined as the development of 2 new bone lesions. Confirmatory bone imaging is not required to define further progression in bone. Upon documentation of further progression, permanently discontinue study treatment unless the clinical judgement of the investigator is that continuing treatment is in the patient's best interest.

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 least 15 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.

8.1.3 Post-study Intervention Study Follow-up

In this study, rPFS is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study intervention must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

If progression has not occurred before treatment discontinuation, tumor assessments should continue according to the Schedule of Activities.

Participants should undergo 100 days of safety follow-up post last dose of study intervention (follow-up Day 30, 60, and 100). All participants who received study interventions will also be followed for survival data.

Participants in Arm 2d who crossover after discontinuing docetaxel treatment and who re-enter the follow-up period will repeat the 100-day Safety Follow-up visits (Day 30, 60, and 100).

Participants who discontinue study intervention may continue to be followed.

BMS may request that survival data be collected on all treated/randomized participants outside of the protocol defined window (Table 2-3). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contact or is lost to follow-up.

8.2 Discontinuation From the Study

Participants who request to discontinue study intervention 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.
- 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 intervention 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.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- 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 (3)** documented phone calls, faxes, or emails, as well as lack of response by participant to one (1) 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 the 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 the 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 (Section 2).
- 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 treatment assignment (Part 1) and randomization (Part 2). 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 (eg, 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.
- Images will be submitted to a central imaging vendor for BICR at any time during the study. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA022009 Imaging Manual provided by the central imaging vendor.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Perform additional measures, including non-study required laboratory tests, 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.
- Evaluate participant immediately to rule out cardiac or pulmonary toxicity if participant shows cardiac or pulmonary-related signs (hypoxia, abnormal heart rate or changes from baseline) or symptoms (eg, dyspnea, cough, chest pain, fatigue, palpitations).
- 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

9.1.1 Imaging Assessment for the Study

Images will be submitted to a central imaging vendor for blinded independent central review (BICR) during the study. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the CA022009 Imaging Manual provided by the central imaging vendor. Screening and on study images should

be acquired as outlined in Section 2 (Schedule of Activities). Tumor assessments at other timepoints may be performed if clinically indicated and should be submitted to the central imaging vendor as soon as possible. Unscheduled bone scans and CT/MRI should be submitted to the central imaging vendor. X-rays that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should be submitted to the central imaging vendor. Otherwise, they do not need to be submitted centrally.

Collect any additional imaging that may demonstrate tumor response or progression (including scans performed at unscheduled timepoints and/or at an outside institution) for PCWG3 tumor assessment and submit to the BICR.

9.1.1.1 Methods of Measurement

Bone lesions, including those with soft tissue component, will be assessed using Technetium-99m (Tc-99m) based radionuclide bone scans and not by CT or MRI.

Contrast-enhanced CT of the, chest, abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging timepoints. Tumor measurements should be made by the same investigator or radiologist for each assessment, whenever possible. Change in tumor measurements and tumor response to guide ongoing study treatment decisions will be assessed by the investigator using the PCWG3 criteria (refer to Appendix 5).

If a participant has a contraindication for CT intravenous contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for both MRI and CT intravenous contrasts, then a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for MRI (eg, incompatible pacemaker) in addition to contraindication to CT intravenous contrast, then a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

MRI of brain (without and with contrast) should be acquired as outlined in Section 2 (Schedule of Activities). CT of the brain (without and with contrast) can be performed if MRI is contraindicated.

9.1.1.2 Imaging Assessment

Tumor assessments should continue even if dosing is delayed or discontinued. Changes in tumor measurements and tumor responses will be assessed by the same investigator or designee using PCWG3 criteria (refer to Appendix 5). Assessments of PR and CR must be confirmed at least 4 weeks (28 days) after initial response. A best overall response (BOR) of SD requires a minimum of 56 days on study from date of randomization to the date of the first imaging assessment.

9.1.1.3 BICR Confirmation of Progression

Sites should submit scans to the central imaging vendor on a rolling basis, throughout the duration of the study. BICR of scans will occur on a rolling basis, blinded to treatment arm, clinical data, and investigator assessment of submitted scans. When progression per PCWG3 criteria (refer to Appendix 5) is assessed by the investigator, the site will inform the central imaging vendor, in order for BICR assessment of progression to be performed. The BICR will be completed and the results provided to the site as specified in the imaging vendor documents, provided there are no pending imaging queries to the site. All details on the timelines and associated process requirements will be outlined in the Imaging Manual.

Participants whose radiographic progression is not confirmed by the BICR will be required to continue tumor assessments (if clinically feasible) according to the protocol-specified schedule, or sooner if clinically indicated. Also, if participants discontinue treatment without radiographic progression, tumor assessments will continue according to the protocol-specified schedule, as noted in Section 2 (Schedule of Activities) until progression has been confirmed by BICR. In case subsequent therapy has begun, imaging must continue until radiographic progression per PCWG3 is confirmed by BICR.

All study treatment decisions will be based on the investigator's assessment of tumor images and not on the BICR assessment.

9.1.2 Clinical Outcomes Assessments

The evaluation of clinical outcomes assessments (COAs) is an increasingly important aspect of clinical efficacy in oncology trials. Such data provide an understanding of the impact of treatment from the participant's perspective and offer insights into patient experience that may not be captured through physician reporting. Participants in Part 2 will complete the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the single item Functional Assessment of Chronic Illness Therapy General Physical Item 5 (FACIT GP5) as indicated in Section 2 (Schedule of Activities). The questionnaires will be provided in the participant's preferred language, if available, and may be administered using electronic devices or a web-based platform.

If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required, after consultation with the Sponsor or the Sponsor's representative.

9.1.2.1 EORTC QLQ-C30

The European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) will be used to assess the effects of disease symptoms on functioning and well-being.[64] The EORTC QLQ-C30 is the most commonly used quality of life instrument in oncology trials. The instrument's 30 items are divided among 5 functional scales (physical, role, cognitive, emotional, and social), 9 symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health/quality of life scale. With the exception of 2 items included in the

global health/quality of life scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Raw scores for the QLQ-C30 are transformed to a 0 to 100 metric such that higher values indicate better functioning or quality of life or a higher level of symptoms. A score difference of 10 will be used as an estimate of the minimally important difference (MID) for the subscales of the EORTC QLQ-C30.[65]

The EORTC QLQ-C30 will be administered during the treatment period only and not in Safety or Survival Follow-up periods.

9.1.2.2 FACIT GP5

The Functional Assessment of Chronic Illness Therapy - GP5 Item (FACIT GP5) is a single item from the Physical Well-being subscale of the Functional Assessment of Cancer Therapy - General (FACT-G).[66] The single item "I am bothered by side effects of treatment" (GP5) is rated on a 5-point Likert scale. Item responses are 1 - not at all to 5 - very much. This single item will be administered to assess the overall extent of perceived bother due to symptomatic adverse events. Evidence exists for the validity of this item and its usefulness as an overall summary measure of burden due to symptomatic treatment toxicities.[67]

The FACIT GP5 will be collected for the first 12 weeks of treatment only.

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, or a surrogate).

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

Refer to Appendix 3 for SAE reporting.

Use CTCAE v5 definitions and grading for safety reporting of all AE and SAEs on the case report form.

Contacts for SAE reporting are also specified in Appendix 3**.**

Immune-mediated adverse events (IMAEs) are AEs consistent with an immune-mediated mechanism or immune-medicated 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 [redacted]. Information supporting the assessment will be collected on the participant's case report form.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 100 days following discontinuation of dosing.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study intervention or protocol-specified procedure (eg, a follow-up skin biopsy, insert other appropriate example if needed.).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- 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 or designee within 24 hours of updated information 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 intervention 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.

- The collection of non-serious AEs (with the exception of non-serious AEs related to SARS-CoV-2 infection) should begin at initiation of study treatment and collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.
- All SAEs, and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection must be collected from the date of the participant's written consent until 100 days following discontinuation of dosing.

For participants randomized/assigned to treatment and never treated with study drug, collect SAEs for 30 days from the date of randomization/treatment assignment.

Collect all nonserious adverse events (not only those deemed to be treatment-related) continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

Every adverse event must be assessed by the investigator with regards to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form.

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 intervention and for those present at the end of study intervention 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 AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection will be followed until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up (as defined in Section 8.3) or for suspected cases, until SARS-CoV-2 infection is ruled-out.

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 toward 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 (eg, 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.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A SUSAR (suspected, unexpected serious adverse reaction) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsor or designee. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

If any sexual activity involving penile intercourse (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom during and at least for

3 months, after study product administration, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE eCRF, 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 intervention 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 (eg, anemia vs low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury

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 DILI is defined as:

- AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
  AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase not attributed to bone metastasis)
  AND
- 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 of conditions noted during interim or final physical examinations, ECG, radiographic imaging, or any other potential safety assessment required or not required by the protocol should also be recorded as a nonserious AE or SAE, 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. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

In the event of an overdose, the treating physician should:

- Contact the Medical Monitor immediately
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities until at least 5 times the projected elimination half-life of BMS-986218 (5× 15 days = 75 days), of nivolumab (5× 25 days = 125 days), and of docetaxel (5× 11 hours = 55 hours)
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis)
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF

There are a few reports of docetaxel overdose. There is no known antidote for docetaxel overdose. In case of overdose, the participant should be kept in a specialized unit and vital functions closely monitored. Exacerbation of AEs may be expected. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neurotoxicity, and mucositis. Participants should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

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.

Table 9.4.4-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST)[a] Alanine aminotransferase (ALT)[a] Total bilirubin, with reflex direct bilirubin[b] if > ULN Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine Blood urea nitrogen (BUN) or serum UREA Glucose	Total protein Albumin - screening only Sodium Potassium Chloride Calcium Phosphorus Creatine kinase TSH, free T3 and free T4 - screening TSH, with reflexive free T3 and free T4 if TSH is abnormal - on treatment
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	
Serology	
HIV-1 and -2 antibody (screening only, where mandated locally; refer to Appendix 7) Hepatitis B/C, (HBV sAG, HCV antibody or HCV RNA), - screening only	
Other Analyses	
Prostate Specific Antigen ([PSA]; PSA should be performed by the same lab throughout the treatment period to avoid variations in results between cycles)	
Testosterone (at screening only)	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HBV, hepatitis B virus; HBV sAG, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; RNA, ribonucleic acid; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

[a] INR is optional to better evaluate elevated liver function tests

[b] Direct bilirubin testing for all participants with Gilbert's syndrome

9.4.5 Imaging Safety Assessment

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.

9.5 Pharmacokinetics

Separate serum samples will be collected for PK and anti-drug antibody (ADA) assessments of BMS-986218, following the schedule presented in the following tables for participants treated with BMS-986218 and docetaxel (Table 9.5-1 for Part 1A and Part 2, Arm 2b) or BMS-986218, nivolumab, and docetaxel (Table 9.5-2 for Part 1B and Part 2, Arm 2c). Separate serum samples will be collected for PK and ADA assessments of nivolumab, following the schedule presented in the Table 9.5-2 for participants treated with BMS-986218, nivolumab, and docetaxel.

Table 9.5-1: Pharmacokinetic and Anti-Drug Antibody (ADA) Sampling Schedule for BMS-986218 Q3W when Co-administered with Docetaxel in Part 1A and Part 2 (Arm 2b)

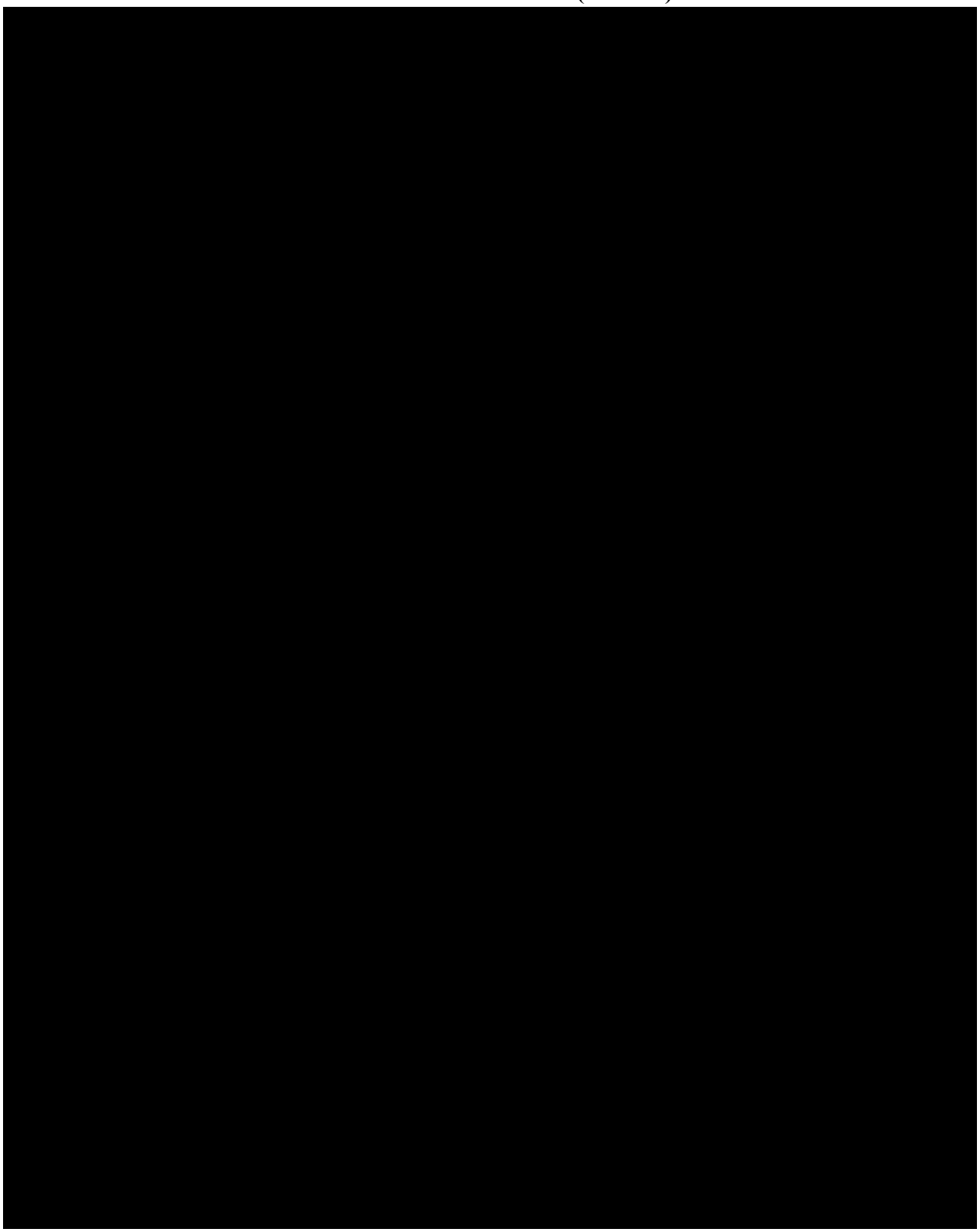


Table 9.5-2: Pharmacokinetic and Anti-Drug Antibody (ADA) Sampling Schedule for BMS-986218 Q3W in Combination with Nivolumab and Docetaxel for Part 1B and Part 2 (Arm 2c)

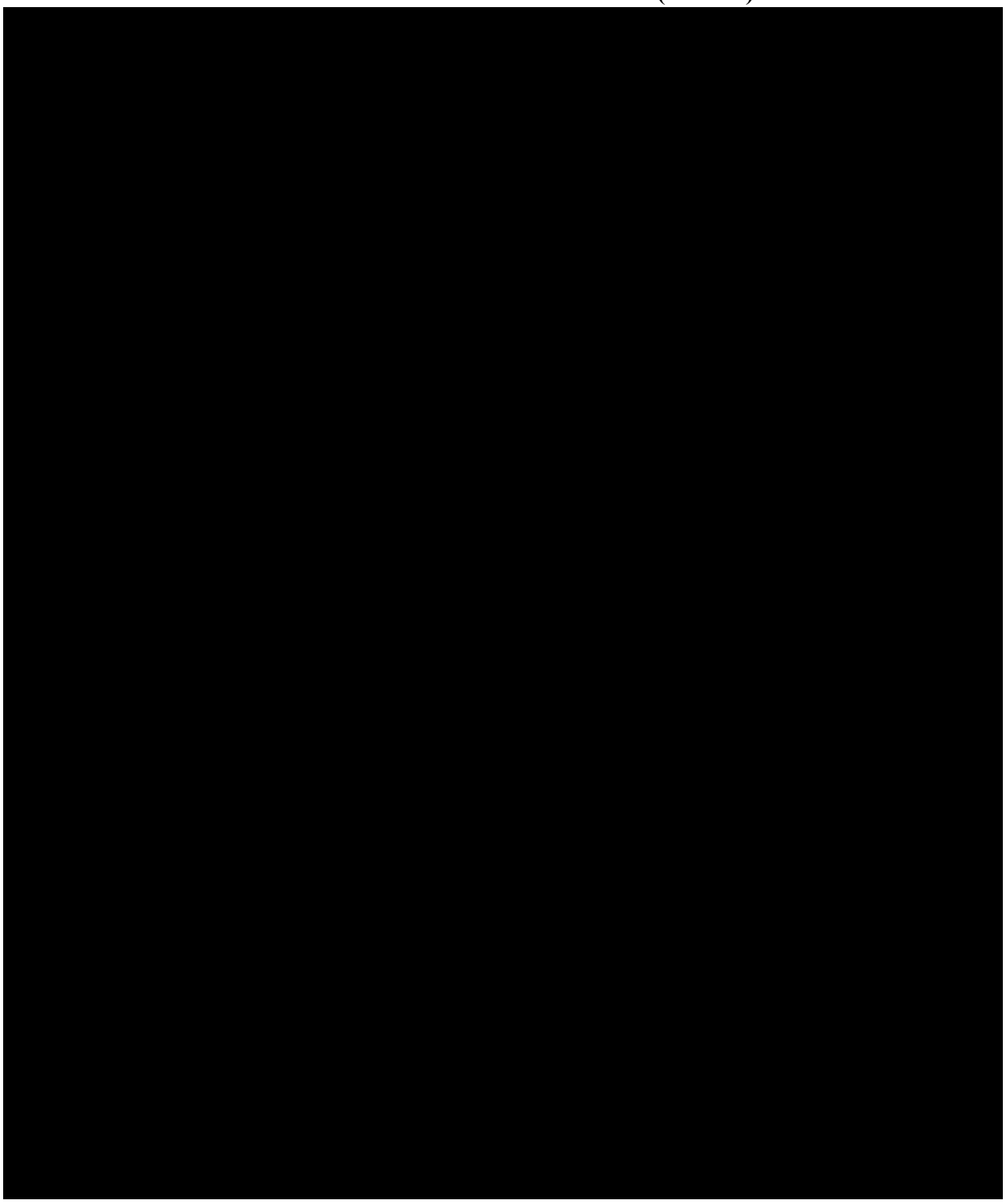


Table 9.5-2: Pharmacokinetic and Anti-Drug Antibody (ADA) Sampling Schedule for BMS-986218 Q3W in Combination with Nivolumab and Docetaxel for Part 1B and Part 2 (Arm 2c)

Individual participant PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses. The following PK parameters for BMS-986218 and nivolumab will be reported:

Ceoi	End of infusion concentration
Ctrough	Trough-observed serum concentration

BMS-986218 PK data may also be used in an integrated population PK or exposure-response analysis along with data from other BMS-986218 studies, which would be the subject of a separate report.

Sparse nivolumab PK data will be collected and may be used in an integrated population PK or exposure-response analysis along with data from other nivolumab studies, which would be the subject of a separate report.

All on-treatment timepoints are intended to align with days on which study intervention is administered. If it is known that a dose is going to be delayed, then the predose sample, if appropriate, should be collected just prior to the delayed dose. However, if a predose sample is

collected but the dose is subsequently delayed, an additional predose sample should not be collected. Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. If the infusion was interrupted, the interruption details will also be documented on the CRF. Further details of sample collection, processing, and shipment will be provided in the laboratory/procedure manual. Treatment assignments will be released to the bioanalytical laboratory in order to minimize unnecessary analysis and/or reanalysis of PK/ADA samples.

Concentration analyses for BMS-986218 and nivolumab will be performed by validated bioanalytical method(s).

Bioanalytical samples designated for assessments (eg, immunogenicity, PK, or biomarker) from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to, insufficient volume for complement assessment, to follow-up on suspected immunogenicity related AE, etc).

Additionally, residual bioanalytical samples will be archived and may be used for potential exploratory bioanalysis (including, but not limited to, analysis of drug-ADA immune complexes, metabolite analyses, etc) and or for additional method purposes (including, but not limited to, cross-validation, ADA/PK selectivity, cutpoint, etc).

9.6 Immunogenicity Assessments

Antibodies to BMS-986218 or nivolumab will be evaluated in serum samples collected from all participants according to the Table 9.5-1 and Table 9.5-2. Serum samples will be screened for antibodies binding to BMS-986218 or nivolumab, and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of BMS-986218 and nivolumab.

The detection and characterization of antibodies to BMS-986218 and nivolumab will be performed using validated method(s). Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to BMS-986218 and nivolumab. Additionally, residual samples may be used for additional method purposes (including but not limited to cross-validation, ADA/PK selectivity, cut point, etc).

9.7 Genetics

See Section 9.8.3 and Section 9.8.4 for relevant planned genomic analysis in blood and tumor samples from pre-treatment and on-treatment samples.

9.8 Biomarkers

Biomarker measures of baseline and on-treatment peripheral blood, serum, and tumor samples will be used to identify pharmacodynamic markers associated with treatment. Additional biomarkers related to mechanism of action, safety biomarkers, and associations with response to docetaxel, BMS-986218 + docetaxel and BMS-986218 + nivolumab + docetaxel will be explored.

Peripheral blood and tumor tissue will be collected prior to therapy and on treatment. A biopsy (block or slides) should also be performed if medically feasible at the time of progression for participants on treatment for more than 6 cycles, for all study parts. If biomarker samples are drawn but study treatment(s) is not administered, samples will be retained. A detailed description of each assay system is provided below and a schedule to evaluate biomarkers of response is provided in Table 9.8-1. Further details of blood and tumor collection and processing will be provided to the site in the procedure manual.

Table 9.8-1: Biomarker Sampling Schedule for Part 1 and Part 2

Study Day of Sample Collection (1 cycle = 3 weeks)	Event	Tumor Biopsy[a]	Serum (Cytokines)[a]	Whole Blood Plasma (ctDNA)[a]	Whole Blood (germline and TCR)[a]	Whole Blood (PAXgene)[a]	Blood (Immuno-phenotyping)[a]	Anti-SARS-CoV-2 Serology[a]
Screening		X	X	X				X
Cycle 1 Day 1	Predose[b]		X	X	X	X	X	
Cycle 1 Day 8			X				X	
Cycle 1 Day 15				X			X	
Cycle 2 Day 1	Predose[b]		X			X	X	
Cycle 2 Day 15		X[c]	X[d]	X[d]	X[d]	X[d]	X[d]	
Cycle 3 Day 1	Predose[b]		X					
Cycle 4 Day 1	Predose[b]			X	X			
Every fourth cycle starting with Cycle 9 Day 1 until EOT (Cycle 13 Day 1, Cycle 17 Day 1, Cycle 21 Day 1, Cycle 25 Day 1, etc)	Predose[b]			X				
Approximately every 6 months during study treatment								X

Table 9.8-1: Biomarker Sampling Schedule for Part 1 and Part 2

Study Day of Sample Collection (1 cycle = 3 weeks)	Event	Tumor Biopsy[a]	Serum (Cytokines)[a]	Whole Blood Plasma (ctDNA)[a]	Whole Blood (germline and TCR)[a]	Whole Blood (PAXgene)[a]	Blood (Immuno-phenotyping)[a]	Anti-SARS-CoV-2 Serology[a]
Approximately 4 weeks after documented or suspected SARS-CoV-2 infection								X
At progression		X	X	X	X	X	X	X[e]

Abbreviations: ctDNA, circulating tumor deoxyribonucleic acid; EOT, end of treatment; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCR, T-cell repertoire.

[a] Instructions for the collection and processing of all samples will be provided in the laboratory manual. Crossover participants in Arm 2d will not have any biomarkers samples drawn or tumor biopsies performed with the exception of anti-SARS-CoV-2 serology, which should follow the above table.

[b] All predose samples should be taken prior to infusion.

[c] Tumor biopsies to be performed, if medically feasible, between Cycle 2 Day 15 and Cycle 3 Day 1 (prior to dosing; if there is a delay in dosing Cycle 3, biopsy can be taken up until Cycle 2 Day 28 as long as it is prior to the Cycle 3 dose). A biopsy should also be performed, if medically feasible, at the time of progression for participants on-treatment for more than 6 cycles, for all study parts (excluding crossover participants in Arm 2d). For participants who have toxicities related to study therapy (ie, cytopenia) that may put them at increased risk from the biopsy, the on-study biopsy is not required. If the only site amenable to biopsy is also the only site of measurable disease, the investigator should prioritize maintaining a measurable target lesion (by RECIST v1.1) if there is a concern that the biopsy might impact tumor assessment. Investigators can provide an additional tumor biopsy during the course of the study if the tumor samples are obtained as part of standard care.

[d] For participants undergoing on-treatment tumor biopsies, collections to be aligned with tumor biopsies.

[e] Will be collected during a 30-day window during the follow-up period.

9.8.1 Peripheral Blood Biomarkers

A variety of factors that may impact the immunomodulatory properties and efficacy of BMS-986218 will be investigated in peripheral blood specimens taken from all participants prior to or during treatment. Results from these investigations will be evaluated for associations with dose, response, survival, and/or safety (AE) data. Several analyses will be completed and are described briefly below.

9.8.2 Exploratory Serum and Plasma Biomarkers

Blood samples for exploratory biomarker analyses will be drawn pre- and post-treatment at specified time points in Table 9.8-1, processed for serum and plasma, and retained in frozen storage. Serum and plasma samples may be assessed by enzyme-linked immunosorbent assay (ELISA), circulating tumor DNA (ctDNA) measurements, or metabolomics for prostate or immune-related factors that will predict for safety and efficacy of docetaxel, BMS-986218 + docetaxel and BMS-986218 + nivolumab + docetaxel. Serum/plasma-based analyses may include, but not necessarily be limited to, soluble CXCL9, CXCL10, CTLA-4, MIC-A, MIC-B, interleukin 6 (IL-6), cytochrome P450 enzymes, ICOS, anti-SARS-CoV-2 antibodies, and ctDNA.

9.8.2.1 Plasma ctDNA

The presence of cell-free DNA in circulating blood is a well-documented phenomenon. Fragments of DNA are shed into the blood stream from dividing cells during cell proliferation or cell death. In subjects with cancer, a fraction of this DNA is tumor-derived and is termed circulating tumor DNA (ctDNA). Albeit small, fragments of DNA average between 180 to 200 base pairs and specific genomic regions can be amplified with polymerase chain reaction (PCR). Moreover, several studies have detected mutations in ctDNA that exactly correspond to mutations from the parent tumor. Using tissue and plasma, BEAMing or similar technology will be utilized to measure cell-free DNA and the presence/frequency of various mutations in the circulation. TMB will also be assessed in plasma.

9.8.3 Immunophenotyping

The proportion of specific lymphocyte subsets and expression levels of T-cell co-stimulatory markers in peripheral blood mononuclear cell preparations will be quantified by flow cytometry. Analyses may include, but not necessarily be limited to, the proportion of T-, B-, and natural killer cells, granulocytes, the proportion of memory, effector, and Tregs subsets, as well as expression levels of CTLA-4, NKG2D, ICOS, and Ki67.

9.8.3.1 T-cell Repertoire Analysis

The diversity of the peripheral T-cell compartment and changes over the course of treatment with immunotherapeutic agents may be related to the mechanism of action of BMS-986218. In order to explore whether a diverse T-cell repertoire (TCR) is associated with response to therapy, next-generation, high-throughput, deoxyribonucleic acid (DNA) sequencing will be performed on DNA isolated from peripheral blood and tumor tissue to quantitate the composition of the TCR prior to and during therapy.

9.8.3.2 Germline DNA Variants

Whole blood will be collected from all participants prior to treatment to generate genomic DNA for single nucleotide polymorphism (SNP) analyses and to serve as a reference for tumor genomic testing, including tumor mutational load assessment. These genomic analyses will include assessment of SNPs within genes associated with CTLA-4 and other immunoregulatory signaling pathways (eg, CD16) to determine if natural variation within those genes is associated with response to BMS-986218 and/or with AEs during treatment.

9.8.3.3 Gene Expression Profiling

Whole blood collected in PAXgene tubes or equivalent fixative will be examined for messenger ribonucleic acid (mRNA) gene expression by RNA sequencing (RNAseq) or quantitative real-time polymerase chain reaction (qRT-PCR) to characterize gene expression profiles associated with immune modulation or outcome following treatment with BMS-986218.

9.8.4 Tumor Samples

Fresh tumor biopsy specimens will be obtained at screening prior to treatment from participants who have soft tissue lesion that is suspected to represent metastatic disease based on local review of imaging and is considered accessible for biopsy by an interventional radiologist (or other appropriate specialist) to characterize immune cell populations and expression of selected tumor markers. Lymph nodes must measure at least 1 cm in diameter along the short axis in order to be considered for biopsy. Fresh biopsy specimens are mandatory for these participants. Tumor specimens may be collected between Cycle 2 Day 15 and Cycle 3 Day 1; if there is a delay in Cycle 3 dosing, biopsy can be taken up until Cycle 2 Day 28 as long as it is prior to the Cycle 3 dose. Bone lesion biopsies are unacceptable for submission. See Table 9.8-1 for the tumor collection schedule. Tissue biopsies will also be performed on treatment to characterize pharmacodynamic changes, including CTLA-4-expressing immune cell populations, and tumor factors. Pharmacodynamic changes within biomarkers in the tumor biopsy collected at progression will be utilized to evaluate the underlying mechanism(s) of acquired resistance to study treatment. If available, correlative analyses via gene expression and immunohistochemistry (IHC) expression characterization can be performed with fresh formalin-fixed, paraffin-embedded (FFPE) tissue samples. Investigators can provide an additional tumor biopsy during the course of the study if the tumor samples are obtained as part of standard care.

- Both the screening and on-treatment tumor biopsies should be preferentially collected from the same site, if feasible. At the time of progression, the biopsy should be performed using a progressive lesion or a new lesion, if feasible.
- Tumor biopsy samples should be obtained from core biopsy, punch biopsy, excisional biopsy, or surgical specimen, as fine needle aspirates and other cytology specimens are insufficient for downstream biomarker analyses. Bone lesion biopsies are unacceptable for submission.
- On-treatment and progressive disease (PD) biopsies are mandated at acceptable clinical risk (as determined by the investigator). Please notify the BMS Medical Monitor (or designee) if on-treatment biopsy may pose unacceptable clinical risk or if tumor at the time of on-treatment biopsy is not accessible for sampling. Institutional guidelines for the safe performance of biopsies should be followed.

- If the only site amenable to biopsy is also the only site of measurable disease, the investigator should prioritize maintaining a measurable target lesion (by RECIST v1.1) if there is a concern that the biopsy might impact tumor assessment.

Note: For participants with bone-only disease, inaccessible soft tissue lesions, or if the biopsy procedure would pose an unacceptable clinical risk for the participant, submission of tumor tissue obtained from a fresh biopsy is not required.

9.8.4.1 Characterization of Tumor Immune Microenvironment

Immunohistochemistry (IHC) will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within FFPE tumor tissue before and after exposure to therapy. These IHC analyses will include, but not necessarily be limited to, the following markers: FOXP3, CTLA-4, CD16, CD3, CD8, PD-L1, and Granzyme B.

9.8.4.2 Characterization of Tumor T-cell Repertoire

As described above, DNA sequencing may be performed on pre- and post-treatment tumor tissue to assess the composition of the TCR. DNA will be isolated from either the FFPE tumor block or equivalent preparations.

9.8.4.3 Gene Expression Profiling

Fresh tumor biopsies that are collected at screening will be examined for mRNA gene expression by RNAseq, quantitative polymerase chain reaction (qPCR), or other technologies to characterize gene expression profiles associated with outcome following treatment with BMS-986218 in combination with docetaxel and BMS-986218 in combination with docetaxel plus nivolumab.

9.8.4.4 Mutational and DNA Methylation Analyses

DNA from tumor samples will be collected between Cycle 2 Day 15 and Cycle 3 Day 1 and analyzed using whole exome sequencing to determine the number and identity of mutations found within a tumor.

9.9 Additional Research

All PK, biomarker, cytokine, and residual samples will be collected for additional research (AR). Sample retention for additional research is mandatory for all participants, except where prohibited by local laws or regulations.

This protocol will include residual sample storage for AR.

For All US sites:

Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, prohibited by local laws or regulations, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

For non-US Sites:

Additional research is optional for all study participants, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

Additional research is intended to expand the R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression, and response to treatment etc.

All requests for access to samples or data for additional research will be vetted through a committee of the study Sponsor's senior leaders in Research and Development to ensure the research supports appropriate and well-defined scientific research activities.

Sample Collection and Storage

- Residual blood, serum, plasma, and tumor biopsies from available biomarker collection timepoints (Table 9.9-1) will also be retained for additional research purposes

Samples kept for future research will be stored at the BMS Biorepository in [redacted] or an independent, BMS-approved storage vendor.

The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.

Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual**.**

Table 9.9-1: Residual Sample Retention for Additional Research Schedule

Sample Type	Timepoints for which residual samples will be retained
Residual Serum and Plasma	All biomarker collections and all PK collections
Tumor Biopsy and Blood Collection	Screening, on-treatment, and at disease progression (if available)

Abbreviation: PK, pharmacokinetic.

9.10 Other Assessments

Whole blood, serum and plasma samples will be collected at the times indicated in Table 9.8-1 for the measurement of DNA, RNA, and protein biomarkers. These measurements may include, but are not limited to, assessments of SARS-CoV-2 serologic status. Serum will be collected as indicated in Table 9.8-1 for possible measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG antibody).

9.11 Health Economics OR Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

BMS-986218 or BMS-986218 plus nivolumab will be safe and tolerable in combination with docetaxel and will improve clinical activity in participants with mCRPC as measured by rPFS.

10.2 Sample Size Determination

Sample Size Justification for Safety Lead-in Portion (Part 1):

Escalation/de-escalation decisions will be guided by the BOIN design (refer to Appendix 9). Though the exact number treated at a dose level will depend on the number of participants with a DLT, approximately 12 DLT-evaluable participants may be treated in Part 1A to assess the tolerability of BMS-986218 in combination with docetaxel. Similarly, in Part 1B, approximately 12 to 18 participants may be treated with BMS-986218 in combination with docetaxel and nivolumab. With a maximum of 12 DLT-evaluable participants at a dose level, there will be above 80% probability to observe at least 1 occurrence of a safety event if the event rate in the population is 13%. Similarly, with 6 or 9 DLT-evaluable participants at a dose level, there will be above 80% probability to observe at least 1 occurrence of the safety event if the event rate in the population is 24% or 17%, respectively. A minimum of 6 DLT-evaluable participants and no more than 12 DLT-evaluable participants will be evaluated at a dose level in Part 1A or Part 1B to ensure tolerability prior to initiating enrollment in Part 2 at these dose levels. Therefore, a total of approximately 30 DLT-evaluable participants may be evaluated during the safety lead-in,

including at least 6 participants (with 0 or 1 DLT) at each of the BMS-986218 + docetaxel and BMS-986218 + nivolumab + docetaxel combination doses that will be evaluated in Part 2.

Sample Size Justification for Randomized, Controlled Portion (Part 2):

The sample size of the study is calculated to have sufficient power for the primary efficacy endpoint of rPFS to compare Arm 2c to Arm 2a and Arm 2b to Arm 2a. Assuming that Arm 2a median rPFS is 6 months and a constant HR of 0.55 for the Arm 2c to Arm 2a comparison (for target median rPFS = 10.9 months), a total of 78 rPFS events will need to be observed across these 2 arms, in order to have 91.3% power to show a difference at the 20% 2-sided alpha level, in this population, based on 58 participants per arm. Based on hierarchical testing of Arm 2b vs Arm 2a, assuming there was statistical significance in the Arm 2c vs Arm 2a comparison, and a constant HR of 0.62 for the Arm 2b to Arm 2a comparison, a total of 79 rPFS events will need to be observed across these 2 arms, with 58 participants per arm in order to have 80% power to show a difference at the 20% 2-sided alpha level. These calculations assume 18 months for accrual and a minimum of 10 months follow up. A total of 174 participants will need to be randomized assuming about 21% dropout rate across arms (5% in control arm, 9% in the BMS-986218 + docetaxel arm, and 7% in the BMS-986218 + nivolumab + docetaxel arm).

The actual time of the final analysis will be based on the number of events observed, which will be monitored separately among Arm 2c and Arm 2a and among Arm 2b and Arm 2a during the study conduct.

10.3 Analysis Sets

For the purpose of analysis, the following populations are defined in Table 10.3-1:

Table 10.3-1: Analysis Sets

Population	Description
Enrolled	All participants who sign informed consent and are registered in IRT
Treated	All participants who received any amount of study intervention
Randomized	All participants who were randomized using IRT in Part 2
Response-evaluable	All participants who received at least 1 dose of study intervention, have a baseline tumor assessment with measurable disease, and 1 of the following: 1) At least 1 evaluable on-treatment tumor assessment, 2) Clinical progression, or 3) Death prior to the first on-treatment tumor evaluation
PSA-response Evaluable	Participants with PSA values ≥ 2 ng/mL at baseline and at least 1 post-baseline assessment

Table 10.3-1: Analysis Sets

Population	Description
DLT-evaluable	All treated participants in Part 1A or Part 1B who have received study intervention (all components) and have completed the DLT-evaluation period of 6 weeks, or who discontinued any study intervention due to toxicity prior to completing the DLT-evaluation period
Pharmacokinetic	All treated participants who have evaluable concentration-time data
Immunogenicity	All treated participants who have baseline and at least 1 post-baseline pre-infusion immunogenicity assessment
Biomarker	All treated participants with available biomarker data
Clinical Outcomes Assessments (COAs)	All participants with baseline and at least 1 post-baseline COA assessment

Abbreviations: COA, clinical outcomes assessment; DLT, dose-limiting toxicity; IRT, Interactive Response Technology; PSA, prostate-specific antigen.

10.4 Statistical Analyses

The statistical analysis plan (SAP) 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.

A description of the participant population will be included in the clinical study report, including subgroups of age, gender, race, and other study-specific populations and demographic characteristics. A description of participant disposition will also be included in the clinical study report.

10.4.1 General Considerations

The analysis of safety (Part 1 and Part 2) will be based on All treated population. The efficacy analysis in Part 2 will be based on All randomized population. Part 1 efficacy results will be described separately for All treated population.

Efficacy analysis in Part 2 will be performed with the family-wise error rate controlled at 20%. The primary endpoint of rPFS will be first compared between Arm 2a and Arm 2c at the 2-sided significance level of 20%. The rPFS difference between Arm 2b and Arm 2a will be statistically tested only if the Arm 2c vs Arm 2a comparison meets statistical significance. Otherwise, the Arm 2b vs Arm 2a results will be descriptive.

Statistical analysis of participants in Arm 2a who receive crossover treatment upon progression will be presented separately, after the start of intervention in the crossover arm (Arm 2d).

10.4.2 Primary Endpoint(s)

The primary endpoint for Part 1 is to assess safety based on incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, TRAEs, AEs leading to discontinuation, and deaths. In addition, the selected tolerable dose levels of BMS-986218 in combination with docetaxel (Part 1A) and BMS-986218 in combination with docetaxel and nivolumab (Part 1B) will be determined using the DLT rate within the 6-week DLT window among DLT-evaluable participants in Part 1A and in Part 1B. The incidence of DLTs will be calculated for DLT-evaluable participants and compared to the actions recommended by the BOIN design to guide the dose escalation/stay/de-escalation decision for the BMS-986218 + docetaxel treatment and for the BMS-986218 + nivolumab + docetaxel treatment.

The primary endpoint for Part 2 is rPFS of BMS-986218 + docetaxel and BMS-986218 + nivolumab + docetaxel combination therapies compared to rPFS of docetaxel monotherapy control, in the randomized population. rPFS is defined as the time from randomization to the date of first documented radiographic progression per BICR using PCWG3 or death due to any cause, whichever occurs first. Participants who do not progress or die will be censored on the date of their last evaluable tumor assessment. Participants who did not have any evaluable on-study tumor assessments and did not die will be censored at randomization date.

The primary endpoints and analyses are shown in Table 10.4.2-1.

Table 10.4.2-1: Primary Endpoints and Statistical Analyses

Endpoint Description	Analysis	Timeframe
Safety Lead-in (Part 1A and Part 1B): The primary safety endpoint is the incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, TRAEs, AEs leading to discontinuation, and deaths	AEs will be presented using NCI CTCAE v5. On-study incidence of AEs, SAEs, TRAEs, and AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v5 criteria by System Organ Class and Preferred Term	DLT observation period is up to 6 weeks from start of treatment. All AEs up to 100 days after the last treatment of study drug, eg, 28 months since start of treatment at time of final analysis, and up to the end of survival follow-up (approximately 4 years)
Randomized, Controlled Portion (Part 2): rPFS for randomized participants is the time between randomization date and the first date of documented radiographic progression, or death due to any cause, whichever occurs first. The radiographic progression will be assessed by Blinded Independent Central Review (BICR) per PCWG3	The rPFS curve will be estimated using the Kaplan-Meier product-limit method. A log-rank test stratified by presence of measurable disease (Y/N), will be used to compare rPFS between Arm 2c and Arm 2a. Hazard Ratio (HR) and corresponding 2-sided 95% CI for rPFS primary endpoint analysis will be estimated using a Cox proportional hazard model, with treatment arm as a single covariate, stratified by presence of measurable disease to assist in interpretation of the rPFS analysis. A similar analysis will be performed to compare Arm 2b to 2a, with statistical testing only if Arm 2c to Arm 2a comparison met statistical significance	Time from randomization until the number of needed events are met, expected approximately at 28 months since start of randomization

Abbreviations: AE, adverse event; BICR, blinded independent central review; CI, confidence interval; DLT, dose-limiting toxicity; HR, hazard ratio; NCI CTCAE v5, National Cancer Institute Common Terminology Criteria for Adverse Events version 5; PCWG3, Prostate Cancer Working Group 3; rPFS, radiographic progression-free survival; SAE, serious adverse event; TRAE, treatment-related adverse event; Y/N, yes/no.

Efficacy analysis will be performed with the family-wise error rate controlled at 20%. The BMS-986218 + nivolumab + docetaxel treatment will be first compared vs the docetaxel monotherapy control. rPFS will be compared between the BMS-986218 + nivolumab + docetaxel treatment group and the docetaxel monotherapy control, using stratified log-rank test (presence of measurable disease). If this comparison meets statistical significance, then the BMS-986128 + docetaxel treatment group will be tested similarly versus the docetaxel monotherapy control.

The stratified hazard ratio (stratified by presence of measurable disease) from Cox regression model comparing each combination treatment arm to the control will be presented along with 95% CI.

Median rPFS will be estimated using Kaplan-Meier approach for each arm. A two-sided 95% CI (log-log transformation) for median rPFS will also be computed. rPFS rates at specified time points (ie, 6 months, 12 months, etc) will be computed along with 95% CI using log-log transformation.

10.4.3 Secondary Endpoint(s)

The secondary endpoints (Part 2) and statistical analysis methods are described in Table 10.4.3-1. There is no adjustment for multiplicity for secondary endpoints.

The effect of each treatment will be estimated based on the additional efficacy endpoints using point estimates and 95% CI. Details of censoring rules for the time-to-event endpoints will be provided in the study SAP. All efficacy endpoints analysis will use all randomized population for primary analysis, unless otherwise specified.

Table 10.4.3-1: Secondary Endpoints (Part 2) and Statistical Analyses

Endpoint Description	Analysis	Timeframe
Objective Response Rate per PCWG3 (ORR-PCWG3) is the proportion of participants who have a confirmed complete or partial best overall response (BOR) per PCWG3 among randomized participants who have measurable disease at baseline. The BOR is defined as the best response designation, as determined by the BICR, recorded between the date of randomization and the date of objectively documented radiographic progression, or last tumor measurement, whichever occurs first	Summary statistics of BOR will be tabulated by treatment arm. The ORR estimates and 95% CI will be tabulated by cohort and calculated based on the Clopper-Pearson method the ORR difference between Arm 2b vs Arm 2a and Arm 2c vs Arm 2a will also be tabulated with point estimates and 95% CI	Approximately 28 months since the start of randomization (based on the number of needed rPFS events)
Time to Response per PCWG3 (TTR-PCWG3) is the time from randomization date to the date of the first documented CR or PR per PCWG3, as determined by BICR	TTR-PCWG3 will be tabulated for the responders by treatment arm using summary statistics	Approximately 28 months since the start of randomization (based on the number of rPFS events for primary analysis)
Duration of Response per PCWG3 (DOR-PCWG3) is the time between the date of first response (CR/PR per PCWG3) to the date of first documented radiographic progression per PCWG3 as determined by BICR, or death due to any cause	DOR-PCWG3 will be tabulated by Kaplan-Meier estimates and 95% CI. Participants who neither progress nor die will be censored at the last tumor assessment	Approximately 28 months since the start of randomization (based on the number of rPFS events for primary analysis)
PSA Response Rate (PSA-RR) is the proportion of randomized participants with a 50% or greater decrease in PSA from baseline (defined as Cycle 1 Day 1 pre-treatment) to any post-baseline PSA result. A second consecutive value obtained 3 or more weeks later is required to confirm the PSA response	PSA-RR will be calculated for all participants who are PSA-response evaluable. Summary statistics of PSA-RR will be tabulated by cohort by point estimates and 95% CI based on the Clopper-Pearson method; The PSA-RR difference between Arm 2b vs Arm 2a and Arm 2c vs Arm 2a will also be tabulated with point estimates and 95% CI	Approximately 28 months since the start of randomization (based on the number of rPFS events for primary analysis)

Table 10.4.3-1: Secondary Endpoints (Part 2) and Statistical Analyses

Endpoint Description	Analysis	Timeframe
Time to PSA Progression (TTP-PSA) is the time between randomization date to the date of PSA progression per PCWG3 in randomized participants.	TTP-PSA will be tabulated by Kaplan-Meier estimates and 95% CI. TTP-PSA for participants without a PSA progression, will be censored at the date of last PSA evaluation. For participants with no post-baseline PSA evaluation, the time will be censored at the date of randomization	Approximately 28 months since the start of randomization (based on the number of rPFS events for primary analysis)
Overall Survival (OS) for all randomized participants is the time between randomization date and the date of death from any cause	The OS curve will be estimated for each treatment arm using the Kaplan-Meier product-limit method. Hazard Ratio of Arm 2c: Arm 2a and Arm 2b: Arm 2a and corresponding 2-sided 95% CI for OS will be estimated using a Cox proportional hazard model, with treatment arm as a single covariate, stratified by presence of measurable disease to assist in interpretation of the analysis	4 years since randomization
Overall safety and tolerability will be measured by the incidence of AEs, TRAEs, SAEs, AEs leading to discontinuation, and deaths	AEs will be presented using NCI CTCAE v5. On-study incidence of AEs, SAEs, TRAEs, and AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v5 criteria by System Organ Class and Preferred Term	28 months at the primary endpoint analysis time; in addition, up to 100 days after the last treatment of study drug, or end of survival follow-up eg, at 4 years

Abbreviations: AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; NCI CTCAE v5, National Cancer Institute Common Terminology Criteria for Adverse Events version 5; ORR, objective response rate; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; PSA, prostate-specific antigen; PR, partial response; PSA-RR, PSA response rate; rPFS, radiographic progression-free survival; SAE, serious adverse event; TRAE, treatment-related adverse event; TTP-PSA, time to PSA progression; TTR, time to response.

It may be noted that for the time to PSA progression (TTP-PSA) endpoint, in participants with an initial PSA decline from baseline, the date of PSA progression is the date that an increase of 25% or more and an absolute increase of 2 ng/mL or more from the nadir are documented and confirmed by a second consecutive PSA value at least 3 weeks later. For participants with no PSA decline from baseline, the date of PSA progression is the date that an increase of 25% or more and an absolute increase of 2 ng/mL or more from baseline are documented beyond Week 12.

10.4.4 Exploratory Endpoint(s)

10.4.4.1 Pharmacokinetic Analysis for BMS-986218 and Nivolumab

Statistical analyses for exploratory PK endpoints are summarized in Table 10.4.4.1-1.

Table 10.4.4.1-1: Pharmacokinetic - Statistical Analyses

Endpoint	Statistical Analysis Methods
Ceoi, Ctrough	Summary statistics of PK parameter: geometric means and coefficients of variation, by treatment and by day

Abbreviations: Ceoi, end of infusion concentration; Ctrough, trough-observed serum concentration (this includes predose concentrations [C0] and Ctau); PK, pharmacokinetic.

PK serum concentration-time data for BMS-986218, and nivolumab may be pooled with data from other studies for integrated population PK and ER analyses, which will be presented in a separate report.

10.4.4.2 Immunogenicity Analysis

Statistical analyses for endpoints related to the immunogenicity of BMS-986218 and nivolumab are summarized in Table 10.4.4.2-1 and Table 10.4.4.2-2, respectively.

Table 10.4.4.2-1: Immunogenicity of BMS-986218 - Statistical Analyses

Endpoint	Statistical Analysis Methods
Incidence of ADA to BMS-986218 Baseline ADA-positive participant is defined as a participant who has an ADA-detected sample at baseline.[a,b] ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the treatment	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment

Abbreviations: ADA, anti-drug antibody; SAP, statistical analysis plan.

[a] Baseline sample is the last sample before initiation of the treatment.

[b] Details of the immunogenicity data analysis, including ADA titers, will be provided in the SAP.

Table 10.4.4.2-2: Immunogenicity of Nivolumab - Statistical Analyses

Endpoint	Statistical Analysis Methods
Incidence of ADA to nivolumab Baseline ADA-positive participant is defined as a participant who has an ADA-detected sample at baseline.[a,b] ADA-positive participant is a participant with at least 1 ADA-positive sample relative to baseline after initiation of the treatment	Frequency distribution of baseline ADA-positive participants and ADA-positive participants after initiation of the treatment

Abbreviations: ADA, anti-drug antibody; SAP, statistical analysis plan.

[a] Baseline sample is the last sample before initiation of the treatment.

[b] Details of the immunogenicity data analysis, including ADA titers, will be provided in the SAP.

10.4.4.3 Biomarker Analysis

Statistical analyses related to biomarkers endpoints are summarized in Table 10.4.4.3-1.

Table 10.4.4.3-1: Biomarkers - Statistical Analyses

Endpoint	Statistical Analysis Methods
Summary measures of change (or % change) from baseline in various biomarkers in the tumor and peripheral blood Association measures of biomarker at baseline or of biomarker changes with tumor response measures	• Summary statistics/plots of biomarkers by planned study day and dose in each arm • Plots and summaries of select baseline biomarkers or biomarker changes by tumor response outcome

10.4.4.4 Clinical Outcomes Assessments

As exploratory endpoints, analyses of EORTC QLQ-C30 and FACIT GP5 data will be described in the clinical trial statistical analyses plan. COA analyses will be performed by cohort and total in all treated participants who have had an assessment at baseline (Day 1, assessment prior to administration of drug on day of first dose) and at least 1 subsequent assessment while on treatment. Questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number, will be calculated and summarized at each assessment point.

10.4.5 Other Safety Analysis

10.4.5.1 Continuous Safety Monitoring

A Bayesian continuous monitoring framework will be utilized in the randomized part of the study to monitor for toxicity for a safety-evaluation period of 6 weeks of treatment and detect safety signals that may lead to changes in study conduct.[68] In addition to the study DMC, the ongoing evaluation of the accumulating safety data by the Sponsor will include quantitative safety monitoring based on pre-specified criteria and will be applied to Arm 2b or Arm 2c (see Table 10.4.5.1-1). If the specified safety boundary (number of AEs) is exceeded, the DMC may be contacted for additional evaluations of the safety and risk-benefit as needed.

For this type of monitoring, the proportion of DLT is used to provide formal monitoring boundaries. These boundaries were established using a prior distribution of Beta (0.67, 1.33), which is a weak informative prior reflecting the target DLT % used in escalation). The posterior distribution at any time point is Beta(0.67 + n, 1.33 + [m-n]), where n is the number of participants observed with DLT, and m is the total number of safety-evaluable participants.

The monitoring function for toxicity is defined as the posterior probability of DLT rate > 33% cumulative data) > 0.85. This criterion implies that there is a greater than 85% predictive probability that the toxicity rate is larger than 33%. It will be applied after at least 18 randomized participants across arms are safety-evaluable and can be performed on a continuous basis afterwards. The resulting boundaries are presented below.

If anytime during the randomized phase (first 60 participants in Arm 2b and Arm 2c), this DLT proportion reaches the pre-specified threshold for toxicity in Arm 2b or Arm 2c, then, taking into account all available safety information, additional evaluation will be conducted including triggering adhoc DMC meeting to allow a complete by treatment arm safety assessment and risk benefit evaluation. Therefore, this criterion implies that the study may terminate enrollment toward an arm when there is greater than 85% probability that the toxicity rate is over 33%, corresponding to a final boundary of 13 participants with DLT out of 30 evaluable participants in an arm.

Table 10.4.5.1-1: Safety Continuous Monitoring Boundary for Arm 2b or Arm 2c

Number of Safety-evaluable Participants (per Arm)[a]	Toxicity Boundary (# Evaluable Participants with Event) for > 85% Probability of DLT > 33%
5-7	4
8-9	5
10-12	6
13-15	7
16-17	8
18-20	9
21-23	10
24-25	11
26-28	12
29-31	13

Abbreviation: DLT, dose-limiting toxicity.

[a] Additional thresholds for the monitoring of > 30 participants per arm if needed will be calculated by the statistician.

10.4.6 Other Analyses

Other analyses may include analyses of assessments, which are not defined as endpoints, that need to be prespecified and not necessarily be reported in the clinical study report, such as, but not limited to additional biomarkers, population PK, and health technology assessment-related endpoints.

PK and biomarker exploratory analyses will be described in the SAP finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

Analysis related to the impact of SARS-CoV-2 serologic status on participants receiving study intervention will be described in the SAP.

10.5 Interim Analyses

There is no plan for an official interim analysis of efficacy in Part 2 with any adjustment of the type 1 error rate.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
1L	first line
Ab	antibody
ADA	anti-drug antibody
ADT	androgen deprivation therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cell
AR	androgen receptor
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
AxMP	auxiliary medicinal product
BICR	blinded independent central review
BLRM	basic linear ranking model
BMI	body mass index
BMS	Bristol-Myers Squibb
BOIN	Bayesian Optimal Interval
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
Cavgss	average serum concentration at steady state
CD	cluster of differentiation
Ceoi	end of infusion concentration
cHL	classical Hodgkin lymphoma
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance

Term	Definition
CLss	geometric mean steady-state clearance
cm	centimeter
Cmax	maximum observed concentration
CMO	cystoid macular oedema
CNS	central nervous system
COA	clinical outcomes assessment
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CRF	case report form, paper or electronic
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTCAE v5	Common Terminology Criteria for Adverse Events version 5
ctDNA	circulating tumor deoxyribonucleic acid
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTLA-4-NF	cytotoxic T-lymphocyte-associated protein 4 non-fucosylated
Ctrough	trough-observed serum concentration
CV	coefficient of variation
DCR	disease control rate
DDR	DNA damage repair
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DM	Data Management
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DOR-PCWG3	DOR per PCWG3
DOR-PSA	duration of PSA response
DRESS	drug reaction with eosinophilia and systemic symptoms
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Term	Definition
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EOT	end of treatment
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
FACIT GP5	Functional Assessment of Chronic Illness Therapy General Physical Item 5
FACT-G	Functional Assessment of Cancer Therapy - General
Fc	fragment crystallizable
FcγR	Fcγ receptor
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
fT3	free T3
fT4	free T4
g	gram
GBS	Guillain-Barre Syndrome
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
GnRH	gonadotropin-releasing hormone
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
hIgG1	human immunoglobulin G1
HIV	human immunodeficiency virus
hr	hour
HR	hazard ratio
HRD	homologous recombination deficiency
HRPC	hormone-refractory prostate cancer

Term	Definition
HRR	homologous recombination repair
HuMAb	human monoclonal antibody
IB	Investigator's Brochure
ICF	informed consent form
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	immunoglobulin G
IHC	immunohistochemistry
IL-6	interleukin 6
IMAE	immune-mediated adverse events
IMG	immunogenicity
IMP	investigational medicinal product
INR	international normalized ratio
I-O	immuno-oncology
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
kg	kilogram
L	liter
LAM	lactation amenorrhea method
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAD	maximum administered dose
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
mg	milligram
MG	myasthenia gravis
MID	minimally important difference
min	minute
mL	milliliter
MMR	measles, mumps, rubella
mOS	median overall survival

Term	Definition
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
µg	microgram
N	number of participants or observations
NA	not applicable
NAT	novel antiandrogen therapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NF	non-fucosylated
ng	nanogram
nmCRPC	non-metastatic castration-resistance prostate cancer
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
ORR-PCWG3	ORR per PCWG3
OS	overall survival
PARP	poly ADP ribose polymerase
PC	prostate cancer
PCR	polymerase chain reaction
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PE	physical examination
PFS	progression-free survival
PID	patient identification number
PK	pharmacokinetic
PPK	population PK
PR	partial response
PSA	prostate-specific antigen
PSA-RR	PSA response rate

Term	Definition
PSMA	prostate-specific membrane antigen
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
qPCR	quantitative polymerase chain reaction
QW	every week
R&D	Research and Development
RANKL	receptor activator of nuclear factor kappa-B ligand
RCC	renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
RNAseq	RNA sequencing
rPD	radiographic progressive disease
rPFS	radiographic PFS
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SD	stable disease
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SMT	Safety Management Team
SNP	single nucleotide polymorphism
SOC	standard of care
SUSAR	suspected, unexpected serious adverse reaction
t1/2	geometric mean elimination half-life
T3	triiodothyronine
T4	thyroxine
TB/T.bili	total bilirubin
TCR	T-cell repertoire
TEN	toxic epidermal necrolysis

Term	Definition
TMB	tumor mutational burden
TRAE	treatment-related adverse event
Treg	regulatory T-cell
TSH	thyroid-stimulating hormone
TT-SSE	time to first symptomatic skeletal event
TT-SST	time to initiation of subsequent systemic therapy
TTP-PSA	time to PSA progression
TTR	time to response
TTR-PCWG3	TTR per PCWG3
TTR-PSA	time to PSA response
ULN	upper limit of normal
US	United States
USPI	US Prescribing Information
Vss	geometric mean volume of distribution at steady state
WBC	white blood cell
WOCBP	women of childbearing potential
WWPS	Worldwide Patient Safety
Y/N	yes/no

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements

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

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation) that is likely to affect, to a significant degree, one or more of the following: (1) the rights, physical safety or mental integrity of one or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).

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 (eg, 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, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, administrative letters) annually, or more frequently, in accordance with regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or
- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and all other applicable local regulations.

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 the local Health Authority), except where necessary to eliminate an immediate hazard(s) to study participants.

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 the local Health Authority, must be sent to Bristol-Myers Squibb (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF 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 participants 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 participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with 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 participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by the ICH GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant to inquire about the details of the study.

Obtain an ICF signed and personally dated by participant and by the person who conducted the informed consent discussion.

- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

Revise the ICF 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 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 participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF, and, in the US, the participant's signed HIPAA Authorization.

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

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

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definitions of what constitutes source data can be found in local site guidelines.

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten 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 records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of an 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 INTERVENTION RECORDS

Records for study intervention (whether supplied by BMS, its vendors, or the site) must substantiate study intervention 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 (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, 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 treatment integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

BMS or its 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 (EDC) tool, eCRFs 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 the 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 the Sponsor or designee.

The confidentiality of records that could identify participants 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 and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. For eCRFs, review and approval/signature is completed electronically through the BMS EDC tool. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

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

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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.

Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by the 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 the 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 its 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 its 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 (eg, relocation, retirement), the records shall be transferred to a mutually agreed-upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or its designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS or 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 interventions 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 (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. 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; eg, study treatments sourced from the site's 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 of study interventions, 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 standard operating procedures 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 (eg, 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 Study 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.

STUDY AND SITE START AND CLOSURE

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable

regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the Signatory Investigator:

- Participant recruitment
- Involvement in trial design and interpretation

SCIENTIFIC PUBLICATIONS

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

Scientific publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any Principal Investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND

4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

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 pre-existing medical condition in a clinical investigation participant administered study treatment 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 treatment, whether or not considered related to the study treatment.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.
Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met.

SERIOUS ADVERSE EVENTS

A 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 Bristol-Myers Squibb (BMS) clinical studies: • 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). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • 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 [eg, 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 and 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.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.2.5 for reporting pregnancies.)

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or product information for marketed products in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- **Assessment of Intensity**

For the reporting of all AEs, including intensity or severity, on case report forms, please follow the definitions in National Cancer Institute Common Terminology Criteria for Adverse Events version 5 (NCI CTCAE v5).

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 treatment 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 treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the electronic case report form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile transmission.
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed facsimile transmission.

SAE Email Address: [redacted]

SAE Facsimile Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL OF MALE PARTNERS DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal 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.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their judgement in checking serum FSH levels.

- 1-week minimum for vaginal hormonal products (rings, creams, gels)
- 4-week minimum for transdermal products
- 8-week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

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 3 months after the end of study treatment. Less than highly effective contraception methods are not acceptable.

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

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b]

- Intrauterine device.
- Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b,c]
- Bilateral tubal occlusion.

- Vasectomized partner

Having 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 treatment. 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.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- 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 participant chooses to forego complete abstinence.
- Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, 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. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of > 1% per year when used consistently and correctly.*
• 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. (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • LAM.

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 Appendix 3.

APPENDIX 5 PROSTATE CANCER WORKING GROUP 3 (PCWG3) GUIDELINES

1 EVALUATION OF LESIONS

Bone lesions should be evaluated with Technetium-99m based radionuclide bone scan as per PCWG3.[1]

At baseline, soft tissue lesions/lymph nodes will be categorized as measurable or non-measurable as follows.

1.1 Measurable

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

- 10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥ 2x slice thickness if greater than 5mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

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/MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

All other soft tissue lesions are considered non-measurable, including small lesions (longest diameter < 10mm 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, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 Special considerations regarding bone lesions

- Bone lesions will be assessed with Technetium-99m based radionuclide bone scans as per PCWG3.

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of 20 lesions total (and a maximum of 5 lesions per organ system) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Note: A maximum of 5 lesions can be selected per organ system. For example, a maximum of 5 lung lesions can be selected. A maximum of 5 lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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 above, 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.

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. Pelvic lymph nodes and extrapelvic lymph nodes (retroperitoneal, mediastinal, thoracic and other) may be reported separately, per PCWG3. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). 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').

2 RESPONSE CRITERIA

2.1 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.

- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, 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). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. 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 as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is 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). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 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. Similarly, 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'.

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group 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 (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression (see below) of existing non-target lesions.

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

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

2.2.1.1 When the patient also has measurable disease

In this setting, 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 (see examples in Appendix 2 and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients 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 lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

New bone lesions

New bone lesions should be evaluated as per PCWG3 criteria. Bone lesions will be assessed by radionuclide bone scan only. Radiographic progression on bone scan is defined by the following criteria:

- At least 2 new lesions on the first post-treatment bone scan, confirmed on the next scan (performed at least 6 weeks later) AND with at least two additional lesions as compared to the first post-treatment bone scan. Date of progression is then the date of first post-treatment scan,
- For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan AND confirmed on a subsequent scan (performed at least 6 weeks later). Date of progression is the date of the scan that first documents at least 2 new lesions relative to the first post-treatment scan.

New soft tissue lesions

The appearance of new malignant soft tissue lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. This is particularly important when the patient'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.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). 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 patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued 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.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression per PCWG3 criteria, or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient'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. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients 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 and NE = inevaluable

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease and NE = inevaluable		

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR&PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

[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 patient 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.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

REFERENCES

[1] Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. Scher et al. J Clin Oncol 2016, 34(12):1402-1418.

APPENDIX 6 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS[a]	
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

[a] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655

APPENDIX 7 COUNTRY SPECIFIC REQUIREMENTS/DIFFERENCES

Original Language	Country-specific Language or Differences
Mexico, Greece Section 9.4.4 Clinical Safety Laboratory Assessments, Table 9.4.4-1: Clinical Laboratory Assessments	Add "HIV" to the list of laboratory tests *HIV testing for entry into clinical trials is not a requirement in France, Spain, Italy, UK, NL, Finland, Denmark, Sweden, USA
Mexico, Greece Section 6.2 Exclusion Criteria, Exclusion criterion: 1) l	"Known human immunodeficiency virus (HIV) positive with an AIDS defining opportunistic infection within the last year, or a current CD4 count < 350 cells/μL. Participants with HIV are eligible if: i) They have received antiretroviral therapy (ART) for at least 4 weeks prior to randomization/treatment assignment as clinical indicated while enrolled on study (see Section 7.7.2 for CYP3A4 restriction) ii) They continue on ART as clinically indicated while enrolled on study iii) CD4 counts and viral load are monitored per standard of care by a local health care provider" NOTE: Testing for HIV must be performed at sites where mandated locally. HIV positive participants must be excluded where mandated locally (see Appendix 7)." To be replaced with "Positive test for HIV."

APPENDIX 8 MANAGEMENT ALGORITHMS FOR STUDIES UNDER CTCAE VERSION 5

These general guidelines constitute guidance to the investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Noninflammatory etiologies should be considered and appropriately treated.

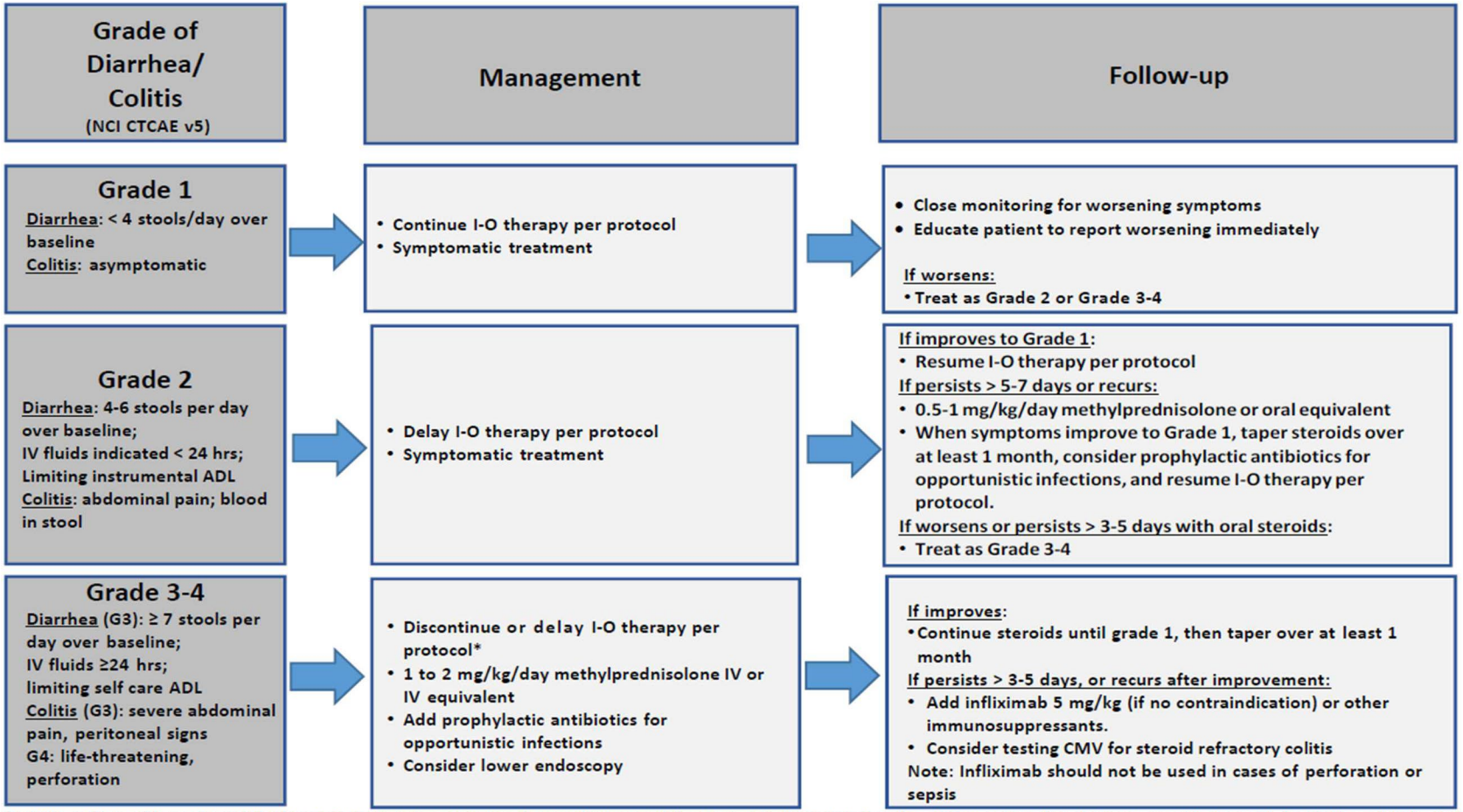
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



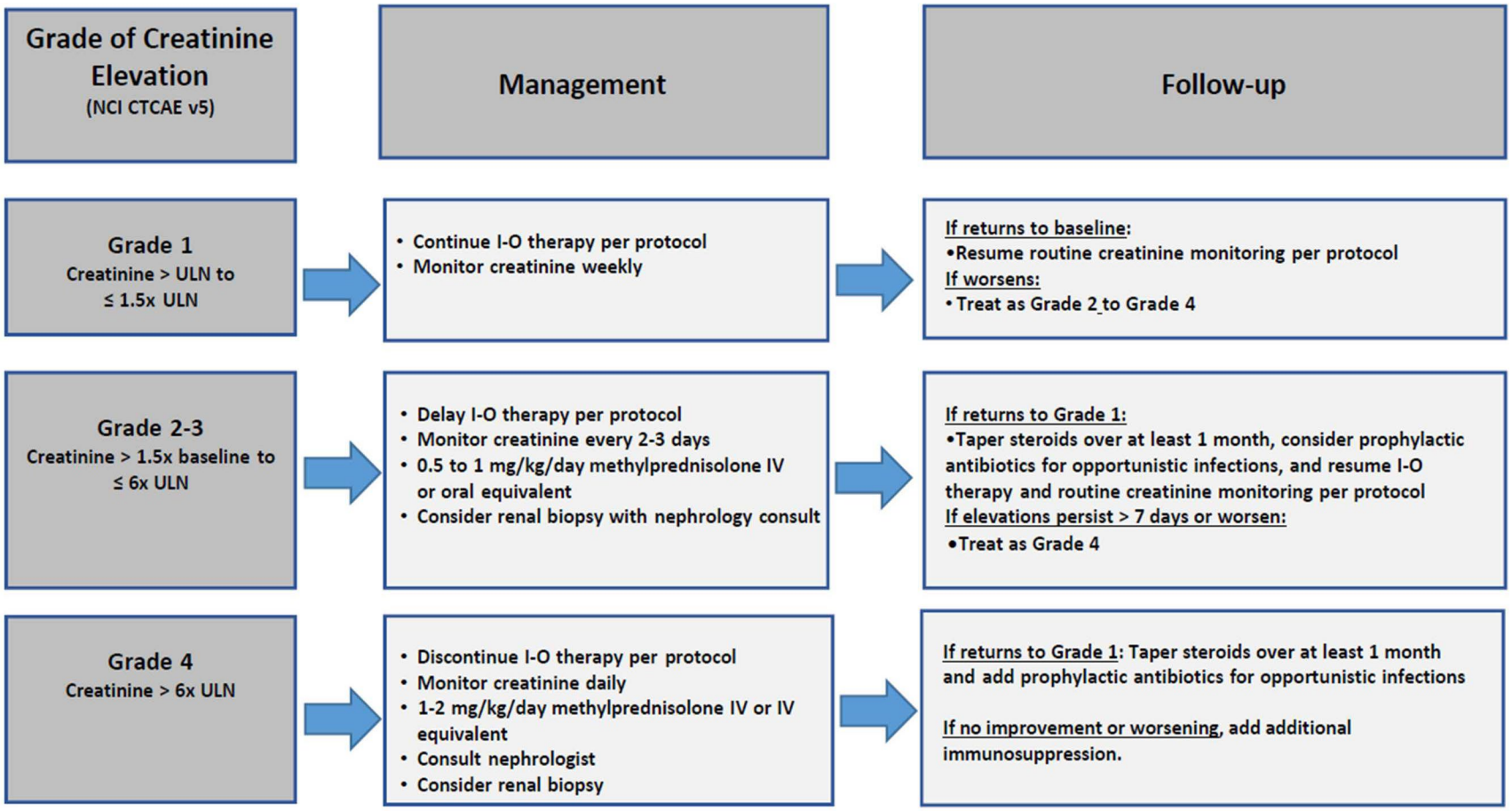
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

28-Sep-2020

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

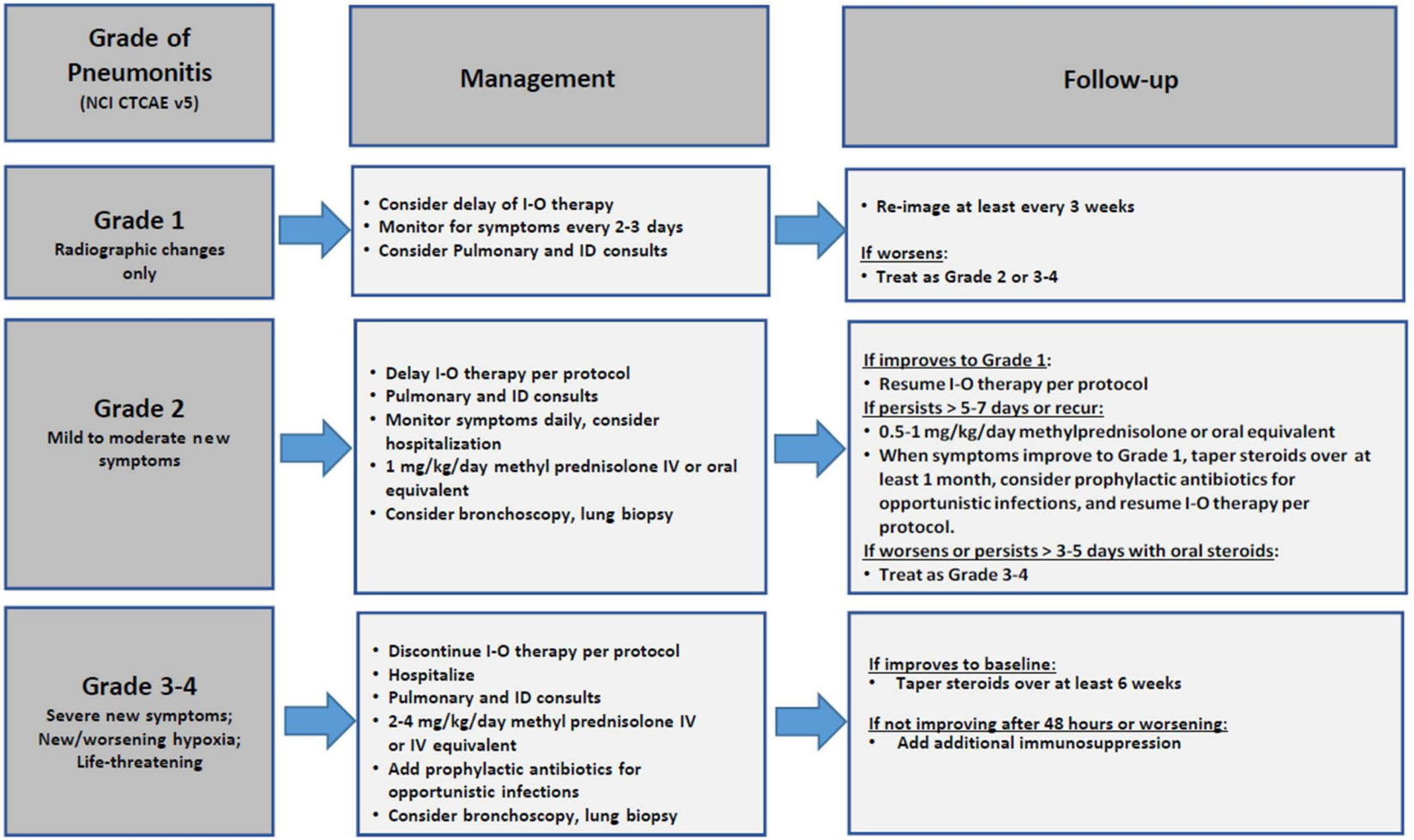


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.

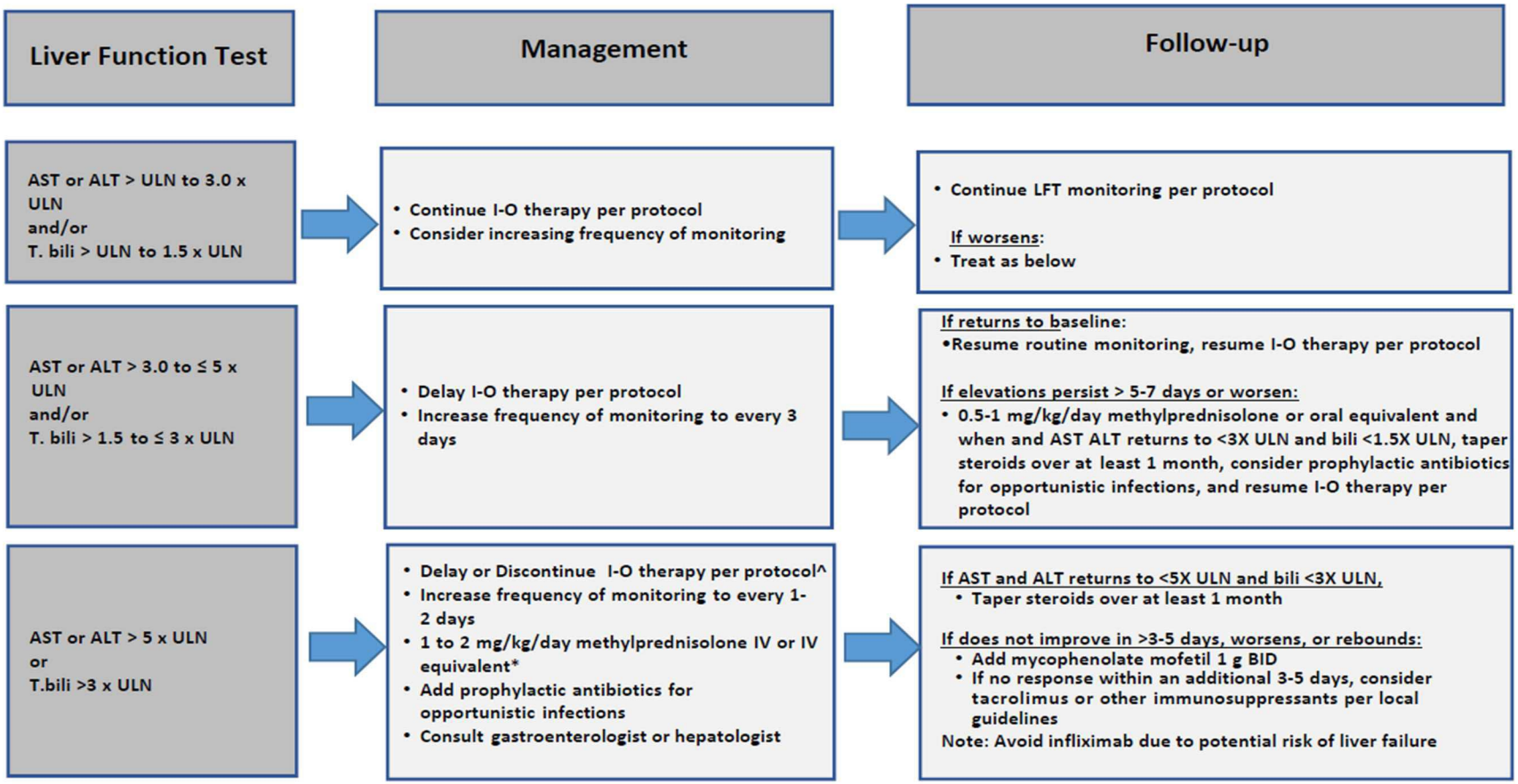


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider imaging for obstruction.

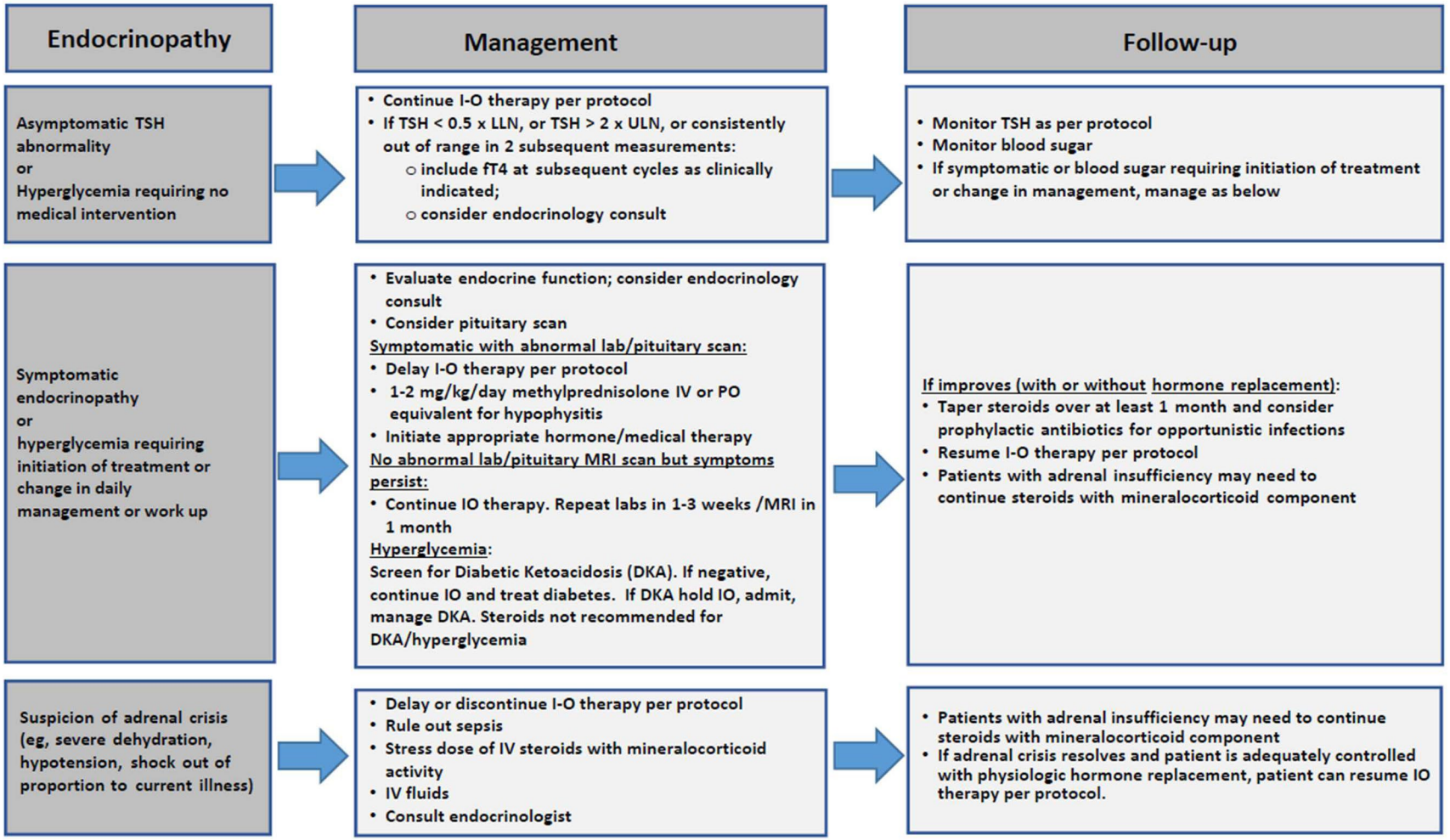


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

28-Sep-2020

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.

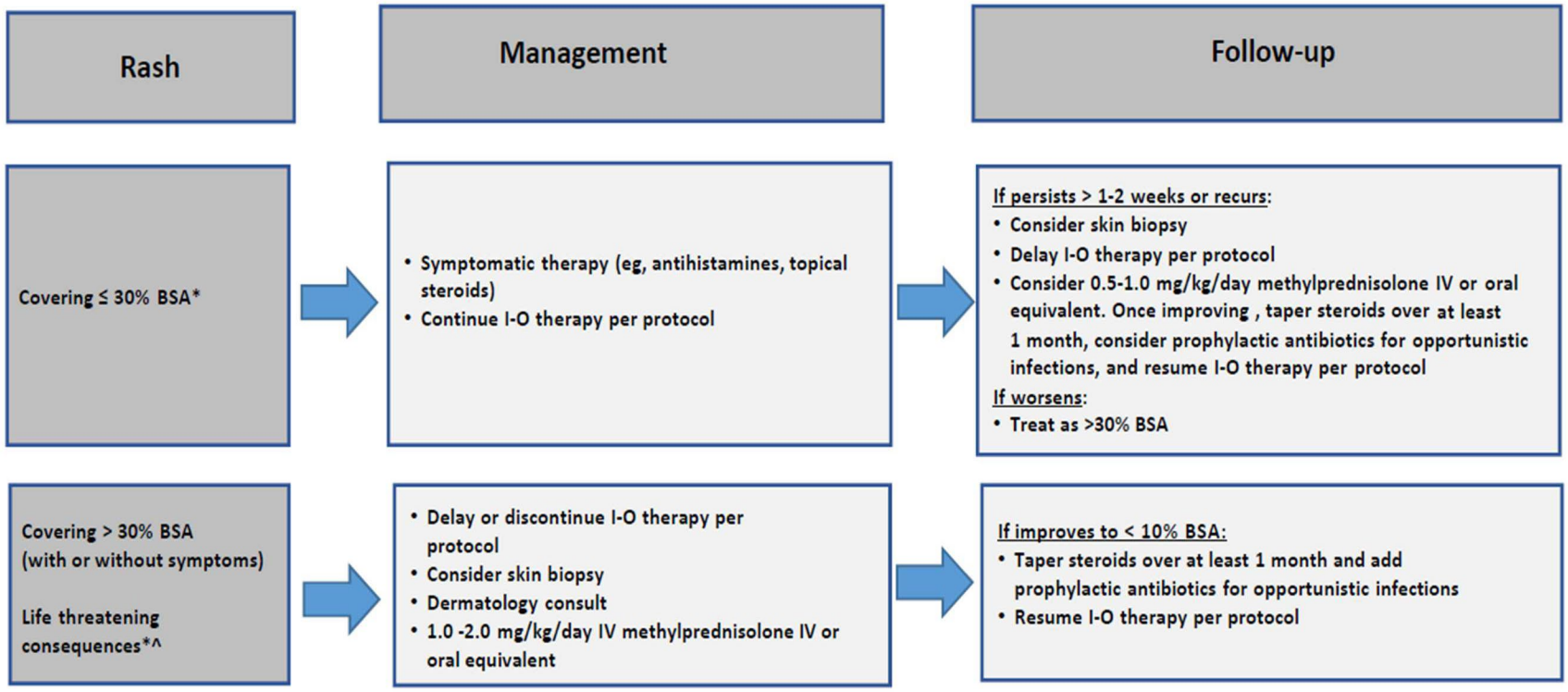


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

28-Sep-2020

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

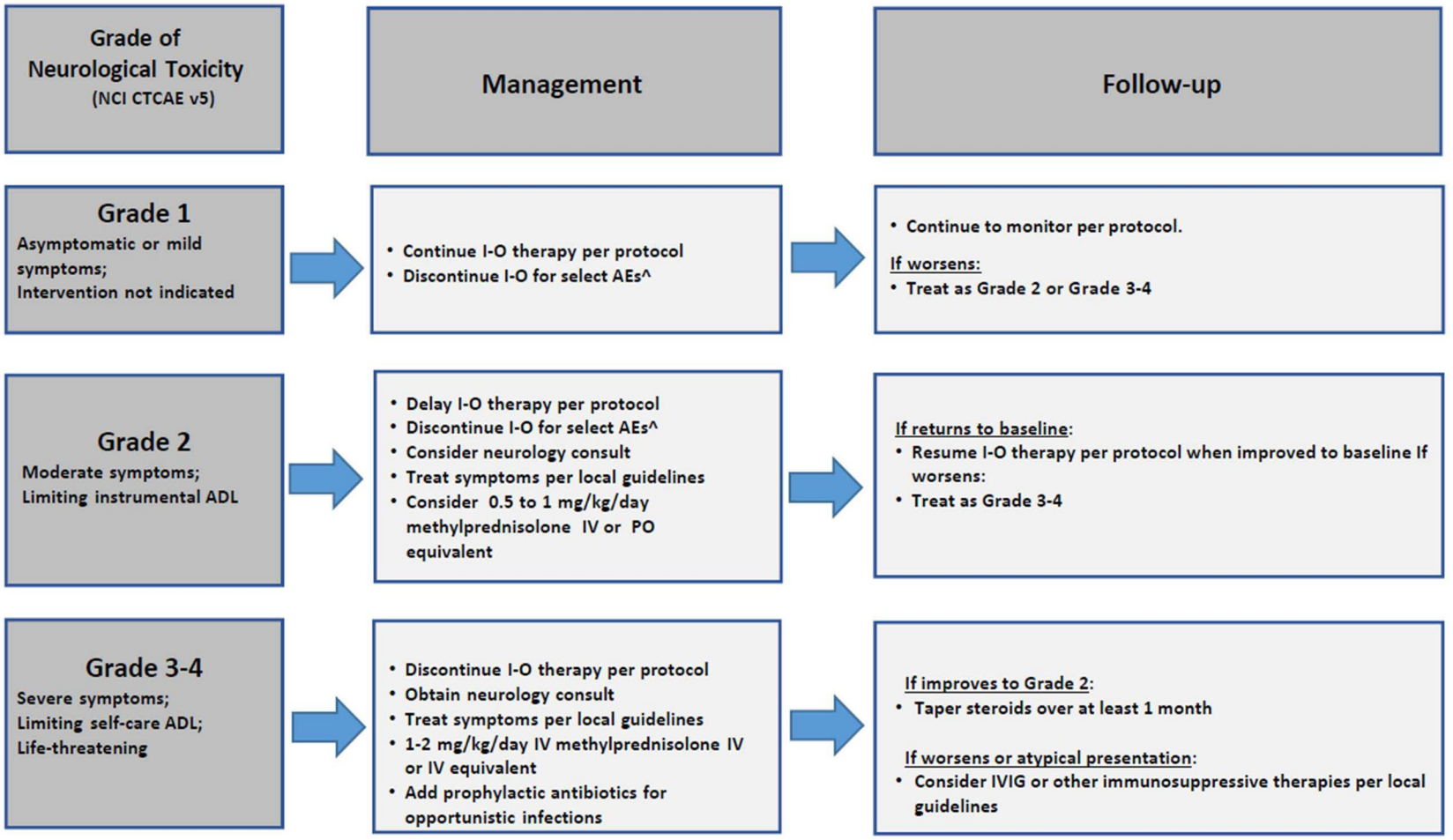
*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

28-Sep-2020

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



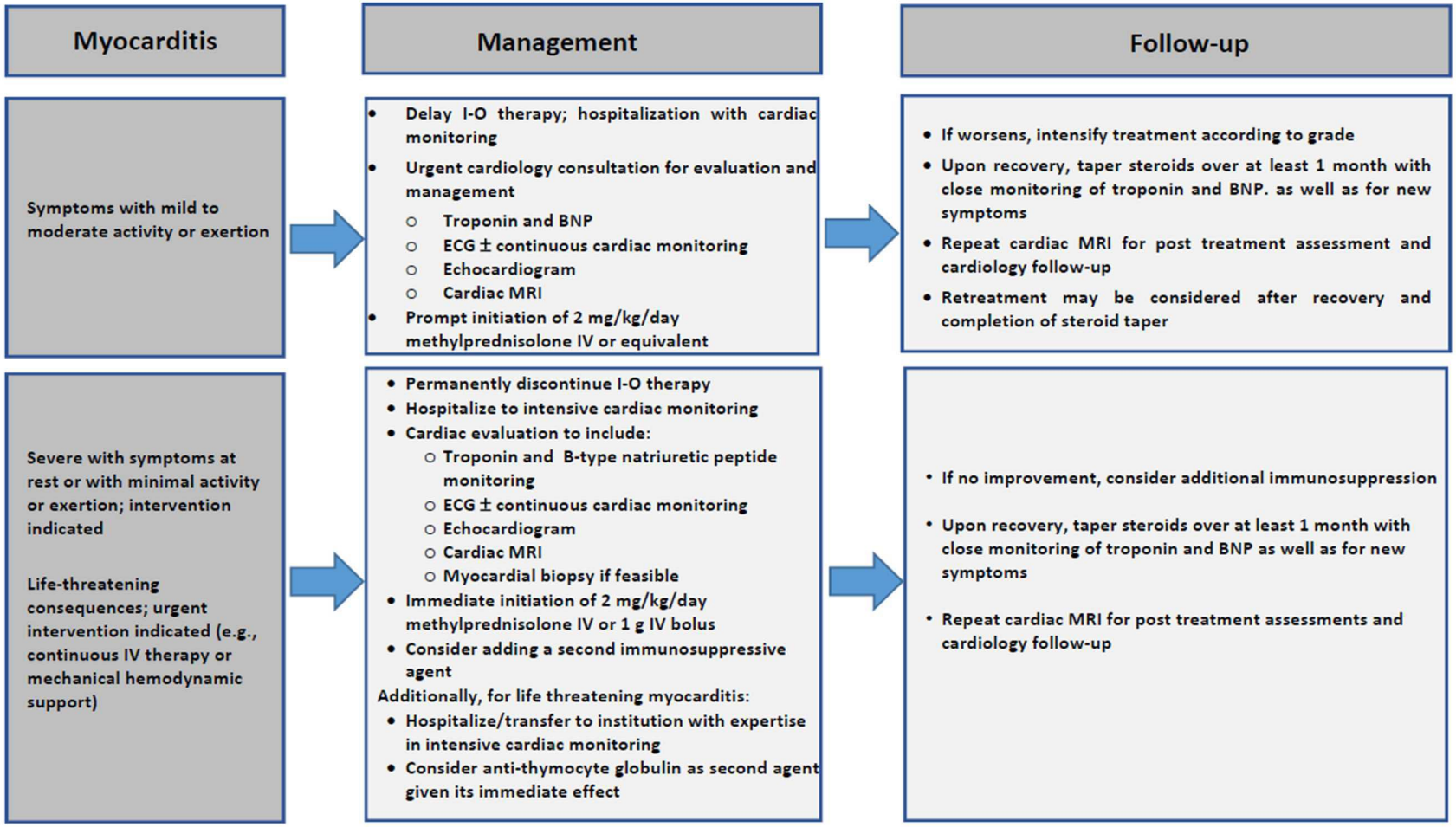
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

28-Sep-2020

Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

28-Sep-2020

APPENDIX 9 BOIN DESIGN DETAILS AND OPERATING CHARACTERISTICS

The Bayesian optimal interval (BOIN) design will be used to guide decisions on safety evaluation (including escalation or de-escalation) of BMS-986218 in combination with docetaxel and docetaxel and nivolumab in Parts 1A and Part 1B of the study.[1,2] The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs. The target toxicity rate for the selected tolerable dose (or maximum tolerated dose [MTD] per the standard escalation) is $\phi = 0.30$ based on clinical rationale and known toxicity for docetaxel and of BMS-986218 in combination with nivolumab. The maximum sample size expected is 12 participants (Part 1A) or 12 to 18 participants (Part 1B) assuming at least 2 dose levels. Treating patients in cohorts of approximate size 3, the BOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment, to guide decisions related to dose escalation/de-escalation:

- if the observed DLT rate at the current dose is ≤ 0.236, it is considered safe to escalate the dose to the next higher dose level;
- if the observed DLT rate at the current dose is > 0.359, it is recommended to de-escalate the dose to the next lower dose level;
- otherwise, stay at the current dose and evaluate additional participants.

In addition, if the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new participants at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.

If the current dose is the highest dose and the rule indicates dose escalation, treat the new participants at the highest dose.

For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.30 \mid \text{data}) > 0.95$ and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT rate of dose level j,$j = 1,\cdots, 3$. This posterior probability is evaluated based on the beta-binomial model $y_j|p_j \sim$ binomial(p_j) with $p_j \sim$uniform(0,1), where y_j is the number of patients experienced DLT at dose level j. When the lowest dose is eliminated, stop the trial for safety. The probability cutoff 0.95 is chosen to be consistent with the common practice that when the target DLT rate $\leq 1/6$, a dose with 2/3 patients experienced DLT is eliminated. The above dose escalation/de-escalation and elimination rule can be equivalently presented in Table 1, which will be used to conduct the trial.

Operating characteristics of the BOIN design are evaluated for three scenarios, assuming that up to 3 dose levels may be evaluated, and starting at Dose level 2 with the option to escalate to a higher dose, de-escalate to a lower dose level, or select current dose level as tolerable . These results are based on 1000 simulations using the BOIN software, with the added restriction to select

a dose with DLT rate below the upper limit (0.334) of the specified target DLT interval as selected tolerable dose.[3]

Table 1: BOIN Design Operating Characteristics, with n <= 12 at a dose

Scenario	Dose 1	Dose 2	Dose 3	N of Patients	% Early Stop
Scenario 1					
DLT Rate	**0.3**	0.40	0.50		
% Selection	39.1	32.1	10.8		18
% Pts treated	29.4	53.9	16.7	11.9	
Scenario 2					
DLT Rate	0.13	**0.3**	0.45		
% Selection	26.6	47.6	20.8		5
% Pts treated	14.8	59	26.2	12	
Scenario 3					
DLT Rate	0.2	0.25	**0.3**		
% Selection	15.6	34.4	46.9		3.1
% Pts treated	10.2	50.8	39	12	

The target DLT rate = 0.30 (0.236,0.359); assuming 3 dose levels, starting at dose level 2, and treating cohort of size 3, total up to n=12, and ≤ 12 participants per dose level. Note: "% Early Stopping"" refers to early stopping due to excessive DLT

Results of the simulations, presenting scenarios with the target DLT rate at the lower dose level, starting (middle) dose level, or higher dose level, show that the dose with the target DLT rate is selected as the tolerable dose most often.

References:

[1] Liu S, Yuan Y. Bayesian optimal interval designs for Phase I clinical trials. J R Stat Soc: Ser C, 2015;64:507-23.

[2] Yuan Y, Hess KR, Hilsenbeck SG, et al. Bayesian optimal interval design: a simple and well-performing design for Phase I oncology trials. Clin Cancer Res 2016; 22:4291-301.

[3] https://www.trialdesign.org/one-page-shell.html#BOIN

APPENDIX 10 CYP3A4 STRONG INHIBITOR AND INDUCER GUIDANCE

The lists below are not meant to be all inclusive. Please consult individual drug labels for further information. Additional information is also available at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Representative Examples of Drugs that are Strong CYP3A4 Inhibitors or Inducers

CYP Enzyme	Strong Inhibitors[a] ≥ 5 fold Increase in AUC Or > 80% Decrease in CL	Strong Inducers ≥ 80% Decrease in AUC
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice[b], indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil[c], nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Avasimibe[d], carbamazepine, phenytoin, rifampin, St. Johns Wort[e]

Abbreviations: AUC = area under the concentration time curve; CL = clearance; CYP = cytochrome P450.

[a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold

[b] The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength)

[c] Withdrawn from the United States market because of safety reasons

[d] Not a marketed Drug

[e] The effect of St John's Wort varies widely and is preparation dependent

APPENDIX 11 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 01, 24-Nov-2021

The overall purpose for Protocol Amendment 01 is to provide updates to increase participant safety (ie, dose-limiting toxicities [DLTs] and adverse events [AEs] for delay, resume, and discontinue of study treatments). Clarification was added to indicate that participants who discontinue study treatment prior to radiographic progression will stay on the same imaging schedule as participants on treatment. Updates were made to clarify that prior radium 223 and ^{177Lu}-prostate-specific membrane antigen(PSMA)-617 treatment for prostate cancer is allowed and to exclude participants whose Technetium-99m bone scan is interpreted as a "superscan," which would preclude assessment of radiographic progression in bone. Updates were made to the hepatic AE criteria for delay, resume, and discontinue of study treatments. Additional language was added to clarify DLT criteria and DLT exceptions. The progression-free survival (PFS) primary endpoint was changed to radiographic progression-free survival (rPFS) throughout the protocol to better articulate how progression will be assessed.

The protocol summary has been revised as applicable to align with the protocol changes.

This protocol amendment applies to all participants.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
All	Updated all references to the PFS endpoint to rPFS	Updated for clarification, as PFS will be determined using Prostate Cancer Working Group 3 (PCWG3) criteria for radiographic progression
Table 2-2: On Study Treatment Procedural Outline (CA022009) Table 2-3: Long-term Follow-up Procedural Outline (CA022009)	Under Efficacy Assessments - Body Imaging/Bone Scan, updated timing of tumor assessments for the first 24 weeks and if progression is not documented prior to discontinuation of study treatment	Updated for clarity; participants who discontinue prior to radiographic progression will stay on the same assessment schedule as participants on study treatment
Section 6.1: Inclusion Criteria	Updated inclusion criterion 2) f) to specify that prior radium 223 and ^{177Lu}-PSMA-617 treatment for prostate cancer is allowed	Updated to clarify acceptable prior treatments

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2: Exclusion Criteria	Added criterion 1) q) specifying that participants with superscan on Technetium-99m radionuclide bone scans are not eligible	Updated to exclude superscan, which would impact the ability to assess efficacy
Section 7.1: Study Interventions Administered	Added flush language following BMS-986218 administration and removed 5% dextrose in water diluent	Updated for clarity and accuracy; BMS-986218 is not compatible with dextrose
Section 7.1: Study Interventions Administered	Added Mosteller formula to calculate body surface area for docetaxel dosing	Added to ensure consistency across all sites
Table 7.4.1-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Nivolumab and BMS-986218	• To Hepatic AEs - AST, ALT or T. bili Increased: Updated notes for the first severity; symptoms of liver inflammation were modified to remove jaundice and pruritus and include fatigue, nausea, vomiting, fever, rash, and/or eosinophilia • Added international normalized ratio (INR) > 1.5 to the third severity	Updated for clarity and completeness
Table 7.4.2-1: Adverse Event Criteria for Delay, Resume, and Discontinue of Docetaxel	To Hepatic AEs - AST, ALT, or T. bili increased with or without alkaline phosphatase increase: modified the second severity to "AST or ALT > 5× ULN or T. bili > 3× ULN, regardless of baseline value or concurrent AST or ALT > 3× ULN and T. bili > 2× ULN or INR > 1.5, regardless of baseline value"	Updated and added INR for clarity and completeness

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4.5: Dose-limiting Toxicities	Updated the definition of DLTs to include details on neutropenic fever, Grade 3 or higher non-hematologic toxicity (with exceptions), and all AEs except those that are clearly and incontrovertibly due to disease progression or extraneous causes	Additional language has been added to increase participant safety and to clarify what defines a DLT, including adding DLT exceptions for non-hematologic AEs
Table 9.4.4-1: Clinical Laboratory Assessments	Added a footnote specifying INR is optional to better evaluate elevated liver function tests	Updated for clarity and completeness