Official Title of Study:

Randomized, Non-comparative Neoadjuvant Phase II Study in Patients with ER+/HER2- Breast Cancer ≥ 2 cm with Safety Run-in, Assessing Nivolumab + Palbociclib + Anastrozole (CheckMate 7A8: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 7A8)

PROTOCOL(S) CA209-7A8

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CLINICAL PROTOCOL CA2097A8

Randomized, Non-comparative Neoadjuvant Phase II Study in Patients with ER+/HER2- Breast Cancer ≥ 2 cm with Safety Run-in, Assessing Nivolumab + Palbociclib + Anastrozole (CheckMate 7A8: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 7A8)

Short Title:

Nivolumab with Palbociclib, plus Anastrozole in Patients with ER+/HER2- Breast Cancer ≥ 2 cm

Revised Protocol 03

[redacted]

24-hr Emergency Telephone Number
USA: [redacted]
International: [redacted]

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	13-Mar-2020	Closed the abemaciclib safety run-in Cohort 1 and removed the abemaciclib-containing combinations from the randomization phase. Removed eligibility criteria based on RECIST 1.1 as it has been covered by inclusion criteria 2.a.i. Added further instructions on unidimensional measurement for response assessment using ultrasound and mammogram as modifications. Incorporated Administrative Letter 01 and Germany specific amendment.
Revised Protocol 02	24-Jul-2019	Added men, additional dose-limiting toxicity (DLT) criteria, and early study termination criteria. Updated definition of DLT, inclusion/exclusion criteria, and dose modifications.
Revised Protocol 01	12-Jun-2019	Decreased and clarified the frequency of assessments and sample collections, clarified participant eligibility and stratification, and reduced the dose-limiting toxicity period. These changes were made to reduce participant burden and increase overall feasibility of the study.
Original Protocol	02-May-2019	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 03:

On 6-Mar-2020, Bristol Myers Squibb (BMS) decided to permanently discontinue enrollment and dosing in the nivolumab + abemaciclib + anastrozole cohorts of the CA2097A8 study. [redacted] The study is currently in the Safety Run-In Phase. At implementation of Revised Protocol 03, the study will only evaluate whether the combination of nivolumab, with palbociclib, plus anastrozole is a safe and effective neoadjuvant treatment for men and postmenopausal women with primary BC ≥ 2 cm that is ER+ and HER2- subtype who are suitable to receive NET and willing to undergo SOC breast surgery after completion of the study treatment. Participants must have histologically confirmed invasive breast carcinoma meeting the characteristics described in the Inclusion Criteria. Participants in screening and not yet treated were offered the option to join the safety lead-in of the nivolumab + palbociclib + anastrozole arm. Participants on treatment with nivolumab + abemaciclib + anastrozole were to be re-consented and continue on anastrozole alone, or taken off study. Safety monitoring for ILD/pneumonitis (baseline chest X-ray, periodic pulse oximetry) as risk mitigation measures have also been included.

Additional changes were made to include the updates from Administrative Letter 01 and clarifications.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03

Section Number & Title	Description of Change	Brief Rationale
All	Removed references where applicable to abemaciclib-containing treatment in the randomization phase	As of 6-March-2020, cohort 1 is closed for enrollment and study will not move forward with abemaciclib-containing treatment in the randomization phase as an urgent safety measure
Section 2 Schedule Of Activities, Table 2-1: Screening Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8) Section 5.1.1 Screening Period Section 6.1 Inclusion Criteria [redacted]	Updated Pretreatment Tumor Sample Submission sample collection timing.	Clarity

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2 Schedule Of Activities, Table 2-1: Screening Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8) Section 5.1 Overall Design	Added Chest X-ray procedure	Safety monitoring for ILD/pneumonitis
Section 2 Schedule Of Activities, Table 2-1: Screening Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8)	Added Estradiol to the required laboratory testing for women ≤ 55	Updated per the Administrative Letter 01 to align with the inclusion criteria
Table 2-2 On-treatment Pre-surgery (Neoadjuvant) Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8)	• Updated footnote b in indicate that participants will undergo surgical treatment within 4 weeks of last dose instead of 1 week. • Footnote e added to table.	• Clarifying inconsistency within the protocol. • Cohort 1 is now closed for enrollment and samples will no longer be collected or analyzed for existing Cohort 1 participants to alleviate patient burdens.
Table 2-2 On-treatment Pre-surgery (Neoadjuvant) Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8) Section 5.1 Overall Design	Pulse Oximetry has been added to Day 1 of the On-treatment Pre-surgery (Neoadjuvant) Procedural Outline	Safety monitoring for ILD/pneumonitis
Table 2-2 On-treatment Pre-surgery (Neoadjuvant) Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8) Section 5.1.2.1 Safety Run-in Phase Section 7.1 Treatments Administered Section 7.1.1 Nivolumab Dosing (Safety Run-in Cohorts and Randomized Phase Arms A, B, D, and E) Section 7.1.2 CDK4/6 Inhibitors and Anastrozole Dosing	Language has been removed regarding first dose of nivolumab being administered following treatment assignment for participants in the Safety Run in Phase	Clarity
Section 3.3 Benefit/Risk Assessment	Added following sentence: As of Protocol Revision 03, the benefit-risk profile of the abemaciclib-containing combination is no longer considered favorable; thus BMS will not move forward with randomization to nivolumab in combination with abemaciclib and anastrozole (see Section 5.1).	As of 6-March-2020, cohort 1 is closed for enrollment and study will not move forward with abemaciclib-containing treatment in the randomization phase as an urgent safety measure

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3.3 CDK4/6 Inhibitor and Nivolumab Combination Safety Profile	Added the following paragraph: In a Phase 2 study of pembrolizumab, palbociclib and letrozole (AI) in patients with metastatic ER+, HER2- BC (NCT02778685), of 20 patients treated with the triple combination, Grade 3 pneumonitis was reported in 1 patient during the DLT assessment period. The median follow up for this study was 13.7 months (95% CI 6.4-16.9) and progression-free survival (PFS) has not been reached. Also in a phase 1 study exploring safety and efficacy of avelumab, palbociclib and axitinib (tyrosine kinase inhibitor) in patients with advanced non-small cell lung cancer (NCT03386929), of 13 patients treated at 3 dose levels, 1 patient with baseline chronic obstructive pulmonary disease at dose level 3 developed a respiratory failure event possibly related to study treatment and died. No Grade 3 or above ILD/pneumonitis events were reported. A randomized Phase 2 trial assessing a triple combination regimen of palbociclib + avelumab (anti-PD-L1 inhibitor) + fulvestrant (estrogen receptor antagonist) for patients with pre-treated metastatic ER+/HER2- BC has been ongoing since Aug-2017; no clinical data have been reported to date. (NCT03147287). Thus, the potential benefit of the palbociclib combination therapy appears to outweigh the known risks and warrants clinical investigation.	Additional supporting information.
Section 4 Objectives and Endpoints	For pCR secondary [redacted] endpoints the definitions of pCR were expanded	Consistency across program protocols.
Section 5.1 Overall Design	Added the following paragraphs and removed reference to equal distribution of participants in both safety run-in cohorts: On 6-Mar-2020, Bristol Myers Squibb (BMS) decided to permanently discontinue enrollment	Cohort 1 is now closed for enrollment.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	and dosing in the nivolumab + abemaciclib + anastrozole cohorts of the CA2097A8 study during the Safety Run-in Phase. [redacted] At implementation of Revised Protocol 03, the study will only evaluate whether the combination of nivolumab, with palbociclib, plus anastrozole is a safe and effective neoadjuvant treatment for men and postmenopausal women with primary BC ≥ 2 cm that is ER+ and HER2- subtype who are suitable to receive NET and willing to undergo SOC breast surgery after completion of the study treatment. Participants must have histologically confirmed invasive breast carcinoma meeting the characteristics described in Section 6.1 (Inclusion Criteria). Participants in screening and not yet treated were offered the option to join the safety lead-in of the nivolumab + palbociclib + anastrozole arm. Participants on treatment with nivolumab + abemaciclib + anastrozole were to be re-consented and continue on anastrozole alone, OR taken off study. In addition, baseline chest X-ray and periodic pulse oximetry are implemented to monitor ILD/pneumonitis in patients who	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	will be treated with nivolumab + palbociclib + anastrozole.	
Figure 5.1-1: Study Design Schematic	Updated study design schematic to remove abemaciclib-containing treatment in the randomization phase and updated study numbers. Added two footnotes to clarify the closing of Cohort 1 to enrollment and the removal of abemaciclib-containing treatment in the randomization phase.	Study will not move forward with abemaciclib-containing treatment in the randomization phase
Section 5.1.2.1 Safety Run-in Phase	Added the following paragraph: As of Revised Protocol 03, Cohort 1 will be discontinued. Participants in screening and not yet treated were offered the option to join the nivolumab + palbociclib + anastrozole arm. Participants on treatment were to be re-consented and continue on anastrozole alone, OR taken off study. Removed references to abemaciclib, and to equal distribution of participants in both safety run-in cohorts. Deleted the following text: At the end of the Safety Run-in Phase, the Sponsor will evaluate the safety profile of the 2 cohorts. In the case that the treatment regimen for 1 of the 2 cohorts is not deemed to be tolerable for use in the Randomization Phase, then the treatment regimen for the other cohort will advance to the Randomization Phase, with the statistical assumptions remaining unchanged for this part, as captured in Section 10 (Statistical Considerations).	Cohort 1 is now closed for enrollment.
Section 5.1.2.1 Safety Run-in Phase	Updated to include additional DLTs	[redacted] Integrated all the AEs that require discontinuation of nivolumab per approved label into the list of DLTs.
Section 5.1.2.2 Randomized Phase	Updated randomization and text to reflect removal of Arms A-C	Study will not move forward with Arms A, B, and C.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.2 Number of Patients Section 10.1 Sample Size Determination [redacted]	Updated participant numbers to reflect the closing of enrollment for Cohort 1 and removal of abemaciclib-containing treatment in the randomization phase	Cohort 1 is now closed for enrollment and study will not move forward with abemaciclib-containing treatment in the randomization phase.
Section 6.1 Inclusion Criteria	Removed the criterion requiring measurable disease per RECIST v1.1.	RECIST 1.1 is not used in this study and the criterion for measurable disease criterion is already included in inclusion criterion.
Section 6.2. Exclusion Criteria	Removed the following exclusion criterion from Medical Conditions: C) Active hepatitis B or hepatitis C with abnormal liver function tests.	Redundant to another criterion.
Section 6.2. Exclusion Criteria	Added the following qualifier to a prior/concomitant therapy exclusion criteria: e) Prior ET or CDK4/6 inhibitors for BC within 5 years	Clarity
Section 6.2. Exclusion Criteria	Updated criterion 1, e. Criterion 3, i no longer applicable Added criterion 3, l Added crterion 3, m	updated language, criterion 3, l and m replace criterion 3, i
Table 7.1-1 Selection and Timing of Dose - Safety Run-in Phase and Table 7.1-2 Selection and Timing of Dose - Randomized Phase	Ddded the following footnote: Note: At the time of Revised Protocol 03, 2 participants had been treated in Cohort 1 (nivolumab + abemaciclib + anastrozole), which was subsequently closed for enrollment.	Cohort 1 is now closed for enrollment and study will not move forward with abemaciclib-containing treatment in the randomization phase.
Section 7.1.2 CDK4/6 Inhibitors and Anastrozole Dosing	Added the following text: The selected CDK4/6 inhibitor cannot be changed or switched to another one once the study treatment has been initiated. At implementation of Revised Protocol 03, the study will only evaluate the combination of nivolumab with palbociclib plus anastrozole. Patients in screening and not yet treated were offered the option to join the nivolumab + palbociclib + anastrozole arm. Patients on treatment were to be re-consented and continue on anastrozole alone, OR taken off study.	Cohort 1 is now closed for enrollment and study will not move forward with abemaciclib-containing treatment in the randomization phase.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Removed text about equal distribution between cohorts.	
Section 7.4 Dosage Modification Section 7.4.1. Dose Modifications for Abemaciclib Section 7.4.2 Dose Modifications for Palbociclib	Removed summary tables of dose reduction, interruption or discontinuation of individual study drugs in the management of study drug-related adverse reactions and added language to consult the individual drug labels Specifically removed Table 7.4.1-1, Table 7.4.1-2, Table 7.4.1-3, Table 7.4.1-4, Table 7.4.1-5, Table 7.4.2-2, and Table 7.4.2-3	Referenced the approved package inserts instead [redacted].
Section 7.7.3.1 Imaging Restriction and Precautions	Removed reference to the image acquisition manual	Per imaging lead.
Section 8.1.2 Abemaciclib Dose Discontinuation	Changed text to read: At the implementation of Revised Protocol 03, abemaciclib dosing will be discontinued in all patients.	No longer studying abemaciclib-containg combination.
Section 9.1.3. Clinical Response Assessments	Removed reference to RECIST v1.1.Added language regarding reporting the longest diameter of the initial lesion as the baseline measurement and used to characterize the objective tumor response.	Clarified expectations and procedures for tumor measurement assessments.
Section 9.1.3.1 Objective Response Rate	Added new section	To define radiographic response assessments
Section 9 Study Assessments And Procedures, Table 9.4.4-1: Clinical Safety Laboratory Assessments, Other Analyses	Added the following text regarding Estradiol levels “Estradiol level - only required to confirm menopause in women ≤ age 55”	Updated per the Administrative Letter 01 to align with the inclusion criteria
Section 10.3.4 Interim Analysis	Removed interim analysis	No longer applicable.
APPENDIX 9 Concomitant Medications	Removed Category and Drug Name for Strong CYP2D6 Inhibitors or Inducers (for participants receiving tamoxifen)	Not applicable for the current treatment regimen.
All	Minor formatting and typographical corrections.	Incorporate corrections for clarity and consistency within the document. These changes were minor, and therefore have not been summarized.

TABLE OF CONTENTS

[redacted]

[redacted]

1 SYNOPSIS

Protocol Title: Randomized, Non-comparative Neoadjuvant Phase II Study in Patients with ER+/HER2- Breast Cancer ≥ 2 cm with Safety Run-in, Assessing Nivolumab + Palbociclib + Anastrozole

Short Title: Nivolumab with Palbociclib plus Anastrozole in Patients with ER+/HER2- Breast Cancer ≥ 2 cm

Study Phase: 2

Rationale:

Blockade of the programmed cell death-1 (PD-1) pathway has demonstrated clinical activity across multiple tumor types, including breast cancer (BC). An accumulating body of evidence supports PD-1/cyclin-dependent kinases (CDK)4/6 blockade potential synergy, as it has become more apparent that CDK4/6 inhibitors affect the tumor immune microenvironment (ie, increases expression of programmed death-ligand 1 [PD-L1], enhances antigen presentation and secretion of cytokines from both tumor and CD8+ T cells, and suppresses proliferation of immunosuppressive regulatory T cells [Tregs]). Preliminary clinical data supporting synergistic activity of the combination of pembrolizumab and abemaciclib has been demonstrated in a Phase 1b study of heavily pretreated participants with metastatic hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) BC. Clinical data on combinations of other CDK4/6 inhibitors coupled with PD-(L)1 inhibition are being generated in multiple clinical trials spanning from the neoadjuvant to metastatic setting (ClinicalTrials.gov: NCT03573648, NCT02778685, NCT03294694).

The aim of CA2097A8 is to assess the potential synergistic activity of nivolumab with palbociclib and anastrozole in participants with newly diagnosed, previously untreated primary estrogen receptor-positive (ER+), HER2- BC ≥ 2 cm, defined by significantly improved residual cancer burden (RCB; 0-I) rate. [redacted] Additional objectives of the study include characterization of safety and tolerability of this combination [redacted].

Study Population:

Participants will include men and postmenopausal women with ER+ and HER2- primary BC ≥ 2 cm.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Safety Run-in Phase: Number of participants with occurrence of DLT.	• DLT is defined as TEAE (graded according to the NCI CTCAE v5.0) that occurs during the first 4 weeks after treatment start and that meets specific criteria.
• Randomized Phase: To assess RCB 0-I rate by central assessment of palbociclib plus anastrozole with or without nivolumab in all participants with untreated primary BC ≥ 2 cm (ER+, HER2-).	• RCB 0-I rate assessed by central assessment at the time of definitive surgery. • RCB is a continuous index combining pathological measurements of primary tumor (size and cellularity) and nodal metastases (number and size) defined by a point system at surgery (refer to Appendix 7).
Secondary	
• To assess the safety and tolerability of palbociclib plus anastrozole with or without nivolumab.	• Incidence of AEs, SAEs, AEs leading to discontinuation, immune-related AEs, deaths, and laboratory abnormalities in all participants.
• To assess pCR rate by local assessment of palbociclib plus anastrozole with or without nivolumab in participants with untreated primary BC ≥ 2 cm (ER+, HER2-).	• pCR rate in all participants assessed by the local pathologist at the time of definitive surgery. pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ie, ypT0/Tis ypN0 in the current AJCC staging system). – pCR, defined as no invasive residual disease in breast or lymph nodes (ie, ypT0/is, ypN0) in the current AJCC staging system.
• To assess ORR (clinical and radiological [ultrasound (preferred) or mammography]) by Investigator assessment and BCS rate of palbociclib plus anastrozole with or without nivolumab in participants with untreated primary BC ≥ 2 cm (ER+, HER2-).	• ORR is defined as the number of participants with a BOR of CR or PR divided by the number of randomized participants for each treatment group at the end of the study treatment period. • BCS rate is defined as the number of participants who undergo BCS after completing the study treatments divided by the number of randomized participants for each treatment group.
[redacted]	

Objectives	Endpoints
[redacted]	

Abbreviations: [redacted] AE = adverse event; AJCC = American Joint Committee on Cancer; BC = breast cancer; BCS = breast-conserving surgery; BOR = best overall response; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; [redacted] HER2- = human epidermal growth factor receptor 2-negative; [redacted] NCI = National Cancer Institute; ORR = objective response rate; pCR = pathological complete response; [redacted] PR = partial response; [redacted] RCB = Residual Cancer Burden; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TIL = tumor-infiltrating lymphocyte; [redacted].

Overall Design:

This randomized, open-label Phase 2 study was to evaluate whether the combination of nivolumab, with palbociclib, plus anastrozole is a safe and effective neoadjuvant treatment for men and postmenopausal women with primary BC ≥ 2 cm that is ER+ and HER2- subtype who are suitable

to receive neoadjuvant endocrine therapy (NET) and willing to undergo standard-of-care (SOC) breast surgery after completion of the study treatment.

On 6-Mar-2020, Bristol Myers Squibb (BMS) decided to permanently discontinue enrollment and dosing in the nivolumab + abemaciclib + anastrozole cohorts of the CA209-7A8 study during the Safety Run-in phase. [redacted]

At implementation of Revised Protocol 03, the study will only evaluate whether the combination of nivolumab, with palbociclib plus anastrozole is a safe and effective neoadjuvant treatment for men and postmenopausal women with primary BC ≥ 2 cm that is ER+ and HER2- subtype who are suitable to receive NET and willing to undergo SOC breast surgery after completion of the study treatment. Participants must have histologically confirmed invasive breast carcinoma meeting the characteristics described in the Inclusion Criteria. Participants in screening and not yet treated were be offered the option to join the safety lead-in of the nivolumab + palbociclib + anastrozole arm. Participants on treatment with nivolumab + abemaciclib + anastrozole were to be re-consented and continue on anastrozole alone, OR taken off study. In addition, baseline chest X-ray and periodic pulse oximetry are implemented to monitor ILD/pneumonitis in patients who will be treated with nivolumab + palbociclib + anastrozole.

The study is divided into 3 periods: Screening Period, On-treatment Pre-surgery (neoadjuvant) Period (Safety Run-in Phase and Randomized Phase), and Safety Follow-up Period.

The study started with a Safety Run-in Phase for the combination of nivolumab, with abemaciclib or palbociclib, plus anastrozole and will begin the Randomized Phase after the regimen is determined to be safe. Participants in the Safety Run-in Phase will move to the Safety Follow-up Period upon completion of the neoadjuvant treatment or upon discontinuation. Potential needs for additional enrollment or for dose de-escalation will be discussed with Investigators and BMS during the Safety Run-in Phase. Once a safe dose for the regimen has been determined by BMS in collaboration with Investigators, the Randomized Phase of the study will begin.

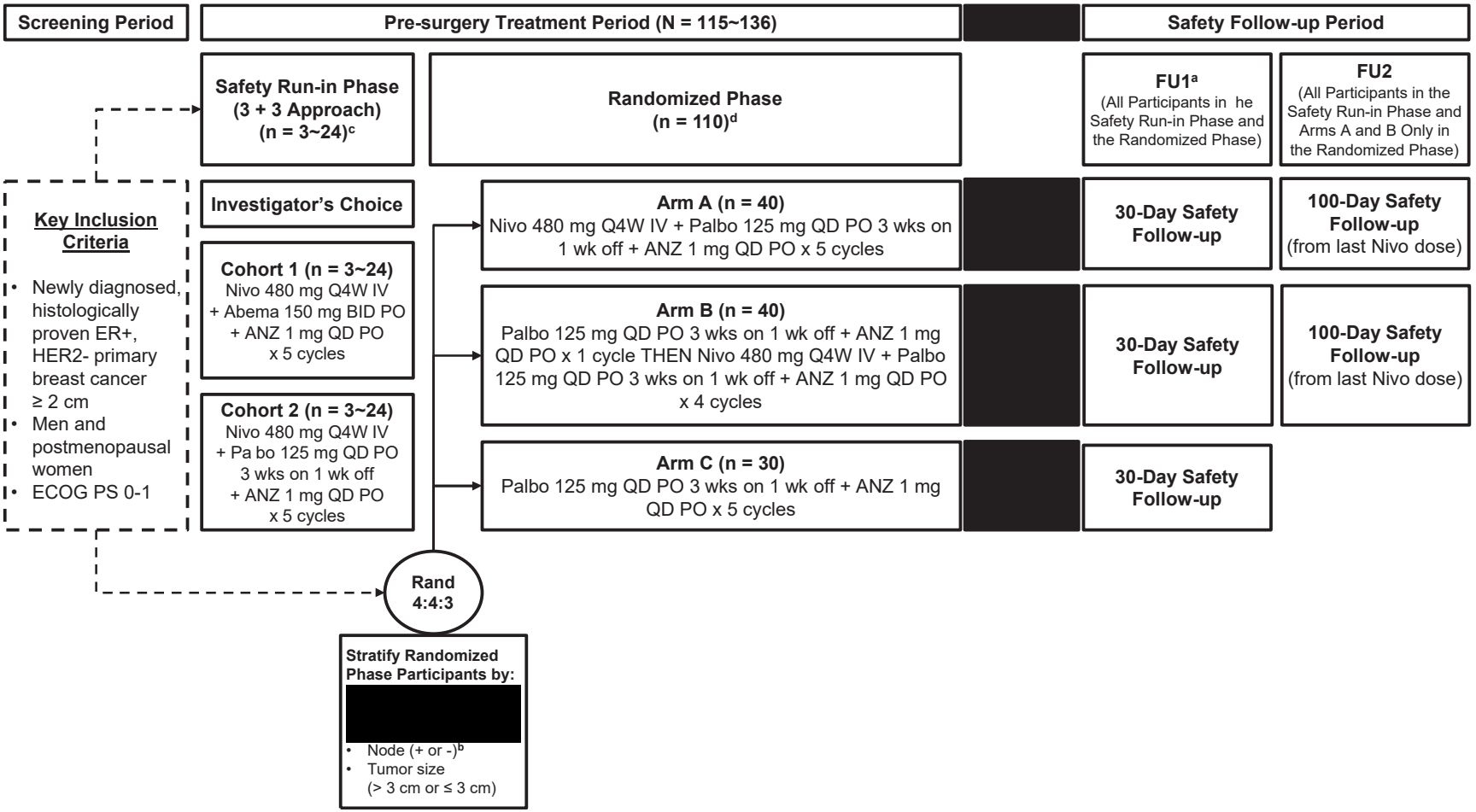
In the Randomized Phase, participants will be randomly assigned by an IRT system to 3 different treatment arms and stratified by the following factors: [redacted] 2) evaluation of lymph nodes (cytologically positive vs radiologically or cytologically negative); and 3) tumor size (> 3 cm or ≤ 3 cm).

For both the Safety Run-in Phase and Randomized Phase, participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks). Participants with progressive disease prior to completion of the 5-cycle study treatment must discontinue all study drugs and proceed to the Safety Follow-up Period. Participants who permanently discontinue the study drugs for any reason are considered to have completed the On-treatment Pre-surgery (neoadjuvant) Period, and hence

reach end of treatment (EOT). After Cycle 5 or EOT, participants must continue to receive anastrozole (as concomitant medication and not as study treatment) until subsequent SOC breast surgery. Following the completion of neoadjuvant treatment, all participants who remain operative candidates will undergo definitive surgery for BC within 4 weeks of the last neoadjuvant treatment administration. If anastrozole can no longer be administered after EOT, participants will go to breast surgery right away. Pre-surgical lymph node biopsy is not allowed. Information on the type of the surgery will be collected and recorded in the electronic case report form (eCRF). Surgical specimens will be collected for the analyses outlined in the protocol. Depending on treatment assignment, up to 2 safety follow-up visits will be conducted in person. The first safety follow-up visit (FU1) will be completed for all participants within 30 days (± 7 days) from the last study treatment (oral or intravenous [IV], whichever occurs later). The second safety follow-up visit (FU2) will occur approximately within 100 days (± 7 days) from the last dose of nivolumab and will be required for participants in the Safety Run-in Phase and participants randomized to Arms A or Bin the Randomized Phase. Further planned treatment of participants in the adjuvant setting (ie, radiotherapy, endocrine treatment, chemotherapy or any other treatment modality) will be at the discretion of the treating physician, following local clinical guidelines, and collected in the appropriate eCRF.

The study design schematic is presented in the Figure below.

Study Design Schematic



Abbreviations: Abema = abemaciclib; ANZ = anastrozole; BID = twice daily; cm = centimeter; ECOG = Eastern Cooperative Oncology Group; ER+ = estrogen-receptor-positive; FU1 = follow-up visit 1; FU2 = follow-up visit 2; HER2- = human epidermal growth factor receptor 2-negative; mg = milligram; IV = intravenous; N = number; Nivo = nivolumab; Palbo = palbociclib; [redacted] PO = per os (by mouth); PS = performance status; Q4W = every 4 weeks; QD = once daily; Rand = randomized; wk = week.

[a] FU1 begins at the end of study treatment.

[b] Cytologically positive vs radiologically or cytologically negative.

[c] At the time of Revised Protocol 03, 2 subjects had been treated in Cohort 1 (nivolumab + abemaciclib + anastrozole), which was subsequently closed for enrollment.

[d] At time of Revised Protocol 03, the decision was made to no longer evaluate abemaciclib in combination with nivolumab plus anastrozole; thus, the abemaciclib-containing combination arms have been removed from the Randomization Phase of the study.

Number of Participants:

A total of approximately 115~136 participants will be treated in the study. It is anticipated that approximately 3~24 participants (up to approximately 30 screened) will be treated in each cohort in the Safety Run-in Phase. At the time of Revised Protocol 03, 2 subjects had been treated in Cohort 1 (nivolumab + abemaciclib + anastrozole), which was subsequently closed for enrollment. Approximately 138 participants will be screened for 110 participants to be treated in the Randomized Phase, assuming a screen failure rate of approximately 20%.

Originally, approximately 3~24 participants will be treated in the Safety Run-in Phase in each cohort (Cohort 1: nivolumab + abemaciclib + anastrozole for 5 cycles; n = 3~6 per dose level of abemaciclib; Cohort 2: nivolumab + palbociclib + anastrozole for 5 cycles; n = 3~6 per dose level of palbociclib). At the time of Revised Protocol 03, 2 subjects had been treated in Cohort 1 (nivolumab + abemaciclib + anastrozole), which was subsequently closed for enrollment. Approximately 110 participants are planned to be randomized in this study at a 4:4:3 ratio into Arm A (nivolumab + palbociclib + anastrozole for 5 cycles; n = 40), Arm B (palbociclib + anastrozole for 1 cycle, followed by nivolumab + palbociclib + anastrozole for 4 cycles; n = 40), and Arm C (palbociclib + anatrozole for 5 cycles; n = 30), respectively. Participants will be stratified by [redacted] node status, and tumor size.

Treatment Arms and Duration:

The treatment arms and duration for the Safety Run-in Phase and Randomized Phase are provided in the tables below.

Selection and Timing of Dose - Safety Run-in Phase

Cohort	Study Treatment	Dosage Level[a]	Frequency of Administration	Start and Duration of Treatment	Route of Administration
1	Nivolumab	480 mg	Q4W	Cycle 1-5	IV
	Abemaciclib	150 mg	BID	Cycle 1-5	PO (with or without food)
	Anastrozole	1 mg	QD	Cycle 1-5[b]	PO (with or without food)
2	Nivolumab	480 mg	Q4W	Cycle 1-5	IV
	Palbociclib	125 mg	QD × 3 weeks on (1 week off)	Cycle 1-5	PO (with food)
	Anastrozole	1 mg	QD	Cycle 1-5[b]	PO (with or without food)

Abbreviations: BID = twice daily; EOT = end of treatment; IV = intravenous; mg = milligram; PO = per os (by mouth); Q4W = every 4 weeks; QD = once daily.

Note: At the time of Revised Protocol 03, 2 subjects had been treated in Cohort 1 (nivolumab + abemaciclib + anastrozole), which was subsequently closed for enrollment.

[a] For abemaciclib and palbociclib, this is the starting dose level. Dose levels may be reduced per Dosage Modification guidelines in the main protocol.

[b] After 5 cycles or EOT, all participants should continue to receive anastrozole until breast surgery. Anastrozole is not considered study therapy beyond completion of Cycle 5 or EOT.

Selection and Timing of Dose - Randomized Phase

Arm	Study Treatment	Dosage Level[a]	Frequency of Administration	Start and Duration of Treatment	Route of Administration
A	Nivolumab	480 mg	Q4W	Cycle 1-5	IV
	Palbociclib	125 mg	QD × 3 weeks on (1 week off)	Cycle 1-5	PO (with food)
	Anastrozole	1 mg	QD	Cycle 1-5[b]	PO (with or without food)
B	Palbociclib	125 mg	QD × 3 weeks on (1 week off)	Cycle 1-5	PO (with food)
	Anastrozole	1 mg	QD	Cycle 1-5[b]	PO (with or without food)
	Nivolumab	480 mg	Q4W	Cycle 2-5	IV
C	Palbociclib	125 mg	QD × 3 weeks on (1 week off)	Cycle 1-5	PO (with food)
	Anastrozole	1 mg	QD	Cycle 1-5[b]	PO (with or without food)

Abbreviations: BID = twice daily; EOT = end of treatment; IV = intravenous; mg = milligram; PO = per os (by mouth); Q4W = every 4 weeks; QD = once daily.

Note: As of Revised Protocol 03, the abemaciclib-containing combination arms have been removed from the Randomization Phase of the study.

[a] For palbociclib, the starting dose level will be the safe dose determined upon completion of the Safety Run-in Phase.

[b] After 5 cycles or EOT, all participants should continue to receive anastrozole until breast surgery. Anastrozole is not considered study therapy beyond completion of Cycle 5 or EOT.

Study Treatment:

Study Drug for CA2097A8

Medication	Potency	IP/Non-IP
Nivolumab Injection	10 mg/mL; 100 mg fill volume and 10 mg/mL; 40-mg fill volume	IP
Abemaciclib Tablets	150 mg, 100 mg, and 50 mg	IP
Palbociclib Capsules	125 mg, 100 mg, and 75 mg	IP
Anastrozole Tablets	1 mg	IP

Abbreviations: IP = investigational product; mg = milligram; mL = milliliter.

Data Monitoring Committee: No

2 SCHEDULE OF ACTIVITIES

Table 2-1: Screening Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8)

Procedure[a]	Screening Visit	Notes All windows are based on calendar days.
Eligibility Assessments		
Informed Consent	X	Must be obtained prior to any study-related procedures. Register in IRT system to obtain participant number.
Inclusion/Exclusion Criteria	X	Must be assessed at screening and must be confirmed prior to: • Safety Run-in participants: first dose • Randomized participants: randomization
Medical History	X	All medical history relevant to the disease under study, including tobacco history.
Documentation of Postmenopausal Status	X	Please see inclusion criterion 3) b) in Section 6.1 (Inclusion Criteria) for a definition of postmenopausal women.
[redacted]		
Pretreatment Tumor Sample Submission	X	A recent archival tumor biopsy (collected within 90 days prior to enrollment) is required in the format of FFPE block (strongly preferred) or 22 unstained tumor slides (sectioned within 60 days prior to enrollment from a tissue sample collected within 90 days prior to enrollment). If a recent tumor specimen is not available, a fresh tumor biopsy collection is required. At least 15 unstained slides must be submitted for a participant to be eligible. If < 15 unstained slides are available, the participant is not eligible. • Safety Run-in participants: Participant can start study treatment before confirmation of receipt of the tumor sample by the central laboratory. However, receipt of the tumor sample by the central laboratory must occur within 28 days of the first dose. [redacted]
Safety Assessments		
Targeted PE, Measurements, Vital Signs, and ECOG PS	X	Height, weight, BP, HR, RR, temperature, and ECOG PS (Appendix 5). Must be collected within 14 days prior to: • Safety Run-in participants: first dose

Table 2-1: Screening Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8)

Procedure[a]	Screening Visit	Notes All windows are based on calendar days.
		• Randomized participants: randomization • Targeted PE must include ocular examination.
ECG	X	Must be performed within 28 days prior to: • Safety Run-in participants: first dose • Randomized participant: randomization
ECHO (preferred) or MUGA	X	Must be performed within 28 days prior to: • Safety Run-in participants: first dose • Randomized participants: randomization
Assessment of Signs and Symptoms	X	Must be performed within 14 days prior to: • Safety Run-in participants: first dose • Randomized participants: randomization
Concomitant Medication Use	X	Must be performed within 14 days prior to: • Safety Run-in participants: first dose • Randomized participants: randomization Vaccine use within 30 days prior to first dose.
Chest X-ray	X	Must be performed within 14 days prior to: • Safety Run-in participants: first dose • Randomized Phase participants: randomization
SAE Assessment	X	SAE collection from time of consent.
Laboratory Tests		
CBC with Differential, Chemistry, Endocrine, and Serology	X	Must be performed within 14 days prior to: • Safety Run-in participants: first dose • Randomized Phase participants: randomization FSH and Estradiol are required for women ≤ 55. See Section 9.4.4 for a list of laboratory tests to conduct.

Table 2-1: Screening Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8)

Procedure[a]	Screening Visit	Notes All windows are based on calendar days.
[redacted]		
Efficacy Assessments		
Documentation of Planned Surgery	X	Record type of planned BC surgery (ie, BCS, mastectomy).
Clinical Breast Examination	X	Clinical breast examination by palpation of breast and axilla.
Breast and Axilla Ultrasound (Preferred) or Mammogram	X	Perform breast and axilla ultrasound (preferred) or a mammogram within 28 days prior to: • Safety-run in participants: first dose • Randomized participant: randomization • Every attempt should be made to image each participant using an identical imaging modality and acquisition protocol for all imaging time points.
Other Imaging (eg, Bone Scan)	X	As clinically indicated per local standards, including pathologic examination of suspected lesions. See Section 9.1 (Efficacy Assessments) for further details.
Axillary Lymph Nodes Fine Needle Biopsy or Core Biopsy	X	This procedure at screening will be omitted if there is no suspicion for positive axillary lymph node(s) radiographically, or if a pathological report of suspicious lymph nodes of the results of a fine needle biopsy or core biopsy are available prior to the Screening Period.

Abbreviations: BC = breast cancer; BCS = breast-conserving surgery; BP = blood pressure; CBC = complete blood count; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; ER = estrogen receptor; FFPE = formalin-fixed, paraffin-embedded; FSH = follicle-stimulating hormone; HR = heart rate; IHC = immunohistochemistry; IRT = Interactive Response Technology; MUGA = multiple gated acquisition; [redacted] PE = physical examination; PS = performance status; RR = respiratory rate; SAE = serious adverse event.

[a] 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.

Table 2-2: On-treatment Pre-surgery (Neoadjuvant) Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8)

Procedure[a]	Neoadjuvant Treatment[b,c] Cycle 1-5 (1 cycle = 4 weeks)				Pre-surgery (within 7 days prior to surgery)	Notes[d]
	Day 1	Day 8	Day 15	Day 22		
Safety Assessments						
Targeted PE, Measurements, Vital Signs, and ECOG PS	X		C2D15 (see Notes)		X	Weight, BP, HR, temperature, and ECOG PS (Appendix 5) on Day 1 of each cycle. Targeted PE must also include ocular examination at C1D1, C2D15, and as clinically indicated.
Pulse Oximetry	X (predose)					For each testing, two measurements are needed, i.e. at rest and immediately post ambulation
ECG	C1D1 (predose)		C1D15 (predose)			Triplicate ECG (collected within ~ 5 minute window) at C1D1, C1D15, and as clinically indicated.
AEs Assessment (including SAEs)	Continuously.					Record at each visit.
Concomitant Medication Review	Continuously.					Record at each visit.
Laboratory Tests						
CBC with Differential, Chemistry Panel, and Endocrine Testing	X		X C1-C2			Must be performed within 3 calendar days prior to dosing for all time points, except C1D1, which does not need to be repeated if performed within 7 days prior to the first dose. See Section 9.4.4 (Clinical Safety Laboratory Assessments) for list of laboratory tests.
Efficacy Assessments						
Clinical Breast Examination	X					Clinical breast examination by palpation of breast and axilla.

Table 2-2: On-treatment Pre-surgery (Neoadjuvant) Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8)

Procedure[a]	Neoadjuvant Treatment[b,c] Cycle 1-5 (1 cycle = 4 weeks)				Pre-surgery (within 7 days prior to surgery)	Notes[d]
	Day 1	Day 8	Day 15	Day 22		
Breast and Axilla Ultrasound (Preferred) or Mammogram	C2D22 (as clinically indicated)				X	Breast and axilla ultrasound (preferred) or mammogram to be done on C2D22 and within 7 calendar days prior to surgery. Every attempt should be made to image each participant using an identical imaging modality and acquisition protocol for all imaging time points.
Documentation of Actual Breast Surgery	See Notes.					Record actual type of BC surgery (ie, BCS, mastectomy) on day of or within 7 days after surgery.
[redacted]						

Table 2-2: On-treatment Pre-surgery (Neoadjuvant) Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8)

Procedure[a]	Neoadjuvant Treatment[b,c] Cycle 1-5 (1 cycle = 4 weeks)				Pre-surgery (within 7 days prior to surgery)	Notes[d]
	Day 1	Day 8	Day 15	Day 22		
[redacted]						
Study Drug						
Randomization	X					First dose to be administered within 3 calendar days following randomization (for Randomized Phase ONLY).
IRT Drug Assignment	X					Register the visit in the IRT for study drug allocation.

Table 2-2: On-treatment Pre-surgery (Neoadjuvant) Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8)

Procedure[a]	Neoadjuvant Treatment[b,c] Cycle 1-5 (1 cycle = 4 weeks)				Pre-surgery (within 7 days prior to surgery)	Notes[d]
	Day 1	Day 8	Day 15	Day 22		
Administer Nivolumab 480 mg (Safety Run-in Cohorts and Arms A and B)	X					To be administered Q4W IV. First dose to be administered within 3 calendar days following randomization. • Randomized Phase: • Arm A and Arm B • Starting at C2D1 for Arm B
Dispense Anastrozole 1 mg and Provide and Review Patient Diary (Safety Run-in Cohorts and all Arms)	X					To be administered QD PO, with or without food. Review patient diary at each study visit. Note: Anastrozole given beyond C5 or beyond EOT will not be considered as study treatment and must be collected as concomitant medication.
AND						
Dispense Abemaciclib and Provide/Review Patient Diary (Safety Run-in Cohort 1)[e]	X					To be administered BID PO with or without food. Review patient diary at each study visit.
OR						
Dispense Palbociclib and Provide/Review Patient Diary (Safety Run-in Cohort 2 and Arms A, B, and C)	X					To be administered QD PO with food during the first 3 weeks of each cycle (1 week off). Review patient diary at each study visit.

Abbreviations: AE = adverse event; BC = breast cancer; BCS = breast-conserving surgery; BID = twice daily; BP = blood pressure; C = cycle; CBC = complete blood count; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; [redacted]; HR = heart rate; [redacted] IRT = interactive response technology; IV = intravenous; mg = milligram; PE = physical examination; [redacted] PO = per os, (by mouth); [redacted] PS = performance status; QD = daily; Q4W = every 4 weeks; SAE = serious adverse event.

[a] The schedule for each procedure should coincide with actual dosing.

[b] Participants will undergo surgical treatment within 4 weeks of the last dose of neoadjuvant treatment (IV or oral, whichever comes later).

[c] On-treatment procedures may generally be performed within a ± 3-day window, unless otherwise specified (eg, breast ultrasound or mammogram, tumor biopsy).

[d] 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.

[redacted]

Table 2-3: Follow-up Procedural Outline (Safety Run-in Phase and Randomized Phase; CA2097A8)

Procedure	30-Day Safety Follow Up (FU1)[a] (± 7 days) (All Participants in the Safety Run-in Phase and the Randomized Phase)	100-Day Safety Follow Up (FU2)[a] (± 7 days) (All Participants in the Safety Run-in Phase and Arms A and B Only in the Randomized Phase)	Notes[b]
Safety Assessments			
Targeted PE, Measurements, Vital Signs, and ECOG PS	X	X	Weight, BP, HR, temperature, and ECOG PS. Targeted PE may include ocular examination, if clinically indicated.
AE Assessment (including SAEs)	X	X	Participants will be followed for treatment-related toxicities until these toxicities resolve, return to baseline, or are deemed irreversible. Note: All AEs will be documented for a minimum of 100 days after last dose of nivolumab for Safety Run-in Cohorts and Arms A and B, and for 30 days from the last dose of study treatment for Arm C.
Concomitant Medication Review	X	X	Record at each visit.
Subsequent Cancer Treatment	X	X	At each visit, record any new surgery, radiotherapy, and systemic cancer therapy given for the disease under study.
Laboratory Tests			
CBC with Differential, Chemistry, and Endocrine	X	X	Must be performed at FU1. If study drug-related toxicities persist, must be repeated at FU2. See Section 9.4.4 (Clinical Safety Laboratory Assessments) for list of laboratory tests to conduct.

Abbreviations: AE = adverse event; BP = blood pressure; CBC = complete blood count; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; FU1 = follow-up visit 1; FU2 = follow-up visit 2; HR = heart rate; [redacted] IV = intravenous; PE = physical examination; [redacted] PS = performance status; SAE = serious adverse event; SOC = standard of care.

[a] Participants must be followed for at least 100 days after last dose of nivolumab. FU1 should occur 30 days (± 7 days) from the last dose of any treatment (IV or oral whichever comes later). FU2 occurs approximately 100 days (± 7 days) from last dose of nivolumab. Both follow-up visits should be conducted in person.

[b] 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.

3 INTRODUCTION

CA2097A8 is an open-label, randomized, non-comparative Phase 2 study assessing nivolumab, plus palbociclib, and anastrozole as either concurrent or phased neoadjuvant treatment for men and postmenopausal women with primary breast cancer (BC) ≥ 2 cm that are estrogen receptor-positive (ER+) and human epidermal growth factor receptor 2-negative (HER2-) with safety run-in.

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype monoclonal antibody (mAb), an immuno-oncologic (IO) checkpoint inhibitor that binds programmed cell death-1 (PD-1) on activated immune cells and disrupts engagement of the receptor with its ligands programmed death-ligand 1 (PD-L1; B7-H1/CD274) and programmed death-ligand 2 (PD-L2; B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host anti-tumor response. Palbociclib is an orally bioavailable and highly selective small-molecule inhibitor against cyclin-dependent kinases (CDK)4/cyclin-D1 and CDK6/cyclin-D3 enzyme complexes, lead to reactivation of retinoblastoma (Rb) protein, binding back of E2F transcription factor and subsequent cell cycle arrest, thus abrogating endocrine-resistant cell proliferation. Anastrozole is a reversible, third-generation, selective nonsteroidal aromatase inhibitor (NSAI) that reduces peripheral estrogen synthesis by blocking the conversion of androgens to estrogens in non-ovarian tissues. A detailed description of the chemistry, pharmacology, efficacy, and safety of the study treatments is provided in the Investigator Brochures (IBs) and package inserts.[1,2,3,4]

The study will assess the efficacy and safety of: i) concurrent therapy with nivolumab in combination with palbociclib, and anastrozole (Arm A), ii) phased therapy with one initial priming cycle of palbociclib and anastrozole followed by nivolumab in combination with palbociclib, and anastrozole (Arm B), and iii) control treatment with palbociclib and anastrozole (Arm C). Participants with newly diagnosed, previously untreated primary ER+ and HER2- BC ≥ 2 cm will be subjected to a total 5 cycles (4 weeks per cycle) of neoadjuvant therapy before definitive surgery. Efficacy will be measured by significantly improved residual cancer burden (RCB) 0-I rate. [redacted]

3.1 Study Rationale

PD-1 pathway inhibition has demonstrated clinical activity across multiple tumor types, including BC.[5] An accumulating body of evidence supports PD-1/CDK4/6 blockade potential synergy, as it has become more apparent that CDK4/6 inhibitors modulate the tumor immune microenvironment[6] (ie, increases expression of PD-L1,[7] enhances antigen presentation[8] and secretion of cytokines from both tumor and CD8+ T cells,[9,10] and suppresses proliferation of immunosuppressive regulatory T cells [Tregs][8]). Preliminary clinical data in support of synergistic activity of the combination of pembrolizumab and abemaciclib has been demonstrated in a Phase 1b study on heavily pretreated participants with metastatic hormone receptor-positive (HR+), HER2- BC.[11] Clinical data on combinations of other CDK4/6 inhibitors with PD-(L)1

blocking agents are being generated in multiple clinical trials spanning from the neoadjuvant to metastatic setting (ClinicalTrials.gov: NCT03573648, NCT02778685, NCT03294694). Additional treatment benefit (improved anti-tumor efficacy and complete tumor regression) was observed in a syngeneic mouse tumor model by priming the anti-cancer immune response with abemaciclib in a phased administration of abemaciclib and an anti-PD-L1 therapy.[12] Therefore, an additional phased therapy arm has been added for each CDK4/6 inhibitor to explore possible treatment benefit in patients.

The aim of the CA2097A8 study is to assess the potential synergistic activity of nivolumab, with palbociclib, and anastrozole in participants with newly diagnosed, previously untreated primary ER+, HER2- BC ≥ 2 cm, defined by significantly improved RCB (0-I) rate. [redacted] Additional objectives of the study include characterization of safety and tolerabilit [redacted].

3.1.1 Research Hypothesis

The combination of nivolumab, with palbociclib, and anastrozole is a safe and effective neoadjuvant treatment for patients with ER+, HER2- primary BC ≥ 2 cm.

3.2 Background

3.2.1 ER+/HER2- Breast Cancer

BC ranks second as a cause of cancer death in women after lung cancer.[13] An estimated 42,260 BC deaths (41,760 women) are expected in 2019 in the United States (US). In clinical practice, BC tumors are classified by the expression status of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2). The BC subtypes identified on the basis of these receptors have been reported to bear distinct gene expression profiles,[14,15] as well as different prognoses and treatment vulnerabilities. Seventy percent of invasive BC in women > 45 years of age express ER and/or PgR, but not HER2, and are termed hormone receptor-positive (HR+), HER2-.[16] Seminal studies performed with gene expression profiling analysis of primary BC samples indicated that the tumors in the HR+ group are characterized by the relatively high expression of genes related to luminal phenotype (ER-responsive genes, luminal cytokeratins, and other luminal-associated markers); consequently, HR+, HER2- BC was found to be significantly enriched with the so called luminal BC intrinsic subtypes, namely: luminal A (50-60% of all BC, showing higher dependence on ER signaling, slower proliferation rate and overall more indolent clinical course) and luminal B (15-20% of all BC, showing lower dependence on ER signaling, higher proliferation rate, and overall, a more aggressive clinical course and worse prognosis, as compared to their luminal A counterparts).[17]

3.2.2 Neoadjuvant Endocrine Treatment

While, traditionally, neoadjuvant chemotherapy has been used to downstage locally advanced and unresectable primary BC, a number of studies have highlighted the role of neoadjuvant endocrine treatment (NET) as an alternative option to chemotherapy in patients with HR+, HER2- primary tumors,[18] particularly for postmenopausal women. Available data suggest that NET is associated with similar response rates and rates of breast-conserving surgery (BCS) as neoadjuvant chemotherapy, albeit with lower toxicity in postmenopausal women with HR+ BC.[18,19,20,21,22] For postmenopausal women receiving NET, the administration of an aromatase inhibitor (AI) is recommended instead of tamoxifen, based on evidence suggesting improved outcomes for women treated with AIs across clinical trials and meta-analyses.[21,23,24,25,26,27,28,29] Similar clinical outcomes (rate of BCS) in the neoadjuvant setting among the AIs were observed in 377 postmenopausal women with Stage II or III strongly ER+ BC who were randomly assigned to treatment with exemestane, letrozole, or anastrozole for 16-18 weeks before surgery in the American College of Surgeons Oncology Group (ACOSOG) Z1031 trial.[28]

3.2.3 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immune surveillance and escape effective innate and adaptive immune responses.[30,31,32] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[33] Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the cluster of differentiation 28 (CD28) family of T cell co-stimulatory receptors that also includes CD28, cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), inducible T cell co-stimulator (ICOS), and B- and T-lymphocyte attenuator (BTLA).[34] PD-1 signaling has been shown to inhibit CD28-mediated upregulation of interleukin (IL)-2, IL-10, IL-13, interferon-γ (IFN-γ), and B-cell lymphoma-extra large (Bcl-xL). PD-1 expression has also been noted to inhibit T cell activation and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[35] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon a host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (half-maximal effective concentration [EC50] 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (half-maximal inhibitory concentration [IC50] ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) re-stimulation assay with human peripheral blood mononuclear cells (PBMCs), the effect of nivolumab on antigen-specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner vs isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[36]

3.2.4 CDK 4/6 Inhibitors and Mechanism of Action

Cell cycle progression is regulated by cyclin-dependent serine-threonine protein kinases. Extracellular growth and adhesion signals increase the level and function of cyclin D proteins within the cell. In turn, the cyclin D proteins associate with and activate CDK4 and CDK6.[37] CDK4 and CDK6 phosphorylation leads to inactivation of the Rb protein and thus releases E2F, which in turn leads to the transcription initiation of proteins involved in cell cycle propagation and proliferation.

The luminal A and B subtypes of BC (85% of which are ER+, HER2-) have high rates of cyclin D/CDK activation; in the luminal A and B subtypes, cyclin D1 (CCND1) amplifications were observed in 29% and 58%, and CDK4 amplifications were observed in 14% and 25%, respectively.[38,39] Luminal A subtype tumors also have loss of CDKN2A, which encodes p16INK4A, a CDK inhibitor.[40] The luminal subtypes also maintain expression of Rb, which is essential for benefit from treatment with a CDK4/6 inhibitor.[41]

Dysregulation of cell cycle checkpoints is common in BC, and in all cancers in general, and may have clinical and therapeutic significance. For example, patients with HR+ BC exhibiting a gene expression signature of Rb loss had a shorter recurrence-free survival following adjuvant tamoxifen.[42] A tumor gene expression signature of E2F activation is also associated with higher residual tumor cell proliferation following neoadjuvant AI therapy. Therefore, activation of the CDK4/6-Rb-E2F pathway promotes endocrine resistance, and treatment with a CDK4/6 inhibitor or knockdown of CDK4 expression leads to reactivation of Rb, binding back of E2F and subsequent cell cycle arrest thus abrogating endocrine-resistant cell proliferation. A seminal preclinical study exploring 47 human BC cell lines reported that palbociclib monotherapy was active in luminal BC cell lines compared to non-luminal BC cells lines, and that palbociclib potentiated tamoxifen and trastuzumab activity in ER+ and human epidermal growth factor receptor 2-positive (HER2+) BC cell lines, respectively.[43]

3.2.5 Clinical Experience with Nivolumab

The overall clinical safety experience with nivolumab, as either monotherapy or in combination with other therapeutics, is based on experience in approximately 17,700 participants.[3] Nivolumab monotherapy is approved in multiple regions, including the US and Europe (EU), for unresectable or metastatic melanoma, previously treated metastatic non-small cell lung cancer (NSCLC), previously treated advanced renal cell carcinoma (RCC), previously treated relapsed or refractory classical Hodgkin lymphoma, previously treated advanced or metastatic urothelial carcinoma, and for the treatment of previously treated recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN); it is also approved for previously treated colorectal cancer (CRC), previously treated hepatocellular carcinoma (HCC), and the adjuvant treatment of melanoma in the US. In addition, nivolumab has been approved for use in combination with ipilimumab for RCC in the US and unresectable melanoma in multiple countries, including the US and EU.[3]

In 39 patients with BC, nivolumab alone or in combination with ipilimumab were tolerable without additional safety signal detected in the CheckMate 32 study (unpublished data). In 66 patients with metastatic triple negative breast cancer (TNBC), nivolumab with or without various induction therapies (radiation therapy, cyclophosphamide, cisplatin, or doxorubicin) demonstrated ORRs from 17% without induction therapy to 35% with doxorubicin induction therapy (TONIC trial).[44] An additional 37 clinical trials of nivolumab alone or in combination treating patients with BC are currently ongoing (eg, ClinicalTrials.gov: NCT03414684, NCT03789110, NCT03316586).

Details on the clinical safety and PK profile of nivolumab, including results from other clinical studies, are summarized in the nivolumab IB.[3]

3.2.6 Clinical Experience with CDK 4/6 Inhibitors and Endocrine Therapy

The clinical development of second generation, CDK4/6-selective inhibitors, namely palbociclib, abemaciclib, and ribociclib, led to practice-changing results in the setting of advanced HR+, HER2- BC. In combination with aromatase inhibitors in the first-line setting and fulvestrant in the second-line setting, CDK4/6 inhibitors not only significantly increased ORR and prolonged progression-free survival (PFS),[45] but also achieved clinically meaningful overall survival (OS) benefit from treatment combining palbociclib and fulvestrant, albeit not statistically significant.[46] In addition, single-agent abemaciclib demonstrated an ORR of 19.7% in heavily pretreated patients with refractory HR+, HER2- metastatic BC.[47] Selective CDK4/6 inhibitors are currently assessed in early-stage HR+, HER2- primary BC (neoadjuvant and adjuvant setting) as well as other BC subtypes. In the neoadjuvant setting, the combination of palbociclib and letrozole markedly enhanced the suppression of malignant cell proliferation as assessed by Ki67, a marker of cellular proliferation, but did not substantially increase the clinical response of primary ER+ BC over a 14-week period.[48,49] Therefore, novel combinations are needed in this setting to optimize efficacy.

Details on the clinical safety and PK profile of palbociclib, including results from other clinical studies, are summarized in its respective product label.[4]

3.3 Benefit/Risk Assessment

Based on preclinical and clinical data, treatment of nivolumab and palbociclib in combination with endocrine therapy (ET) is expected to be tolerable and toxicities of the treatment are expected to be manageable and reversible upon dose reduction, treatment interruption, or discontinuation.

Participants in this study will be carefully monitored for key toxicities. Risks will be further minimized by adherence to inclusion/exclusion selection criteria (see Section 6 [Study Population]), avoidance of prohibited medication (see Section 7.7 [Concomitant Therapy]), close safety monitoring (see Section 9.2 [Adverse Events], Section 9.2.9 [Management Algorithms for Nivolumab], and Section 9.4 [Safety]), and dose adjustment guidelines (see Section 7.4 [Dosage Modification]). These will also be clearly discussed and highlighted during site visits.

A Study Steering Committee (SSC; see Section 5.1.4.1 [Study Steering Committee]) will be established comprising of Investigators and BMS personnel participating in the trial to ensure transparent management of the trial according to the protocol. A BMS Safety Management Team will review and evaluate all emerging data across the program for potential safety signal assessment in a timely manner.

More detailed information about the known and expected benefits and risks and reasonably anticipated adverse events (AEs) of study treatments may be found in the IB,[3] Patient Information Leaflet, Package Insert,[1,2,4,50] Development Safety Update Report, or Summary of Product Characteristics (SmPC).

Due to the need to develop improved therapies to reverse or delay resistance to current ET in ER+, HER2- BC, and on the basis of the clinical and nonclinical data in support of the current study, BMS feels that the benefit-risk profile of nivolumab in combination with palbociclib and anastrozole in men and postmenopausal women with ER+, HER2- early-stage BC is favorable for proceeding with the proposed randomized Phase 2 clinical trial. As of Protocol Revision 03, the benefit-risk profile of the abemaciclib-containing combination is no longer considered favorable; thus BMS will not move forward with randomization to nivolumab in combination with abemaciclib and anastrozole (see Section 5.1).

3.3.1 Nivolumab Safety Profile

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

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix 6. 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]

3.3.2 CDK 4/6 Inhibitor and Endocrine Therapy Combination Safety Profile

Overall, the safety profile of palbociclib monotherapy, as well as in combination with ET is manageable and generally consistent across completed and ongoing clinical trials.

For palbociclib, the most common adverse reactions (incidence ≥ 10%) were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, and pyrexia.[4]

For anastrozole:

- In the early BC study (ATAC), the most common (incidence of > 10%) side effects were hot flashes, asthenia, arthritis, pain, arthralgia, pharyngitis, hypertension, depression, nausea and vomiting, rash, osteoporosis, fractures, back pain, insomnia, headache, peripheral edema, and lymphedema, regardless of causality.[2]
- In the advanced BC studies, the most common (> 10%) side effects were hot flashes, nausea, asthenia, pain, headache, back pain, bone pain, increased cough, dyspnea, pharyngitis, and peripheral edema.[2]

Extensive details on the safety profile of palbociclib and anastrozole are available in the Patient Information Leaflet, Package Insert, or SmPC.

3.3.3 CDK4/6 Inhibitor and Nivolumab Combination Safety Profile

The safety profile of nivolumab is well characterized and manageable when administered alone or in combination with other treatments, including regimens where it is administered in combination with chemotherapy, targeted agents, as well as additional IO products. In a Phase Ib study, the combination of pembrolizumab (a PD-1 inhibitor with similar safety profile) and abemaciclib at Food & Drug Administration (FDA)-approved doses of the respective agents demonstrated a manageable safety profile, with a confirmed ORR of 28.6% in 28 heavily pretreated participants with metastatic BC (HR+, HER2- subtype)[11]

In a Phase 2 study of pembrolizumab, palbociclib and letrozole (AI) in patients with metastatic ER+, HER2- BC (NCT02778685), of 20 patients treated with the triple combination, Grade 3 pneumonitis was reported in 1 patient during the DLT assessment period. The median follow up for this study was 13.7 months (95% CI 6.4-16.9) and progression-free survival (PFS) has not been reached.[51] Also in a phase 1 study exploring safety and efficacy of avelumab, palbociclib and axitinib (tyrosine kinase inhibitor) in patients with advanced non-small cell lung cancer (NCT03386929), of 13 patients treated at 3 dose levels, 1 patient with baseline chronic obstructive pulmonary disease at dose level 3 developed a respiratory failure event possibly related to study treatment and died. No Grade 3 or above ILD/pneumonitis events were reported.[52] A randomized Phase 2 trial assessing a triple combination regimen of palbociclib + avelumab (anti-PD-L1 inhibitor) + fulvestrant (estrogen receptor antagonist) for patients with pre-treated metastatic

ER+/HER2- BC has been ongoing since Aug-2017; no clinical data have been reported to date. (NCT03147287). Thus, the ***potential benefit of the palbociclib combination therapy appears to outweigh the known risks and warrants clinical investigation.***

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• Safety Run-in Phase: Number of participants with occurrence of DLT.	• DLT is defined as TEAE (graded according to the NCI CTCAE v5.0) that occurs during the first 4 weeks after treatment start and that meets specific criteria (see Section 5.1.2.1).
• Randomized Phase: To assess RCB 0-I rate by central assessment of palbociclib plus anastrozole with or without nivolumab in all participants with untreated primary BC ≥ 2 cm (ER+, HER2-).	• RCB 0-I rate assessed by central assessment at the time of definitive surgery. • RCB is a continuous index combining pathological measurements of primary tumor (size and cellularity) and nodal metastases (number and size) defined by a point system at surgery (refer to Appendix 7 [RCB Methods]).
Secondary	
• To assess the safety and tolerability of palbociclib plus anastrozole with or without nivolumab.	• Incidence of AEs, SAEs, AEs leading to discontinuation, immune-related AEs, deaths, and laboratory abnormalities in all participants.
• To assess pCR rate by local assessment of palbociclib plus anastrozole with or without nivolumab in participants with untreated primary BC ≥ 2 cm (ER+, HER2-).	• pCR rate in all participants assessed by the local pathologist at the time of definitive surgery. – pCR, defined as no invasive residual disease in breast or lymph nodes (ie, ypT0/is, ypN0) in the current AJCC staging system.
• To assess ORR (clinical and radiological [ultrasound (preferred) or mammography]) by Investigator assessment and BCS rate of palbociclib plus anastrozole with or without nivolumab in participants with untreated primary BC ≥ 2 cm (ER+, HER2-).	• ORR is defined as the number of participants with a BOR of CR or PR divided by the number of randomized participants for each treatment group at the end of the study treatment period. • BCS rate is defined as the number of participants who undergo BCS after completing the study treatments divided by the number of randomized participants for each treatment group.
[redacted]	

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]

Abbreviations: [redacted] AE = adverse event; AJCC = American Joint Committee on Cancer; BC = breast cancer; BCS = breast-conserving surgery; BOR = best overall response; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; [redacted] HER2- = human epidermal growth factor receptor 2-negative; [redacted] NCI = National Cancer Institute; ORR = objective response rate; pCR = pathological complete response; [redacted] PR = partial response; [redacted] RCB = residual cancer burden; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TIL = tumor-infiltrating lymphocyte; [redacted].

5 STUDY DESIGN

5.1 Overall Design

This randomized, open-label Phase 2 study was to evaluate whether the combination of nivolumab, with abemaciclib or palbociclib, plus anastrozole is a safe and effective neoadjuvant treatment for men and postmenopausal women with primary BC ≥ 2 cm that is ER+ and HER2- subtype who are suitable to receive NET and willing to undergo SOC breast surgery after completion of the study treatment.

On 6-Mar-2020, Bristol Myers Squibb (BMS) decided to permanently discontinue enrollment and dosing in the nivolumab + abemaciclib + anastrozole cohorts of the CA2097A8 study during the Safety Run-in Phase. [redacted]

At implementation of Revised Protocol 03, the study will only evaluate whether the combination of nivolumab, with palbociclib, plus anastrozole is a safe and effective neoadjuvant treatment for men and postmenopausal women with primary BC ≥ 2 cm that is ER+ and HER2- subtype who are suitable to receive NET and willing to undergo SOC breast surgery after completion of the study treatment. Participants must have histologically confirmed invasive breast carcinoma meeting the characteristics described in Section 6.1 (Inclusion Criteria). Participants in screening and not yet treated were offered the option to join the safety lead-in of the nivolumab + palbociclib + anastrozole arm. Participants on treatment with nivolumab + abemaciclib + anastrozole were to be re-consented and continue on anastrozole alone, OR taken off study. In addition, baseline chest X-ray and periodic pulse oximetry are implemented to monitor ILD/pneumonitis in patients who will be treated with nivolumab + palbociclib + anastrozole.

The study is divided into 3 periods: Screening Period, On-treatment Pre-surgery (neoadjuvant) Period (Safety Run-in Phase and Randomized Phase), and Safety Follow-up Period.

The study started with a Safety Run-in Phase for the combination of nivolumab, with abemaciclib or palbociclib, plus anastrozole and will begin the Randomized Phase after the regimen is determined to be safe. Participants in the Safety Run-in Phase will move to the Safety Follow-up Period upon completion of the neoadjuvant treatment or upon discontinuation. Potential needs for additional enrollment or for dose de-escalation will be discussed with Investigators and BMS during the Safety Run-in Phase. Once a safe dose for the regimen has been determined by BMS in collaboration with Investigators, the Randomized Phase of the study will begin.

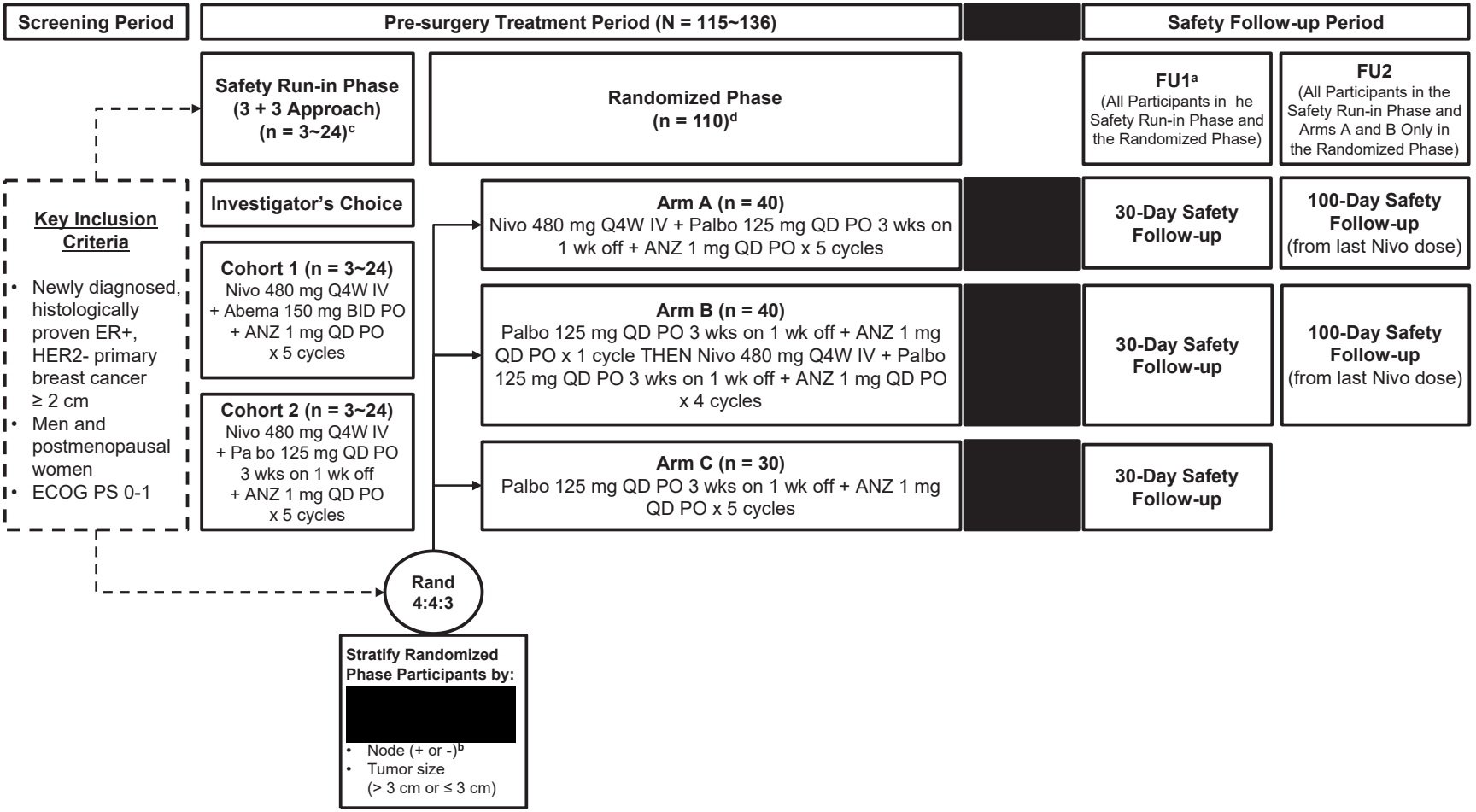
In the Randomized Phase, participants will be randomly assigned by an IRT system to 3 different treatment arms and stratified by the following factors: [redacted]

[redacted] 2) evaluation of lymph nodes (cytologically positive vs radiologically or cytologically negative); and 3) tumor size (> 3 cm or ≤ 3 cm).

For both the Safety Run-in Phase and Randomized Phase, participants will be treated for a maximum of 5 cycles (1 cycle = 4 weeks). Participants with progressive disease prior to completion of the 5-cycle study treatment must discontinue all study drugs and proceed to the Safety Follow-up Period. Participants who permanently discontinue the study drugs for any reason are considered to have completed the On-treatment Pre-surgery (neoadjuvant) Period, and hence reach end of treatment (EOT). After Cycle 5 or EOT, participants must continue to receive anastrozole (as concomitant medication and not as study treatment) until subsequent SOC breast surgery. Following the completion of neoadjuvant treatment, all participants who remain operative candidates will undergo definitive surgery for BC within 4 weeks of the last neoadjuvant treatment administration. If anastrozole can no longer be administered after EOT, participants will go to breast surgery right away. Pre-surgical lymph node biopsy is not allowed. Information on the type of the surgery will be collected and recorded in the electronic case report form (eCRF). Surgical specimens will be collected for the analyses outlined in the protocol. Depending on treatment assignment, up to 2 safety follow-up visits will be conducted in person. The first safety follow-up visit (FU1) will be completed for all participants within 30 days (± 7 days) from the last study treatment (oral or intravenous [IV], whichever occurs later). The second safety follow-up visit (FU2) will occur approximately within 100 days (± 7 days) from the last dose of nivolumab and will be required for participants in the Safety Run-in Phase and participants randomized to Arms A or B in the Randomized Phase. Further planned treatment of participants in the adjuvant setting (ie, radiotherapy, endocrine treatment, chemotherapy or any other treatment modality) will be at the discretion of the treating physician, following local clinical guidelines, and collected in the appropriate eCRF.

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

Figure 5.1-1: Study Design Schematic



Abbreviations: Abema = abemaciclib; ANZ = anastrozole; BID = twice daily; cm = centimeter; ECOG = Eastern Cooperative Oncology Group; ER+ = estrogen-receptor-positive; FU1 = follow-up visit 1; FU2 = follow-up visit 2; HER2- = human epidermal growth factor receptor 2-negative; IV = intravenous; mg = milligram; N = number; Nivo = nivolumab; Palbo = palbociclib; [redacted] PO = per os (by mouth); PS = performance status; Q4W = every 4 weeks; QD = once daily; Rand = randomized; wk = week.

[a] FU1 begins at the end of study treatment.

[b] Cytologically positive vs radiologically or cytologically negative.

[c] At the time of Revised Protocol 03, 2 participants had been treated in Cohort 1 (nivolumab + abemaciclib + anastrozole), which was subsequently closed for enrollment.

[d] At time of Revised Protocol 03, the decision was made to no longer evaluate abemaciclib in combination with nivolumab plus anastrozole; thus, the abemaciclib-containing combination arms have been removed from the Randomization Phase of the study.

5.1.1 Screening Period

Participants will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the participants' standard care. After signing the informed consent form (ICF), participants will be evaluated for entry criteria and be enrolled into Interactive Response Technology (IRT). The screening assessments are shown in Table 2-1.

Participants must provide a pretreatment (baseline) tumor tissue, which must be either in FFPE tissue block containing 20 mm^3 of tissue collected ≤ 90 days prior to enrollment (strongly preferred) or unstained tumor tissue sections (22 unstained slides) sectioned ≤ 60 days prior to enrollment from a tissue sample collected ≤ 90 days prior to enrollment from primary tumor lesion. If a recent tumor specimen is not available, a fresh tumor biopsy (containing 20 mm^3 of tissue) is required. At least 15 unstained slides must be submitted for a participant to be eligible. If < 15 unstained slides are available, the participant is not eligible. Submit samples to the designated central laboratory with an associated pathology report. [redacted]

Safety Run-in participants: Participant can start study treatment before confirmation of receipt of the tumor sample by the central laboratory. However, receipt of the tumor sample by the central laboratory must occur within 28 days of the first dose.

Randomized participants: [redacted] Documentation of tumor size and node status (cytologically positive vs radiologically or cytologically negative) must be provided to IRT prior to randomization.

[redacted]

The Screening Period for each participant ends with the confirmation of full eligibility of the participant or with the confirmation that the participant is a screen failure. This study permits the re-enrollment of a participant that has discontinued the study as a pretreatment failure (ie, participant has not been randomized [or treated in the Safety Run-in Phase]). If re-enrolled, the participant must be re-consented.

5.1.2 On-treatment Pre-surgery (neoadjuvant) Period

A schedule of on-treatment visits and assessments is provided in Table 2-2.

5.1.2.1 Safety Run-in Phase

As of Revised Protocol 03, Cohort 1 will be discontinued. Participants in screening and not yet treated were offered the option to join the nivolumab + palbociclib + anastrozole arm. Participants on treatment were to be re-consented and continue on anastrozole alone, OR taken off study.

The Safety Run-in Phase will be conducted in advance of the Randomized Phase to evaluate the safety and tolerability of the combination of nivolumab, with palbociclib, plus anastrozole, which will be administered during the Randomized Phase.

Participants will receive palbociclib in combination with nivolumab plus anastrozole (Cohort 2) for 5 cycles as neoadjuvant therapy and be followed up for safety (see Section 5.1.3 [Safety Follow-up Period]). . For the purpose of guiding alternative dose levels, all AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and dose-limiting toxicities (DLTs) will be defined based on the incidence, intensity, and duration of the AEs for which no clear alternative cause is identified. For the purpose of participant management, any drug-related AE that meets DLT criteria will lead to discontinuation of study treatment.

Participants who have discontinued due to a DLT or who have received 1 dose of nivolumab and 75% of accumulative doses of palbociclib of the cycle, and have completed the 4-week DLT period will be considered as DLT-evaluable participants. Participants who withdraw from the study during the DLT evaluation period or have received less than 1 dose of nivolumab and 75% of accumulative doses of palbociclib of the cycle for reasons other than a DLT will not be considered as DLT-evaluable participants and may be replaced with new participants at the same dose level.

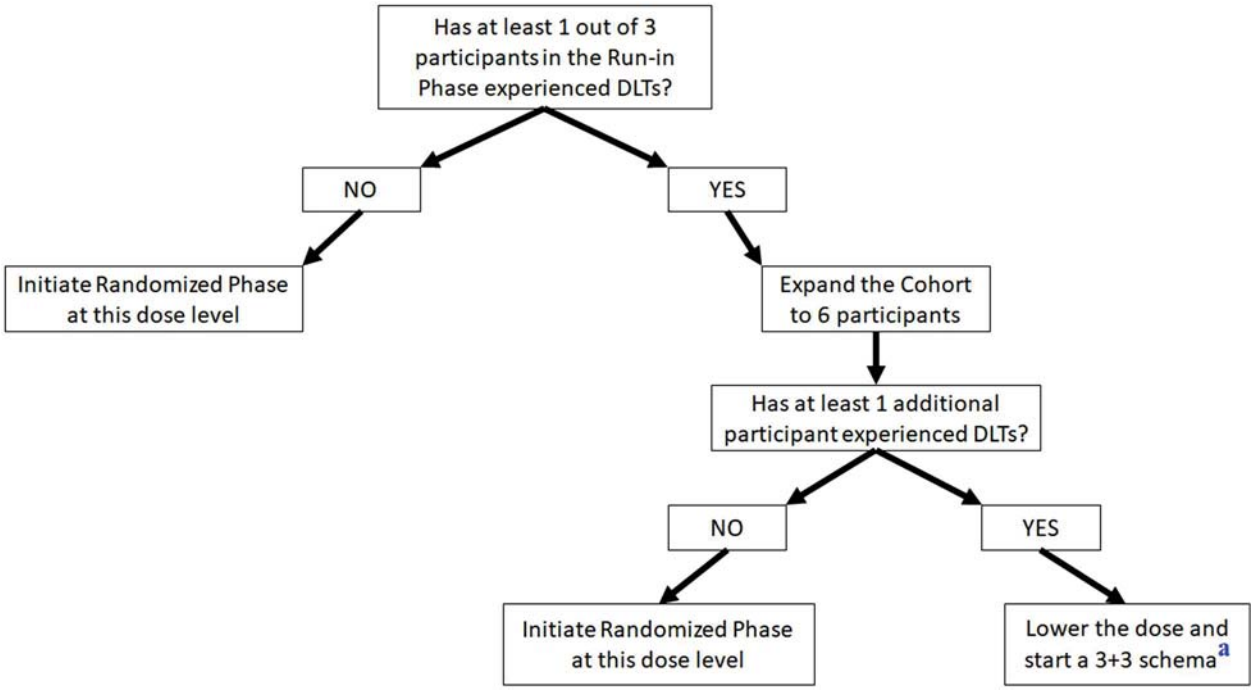
Dose De-escalation Rules

For Cohort 2, 3 DLT-evaluable participants will be treated with the below starting doses:

- Nivolumab: 480 mg every 4 weeks (Q4W) intravenously (IV)
- Palbociclib 125 mg once daily (QD) PO for 3 weeks of each cycle (1 week off)
- Anastrozole: 1 mg QD PO

If no participants (0 of 3 DLT-evaluable participants) experience a DLT during the DLT period (4 weeks), the Randomized Phase will be initiated at this dose level. If 1 evaluable participant (1 of 3 DLT-evaluable participants) experiences DLT, then the cohort will be expanded to 6 DLT-evaluable participants. If no more DLTs are observed (1 of 6 DLT-evaluable participants), then the Randomized Phase will be initiated at the dose level tested. If 1 or more additional evaluable participants (2 of 6 DLT-evaluable participants) experiences DLT during the DLT period, a lower dose will be tested using the same 3 + 3 schema. See Figure 5.1.2.1-1 for an overview of the 3 + 3 approach to be used for the Safety Run-in Phase.

Figure 5.1.2.1-1: Schematic of Safety Run-in Phase 3 + 3 Approach



Abbreviations: DLT = dose-limiting toxicity.

[a] For additional details see Section 7.4 (Dosage Modification).

Continuous evaluation of toxicity events will be performed. If at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across participants treated in a cohort, the findings will be discussed with the Investigators and further enrollment may be interrupted. Any toxicities that occur beyond the DLT period will be accounted for in making final dose level decisions.

Generally, if a cohort is discontinued due to DLT of unclear relevance to nivolumab, a lower dose level of CDK4/6 inhibitor per product label will be tested in the next cohort. See Section 7.4 (Dosage Modification) for additional details on permitted dose adjustment. If a cohort is discontinued due to DLT related to nivolumab, a different dose or dose schedule will be explored per Investigator and Medical Monitor discussion.

For cohort expansion or dose de-escalation decisions, the available toxicity information (including AEs and laboratory abnormalities that are not DLTs), clinical judgment [redacted] will be evaluated by the Investigators and BMS study personnel (including the Medical Monitor and statistician) during a dose decision meeting by teleconference. Drug administration at the next dose level or proceeding to the Randomized Phase must not occur until the Investigator receives written confirmation from BMS indicating that the results of the previous dose level were evaluated and that it is permissible to proceed.

Definition of DLTs: DLTs are defined as any TEAEs specified below that occur during the first 4 weeks (1 cycle) except those clearly and incontrovertibly due to disease progression or extraneous causes.

Gastrointestinal DLTs

- Grade 2 colitis that lasts longer than 7 days, despite best supportive treatment.
- Grade 3 diarrhea or colitis that lasts longer than 72 hours with adequate supportive treatment.
- Grade ≥ 4 diarrhea or colitis.

Hepatic DLTs

- Grade 4 elevations in serum transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT], alkaline phosphatase [ALP]) or total bilirubin.
- Grade 3 elevations in serum AST, ALT, or bilirubin.
- Bilirubin > 2 x upper limit of normal (ULN) in the absence of cholestasis.
- Grade 2 elevations in AST or ALT with symptomatic liver inflammation (eg, right upper quadrant tenderness, jaundice).
- Grade 3 ALP elevation that last longer than 5 days, or is associated with clinical symptoms.
- AST or ALT > 3 × ULN and concurrent total bilirubin > 2 × ULN without initial findings of cholestasis (elevated ALP; eg, findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [p-DILI]). Note that this specific category of DLT uses ULN rather than NCI CTCAE grade for definition.

Hematologic DLTs

- Grade 4 neutropenia ≥ 7 days in duration.
- Grade 4 thrombocytopenia.
- Grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion.
- Grade 3 hemolysis (ie, requiring transfusion or medical intervention such as steroids).
- Neutropenic fever of any duration.
- Grade 4 anemia not explained by underlying disease.

Dermatologic DLTs

- Grade 4 rash or confirmed Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis.
- Grade 3 rash if no improvement (ie, resolution to ≤ Grade 1) after a 1- to 2-week infusion omission for nivolumab.

Other DLTs

- Recurrence of same Grade 3 adverse reactions.

- Any AE that required discontinuation of nivolumab per approved label.
- Any Grade immune-related encephalitis.
- Any incidence of Grade ≥3 prolongation of QT interval corrected using Fridericia's Correction Formula (QTcF) on electrocardiograms (ECGs).Grade 3 hypersensitivity reaction/infusion reaction that does not resolve to Grade 1 in < 6 hours.
- Grade 2 pneumonitis that does not respond to dose modification for nivolumab and systemic steroids within 14 days.
- Any death not clearly due to the underlying disease or extraneous causes.
- Grade 2 uveitis, episcleritis, iritis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment.
- Grade ≥ 3 electrolyte abnormality associated with clinical symptoms.
- Grade 3 fatigue lasting ≥ 1 week.
- Other Grade 3 ≥ toxicity will be considered a DLT, except those clearly and incontrovertibly due to disease progression and extraneous causes. However, the following Grade 3 or 4 events will not be considered DLTs:
  - Isolated Grade 3 or 4 electrolyte imbalances/abnormalities not associated with clinical symptoms and either resolve spontaneously or are corrected with supplementation/appropriate management within 72 hours of their onset. Confirmatory laboratory test is required within 72 hours.
  - Grade ≥ 3 amylase or lipase elevation not associated with symptoms or clinical manifestations of pancreatitis.
  - Grade 3 nausea or vomiting that lasts less than 48 hours and either resolves spontaneously or responds to medical intervention.
  - 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).

5.1.2.2 Randomized Phase

The Randomized Phase will start after the combinations tested in the Safety Run-in Phase are confirmed to be safe by BMS in collaboration with Investigators, and the appropriate dose level communicated to Investigators. Following confirmation of eligibility criteria, participants will be randomized to either Arm A, Arm B, or Arm C in a 4:4:3 ratio, respectively. Participant randomization will be stratified using the following factors:

[redacted]

2) Evaluation of lymph nodes (cytologically positive vs radiologically or cytologically negative), and
3) Tumor size (> 3 cm or ≤ 3 cm).

[redacted] Treatment must begin within 3 calendar days following randomization.

Participants will be randomly assigned to 1 of the 3 treatment arms below:

As of Revised Protocol 03, the abemaciclib-containing combination arms have been removed from the randomization phase of the study.

1) Arm A (concurrent palbociclib treatment arm): nivolumab 480 mg Q4W IV + palbociclib 125 mg QD PO for 3 weeks (1 week off) + anastrozole 1 mg QD PO for 5 cycles
2) Arm B (phased palbociclib treatment arm):
   a) palbociclib 125 mg QD PO for 3 weeks of each cycle (1 week off) + anastrozole 1 mg QD PO for 1 cycle followed by
   b) nivolumab 480 mg Q4W IV + palbociclib 125 mg QD PO for 3 weeks (1 week off) + anastrozole 1 mg QD PO for 4 cycles
3) Arm C (control palbociclib arm): palbociclib 125 mg QD PO for 3 weeks of each cycle (1 week off) + anastrozole 1 mg QD PO for 5 cycles

5.1.3 Safety Follow-up Period

Depending on the treatment arms, there may be up to 2 in-person safety follow-up visits. FU1 will occur 30 days from the last dose (± 7 days) of the study treatment (PO or IV; whichever occurs later) for all arms. FU2 occurs approximately 100 days (± 7 days) from the last dose of nivolumab for Safety Run-in participants and Arms A and B in the Randomized Phase.

5.1.4 External Committees

5.1.4.1 Study Steering Committee

A SSC will be established to obtain scientific guidance and advice on the protocol and conduct of the study. The SSC will meet at least annually and on an ad-hoc basis as necessary. Detailed information can be found in the SSC charter.

5.2 Number of Participants

A total of approximately 115~136 participants will be treated in the study. It is anticipated that approximately 3~24 participants (up to approximately 30 screened) will be treated in each cohort in the Safety Run-in Phase. At the time of Revised Protocol 03, 2 participants had been treated in Cohort 1 (nivolumab + abemaciclib + anastrozole), which was subsequently closed for enrollment. Approximately 138 participants will be screened for 110 participants to be treated in the Randomized Phase, assuming a screen failure rate of approximately 20%. See Section 10.1 (Sample Size Determination) for additional details.

5.3 End of Study Definition

The start of the trial is defined as the first participant's first visit. End of study is defined as the last participant's last study visit or scheduled procedure shown in Section 2 (Schedule of Activities). Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected.

5.4 Early Study Termination Criteria

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence and/or severity of AEs in this or other studies that incorporate similar treatment arm(s) indicates a potential health hazard to participants.
- Further clinical data that might occur from other studies that incorporate similar treatment arm(s) that indicate a potential inappropriate benefit-risk balance for participants in the study, due to lack of activity.

Such decisions shall be communicated promptly, in order to allow the termination procedure to be properly followed. BMS will also notify Investigators if the study is terminated early.

5.5 Scientific Rationale for Study Design

5.5.1 Rationale for the Choice of Patient Population

Men or postmenopausal women with newly diagnosed, histologically proven ER+, HER2- primary BC ≥ 2 cm who are eligible for NET will be included in the study population. Due to the low pathological complete response (pCR) rate, there remains an unmet medical need in this patient population.

Historically, NET has been offered to women with HR+ tumors who are unfit for surgery or refuse this procedure, or to elderly women with short life expectancy, as established by a qualified specialist and based on a validated geriatric assessment tool. NET has also been used to reduce tumor size and third-generation aromatase inhibitors increased likelihood of breast conserving surgery to 36-45%. In patients with a low recurrence score, NET demonstrated a clinical response rate of 59% and a BCS rate of 91%.

NET not only confers clinical benefit to patients with HR+, HER2- BC but also provides important prognostic information and is an excellent platform for the development of investigational drugs, triaging of novel combinations, [redacted] and discovery of mechanisms of drug resistance. Several key mechanisms of action have been assessed in the neoadjuvant space in an exploratory setting, where results from metastatic trials mirror those from their respective neoadjuvant trials (ie, mammalian target of rapamycin [mTOR] blockade + endocrine therapies,[53] phosphoinositide-3 kinase (PI3K) blockade + endocrine therapies,[54,55] and CDK4/6 blockade plus endocrine therapies[49,56,57,58]). Those examples suggest that knowledge gained from NET studies provide information to predict if a new combination is likely to be successful in large adjuvant or metastatic Phase 3 trials. We anticipate that the current study may help to focus the development

of the combination of nivolumab, palbociclib, and anastrozole for use in patients with BC that is ER+ and HER2-.

5.5.2 Rationale for Choice of Endpoint (Residual Cancer Burden 0-I Rate)

There are lack of clinical endpoints predictive of event-free survival after NET in the HR+, HER2- primary BC setting, since pCR is uncommon and is not an effective surrogate of long-term outcome for this tumor type. Failure to achieve a pCR does not imply poor patient outcome since these patients still receive 5-10 years of adjuvant ET. Additionally, many patients with HR+, HER2- BC are likely cured with local treatment and standard adjuvant ET, which is also informed by several well validated prognostic gene signatures. For patients who did not achieve pCR, RCB is a type of pathological response quantification for the extent of residual disease with the RCB index evaluating 5 post-treatment variables: 2-dimensional tumor bed, cellularity, percentage of carcinoma in situ, number of metastatic lymph nodes, and the diameter of the largest nodal metastases. The RCB index classifies the surgical specimen into 4 categories that include RCB-0 (pCR), RCB-I (minimal residual disease), RCB-II (moderate residual disease), and RCB-III (extensive residual disease), and predicts risk of relapse after neoadjuvant chemotherapy to be highest for RCB-III (53.6%), while similar for RCB-0 and RCB-I (2.4% and 5.4%, respectively).[59,60] RCB (0-I) determined by local site pathologists was also prognostic for better long-term survival after neoadjuvant chemotherapy in all subtypes of BC.[61,62] Hence, RCB index is increasingly used in NET studies [redacted]. In addition, a RCB (0-I) rate endpoint can be assessed within several months of initiation of an investigational drug in the neoadjuvant setting that could potentially address an unmet need in a far shorter time frame than would be required via the conventional approach to BC drug development. Use of this surrogate endpoint is expected to innovate the development of novel therapies for BC.

5.5.3 Rationale for CDK 4/6 Plus PD-1 Inhibition

PD-1 inhibition prevents interaction with the receptors PD-1 and B7-1 (a costimulatory cell-surface protein), reversing T-cell suppression and leading to tumor response. The PD-1 inhibitor pembrolizumab as a single agent led to ORR of 12% (3/25) in heavily pretreated patients with ER+ BC that was also PD-L1 positive. In combination with chemotherapy, pembrolizumab improved pCR rates in all HER2- BCs in the neoadjuvant setting.[5] Several preclinical studies point towards PD-1/CDK4/6 blockade synergy as it has become more apparent that CDK4/6 inhibitors affect the tumor immune microenvironment.[6] Within tumor cells, selective CDK4/6 inhibitors increase expression of PD-L1 through the E3 ligase adapter protein, Speckle-type POZ protein (SPOP),[7] and enhance antigen presentation via reduced activity of the E2F target, deoxyribonucleic acid (DNA) methyltransferase 1 (DNMT).[8] Secretion of cytokines from both tumor and CD8+ T cells is also enhanced with CDK4/6 inhibitor treatment,[9,10] whereas proliferation of immunosuppressive Tregs is suppressed.[8] In murine models of BC, selective CDK4/6 inhibitors promote anti-tumor immunity via indirect stimulation of type III interferon (IFN) production and enhancing tumor antigen presentation, plus suppression of the proliferation

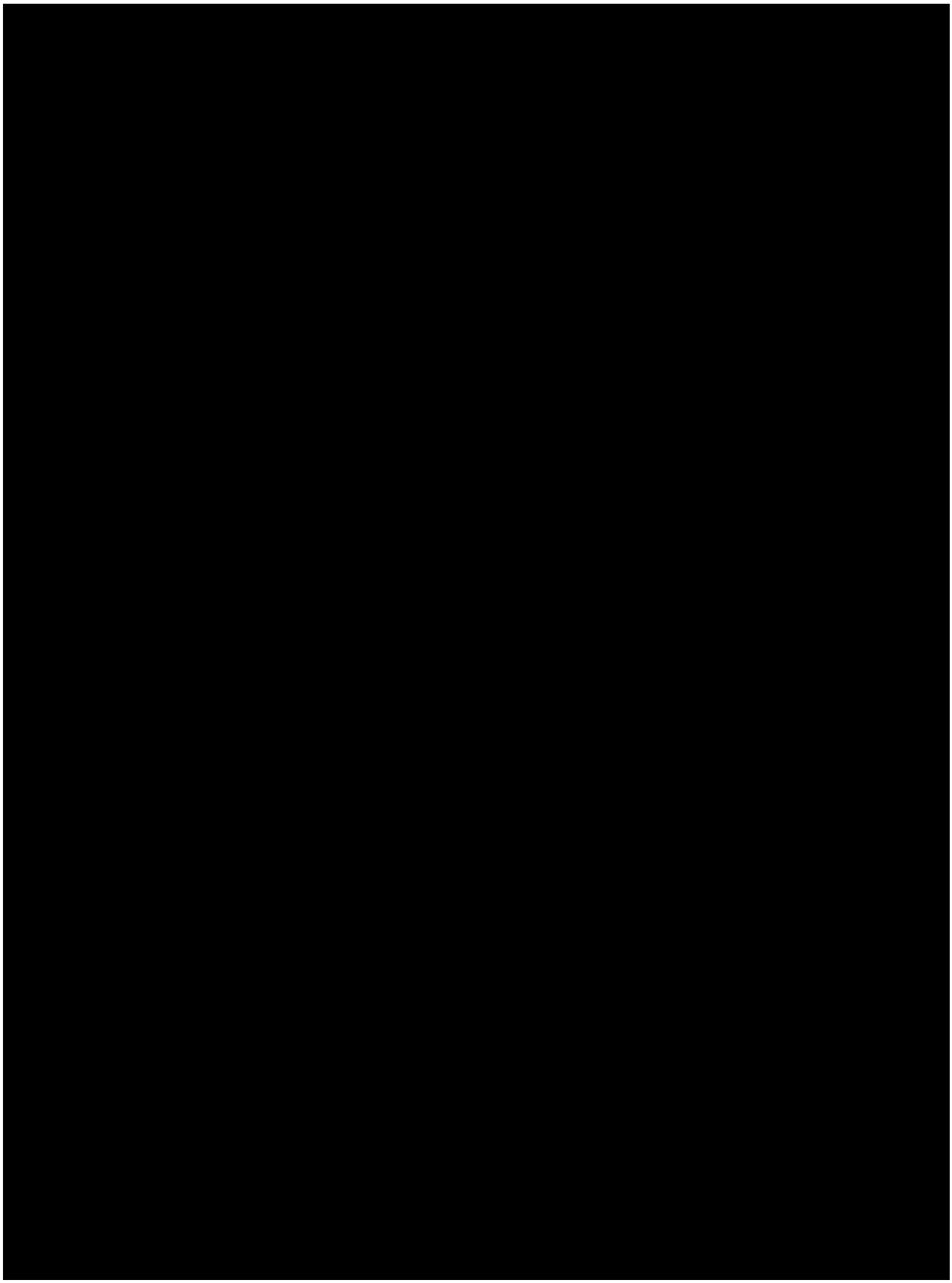
of Tregs.[8,10] In addition, treatment with the CDK4/6 inhibitor abemaciclib alone resulted in tumor growth delay that was associated with an increased T-cell inflammatory signature in tumors. Combination of a CDK4/6 inhibitor with an anti-PD-(L)1 therapy led to complete tumor regression and immunological memory, accompanied by enhanced antigen presentation, a T-cell inflamed phenotype, and enhanced cell-cycle control.[63]

Clinically, in a Phase Ib study, the combination of pembrolizumab and abemaciclib demonstrated a confirmed ORR of 28.6% in heavily pretreated participants with metastatic HR+, HER2- BC.[11] In agreement with the previously mentioned preclinical data indicating CDK4/6 blockade as a mediator of the cancer immunity, abemaciclib alone or in combination with anastrozole has been associated with upregulation of gene expression signatures related to T-cell immune response and antigen presentation in the neoMONARCH study, where 10-16 paired samples in each arm were examined in the primary disease setting.[11] Clinical data on combinations of other CDK4/6 inhibitors with PD-(L)1 blocking agents are being generated in multiple clinical trials spanning from the neoadjuvant to metastatic settings (ClinicalTrials.gov: NCT03573648, NCT02778685, NCT03294694).

The aim of CA2097A8 is to assess the potential synergistic activity of nivolumab, with palbociclib, and anastrozole in participants with newly diagnosed, previously untreated primary HR+, HER2- BC ≥ 2 cm, defined by significantly improved RCB (0-I) rate. [redacted] This trial is part of a broader effort to establish nivolumab as a SOC for the treatment of HR+, HER2- BC.

5.5.4 Rationale for Phased Therapy (Arm B)

Strategies to render the tumor micro-environment (TME) more susceptible to anti-PD(L)1 therapy has been investigated in a phase 2 study (TONIC trial) of 50 participants with metastatic TNBC who received palliative chemotherapy.[44] Priming the anti-cancer immune response with low-dose chemotherapy for 2 weeks or radiation therapy before starting nivolumab resulted in a best objective response rate (ORR) of 24%. In CT26 syngeneic mouse tumor model, a phased administration of abemaciclib and an anti-PD-L1 therapy improves anti-tumor efficacy and induced complete tumor regression.[12] In the same animal model, abemaciclib monotherapy induced intra-tumor immune inflammation on D13 and D20. In agreement with the previously mentioned preclinical data indicating CDK4/6 blockade as a mediator of cancer immunity, abemaciclib in combination with anastrozole has been associated with upregulation of gene expression signatures related to T-cell immune response and antigen presentation in the neoMONARCH study, where 10-16 paired samples in each arm were examined in the primary disease.[49] We therefore chose to test a phased therapy approach in Arm B to investigate whether additional treatment benefit will be observed with these regimens.



5.6 Justification for Dose

5.6.1 Justification for Dose of Nivolumab

Nivolumab 480 mg Q4W infused over 30 minutes was FDA approved in Mar-2018 for the majority of the nivolumab approved indications. The European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use has also recommended adding the option of a 4-week dosing schedule to the label for nivolumab for the treatment of patients with advanced melanoma and previously treated RCC.

Nivolumab 480 mg Q4W infused over 30 minutes will be examined in combination with palbociclib and anastrozole in this study.

5.6.2 Justification for Dose of CDK4/6 Inhibitors

Abemaciclib 150 mg BID PO or palbociclib 125 mg QD PO for 3 weeks of each cycle (1 week off) were approved by FDA in Sep-2017 and Feb-2015, respectively, and by EMA in Sep-2018 and Nov-2016, respectively, in combination with ET for ER+, HER2- BC, based on clinical safety and efficacy.

Abemaciclib 150 mg BID PO or palbociclib 125 mg QD PO for 3 weeks of each cycle (1 week off) will be examined in combination with nivolumab and anastrozole in this study.

As of Revised Protocol 03, examination of abemaciclib + nivolumab + anastrozole will not be continued in this study.

5.6.3 Justification for Dose of Anastrozole

Anastrozole 1 mg QD PO was approved by FDA and in Europe in Jan-1996 and Aug-1995, respectively, for BC.

Anastrozole 1 mg QD PO will be examined in combination with nivolumab and palbociclib in this study.

6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written 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 tests, tumor biopsies, and other requirements of the study.

2) Type of Participant and Target Disease Characteristics

a) Participants must have histologically confirmed unilateral invasive breast carcinoma, with the following characteristics:

i) Primary tumor ≥ 2 cm in largest diameter (cT1-3) by US/mammogram. In the case of a multifocal tumor (defined as the presence of two or more foci of cancer within the same breast quadrant), the largest lesion must be ≥ 2 cm and designated as the "target" lesion for all subsequent tumor evaluations. Please note: N3 disease (defined so either clinically or radiologically) is excluded.

ii) In participants where there may be a reasonable suspicion of advanced disease (eg, large tumors, clinically positive axillary lymph nodes, signs and symptoms), documentation confirming the absence of distant metastasis (M0) as determined by institutional practice is required (staging imaging reports).

iii) *Not applicable per Revised Protocol 03.*

b) Participants must have ER+ and HER2- BC meeting below characteristics:

i) ER+ BC and with or without progesterone-receptor (determined on the most recently analyzed tissue sample and tested by a local laboratory as defined in the relevant American Society of Clinical Oncology [ASCO]-College of American Pathologists [CAP] Guidelines).[72]

ii) HER2- BC defined as a negative in situ hybridization test or an IHC status of 0, 1+, or 2+. If IHC is 2+, a negative in situ hybridization (fluorescence in situ hybridization [FISH], chromogenic in situ hybridization [CISH], or silver in situ hybridization [SISH]) test as defined in the relevant ASCO-CAP Guidelines[73] is required (tested by a local laboratory).

c) Participants must have neoadjuvant endocrine monotherapy deemed to be a suitable therapy.

d) Participants must agree to provide tumor tissue at baseline, on-treatment, and at surgery. The tumor tissue at baseline must be either in FFPE tissue block (20 mm^3) collected within 90 days prior to enrollment or unstained tumor tissue sections (22 slides sectioned within 60 days prior to enrollment from a tissue sample collected within 90 days prior to enrollment) from primary tumor lesion. If a recent tumor specimen is not available, a fresh tumor biopsy (containing 20 mm^3 of tissue) collection is required. At least 15 unstained slides must be submitted for a participant to be eligible. If < 15 unstained slides are available, the participant is not eligible. [redacted]

e) Participants must have the ability to swallow oral medication.

f) Participants must have a performance status (PS) ≤ 1 on the Eastern Cooperative Oncology Group (ECOG) scale.

g) Participants must be deemed eligible for surgery and must agree to undergo surgery after completion of neoadjuvant therapy.

h) Re-enrollment: This study permits the re-enrollment of a participant that has discontinued the study as a pretreatment failure (ie, participant has not been randomized (or treated in the Safety Run-in Phase). If re-enrolled, the participant must be re-consented and inclusion/exclusion criteria reassessed.

3) Age and Reproductive Status

a) Women not of childbearing potential (WNOCBP; refer to Appendix 4) and Men, ages 18 or local age of majority and older, inclusive.

b) Women participants must have documented proof that they are not of childbearing potential including postmenopausal status defined as:

i) Women over age 55 years who, in the absence of other biological or physiological causes, have 12 months of amenorrhea.

ii) Age 55 or younger with no menses (eg, spontaneous or secondary to hysterectomy) for at least 12 months prior to enrollment (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression) and with a documented serum follicle stimulating hormone (FSH) level > 40 mIU/mL and estradiol level in the postmenopausal range according to local institutional/laboratory standard; or

iii) Age ≥ 18 with documented bilateral oophorectomy at least 28 days prior to D1 of treatment.

Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure postmenopausal status. Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (LH-RHa; goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression in this trial.

c) Women who are not of childbearing potential are exempt from contraceptive requirements.

d) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception and fetal protection (Appendix 4) for the duration of treatment with study treatment(s) plus 5 half-lives of the study treatment plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

e) Azoospermic men are not exempt from contraceptive requirements, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

6.2 Exclusion Criteria

1) Medical Conditions

a) Women who are of childbearing potential or breastfeeding

b) The following BC characteristics:

i) History of ipsilateral invasive BC, regardless of treatment, or ipsilateral ductal carcinoma in situ treated with radiotherapy or contralateral invasive BC at any time.

ii) Definitive clinical or radiologic evidence of metastatic disease.

iii) Inflammatory/inoperable BC.

iv) Multicentric BC (the presence of more than 1 tumor in different quadrants of the breast).

v) Bilateral invasive BC.

c) *Not applicable per Protocol Revision 03.*

d) Participants with a history of or active, known or suspected autoimmune disease, or other syndrome that requires systemic steroids above physiological replacement dose or autoimmune agents for the past 2 years, **except**:

i) 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.

ii) Inhaled or topical steroids, and adrenal replacement steroid doses up to physiological replacement dose, are permitted in the absence of active autoimmune disease.

e) Known human immunodeficiency virus (HIV) positive with an AIDS defining opportunistic infection within the last year, or a current CD4 count <350 cells/uL. NOTE: Testing for HIV must be performed at sites where mandated locally (refer to Appendix 9).

f) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

g) Participants with serious or uncontrolled medical disorders.

h) Personal history of any of the following conditions: syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), long or short QT syndrome, Brugada syndrome, or known history of corrected QT prolongation, Torsade de Pointes, or sudden cardiac arrest. Exception: participants with controlled atrial fibrillation for > 30 days prior to study treatment are eligible.

i) Other nonmalignant systemic disease that would preclude the participant from receiving study treatment or would prevent required follow up such as:
   i) Active infection or chronic infection requiring chronic suppressive antibiotics.
   ii) Malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, resection of the stomach or small bowel, or other disease or condition significantly affecting GI function.
   iii) Chronic daily treatment with corticosteroids at a dose above physiological replacement dose (excluding inhaled steroids).
   iv) Seizure disorders requiring medication.
   v) History of interstitial lung disease or pneumonitis.

j) Class III or Class IV myocardial disease as described by the New York Heart Association (refer to Appendix 11)[74]; a recent history (within 6 months prior to enrolment) of myocardial infarction, or symptomatic arrhythmia at the time of randomization/treatment.

k) Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

2) Prior/Concomitant Therapy

a) Any treatment, including radiotherapy, chemotherapy, and/or targeted therapy, administered for the currently diagnosed BC prior to enrollment.

b) Surgical axillary staging procedure prior to enrollment (with exception of fine-needle aspiration or core biopsy).

c) Surgical excisional biopsy of primary tumor.

d) Participants for whom upfront chemotherapy is clinically judged appropriate as optimal neoadjuvant treatment

e) Prior ET or CDK4/6 inhibitors for BC within 5 years.
   Note: Participants who received ≤ 7 days of letrozole or anastrozole for current disease prior to randomization/treatment are eligible.

f) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

g) Use of any medication or substances that are strong inhibitors or inducers of cytochrome p-450 (CYP)3A isoenzymes, or CYP3A substrates with narrow therapeutic index (see Section 7.7 [Concomitant Therapy]).

h) Treatment with botanical preparations (eg, herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. See Section 7.7 for prohibited therapies.

i) Participants who have received a live/attenuated vaccine within 30 days before first treatment.

j) Concurrent use (defined as use within 4 weeks prior to baseline tissue sample being taken) of hormone replacement therapy or any other estrogen-containing medication (including vaginal estrogens).

3) Physical and Laboratory Test Findings

a) White blood cells < 2000/µL

b) Neutrophils < 1500/μL
c) Platelets < 100 $\times 10^3$/μL
d) Hemoglobin < 10.0 g/dL
e) Serum creatinine > 1.5 × ULN, or estimated creatinine clearance < 60 mL/min (as calculated using the method standard for the institutions)
f) AST/ALT: > 1.5 × ULN
g) Total bilirubin > ULN or > 1.5 × ULN in participants with Gilbert Syndrome or similar syndrome involving slow conjugation of bilirubin
h) ALP > 1.5 × ULN
i) *Not applicable per Protocol Revision 03.*
j) Have corrected QT interval of > 470 milliseconds on screening ECG.
k) International normalized ratio must be within normal limits of the local laboratory ranges.
l) Serologic evidence of chronic hepatitis B virus (HBV) infection with an HBV viral load above the limit of quantification. Patients with chronic HBV infection must be on concurrent viral suppressive therapy.
m) Serologic evidence of current hepatitis C virus (HCV) infection with an HCV viral load above the limit of quantification.

4) Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components.

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

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

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions for CDK 4/6 Inhibitor

- Participants must avoid consumption of grapefruit, grapefruit hybrids, pummelos, star-fruit, Seville oranges, pomegranates, or products containing the juice of each during the entire study treatment and preferably 7 days before the first dose of study medications, as they affect CYP and P-glycoprotein (PgP) activity and have a potential to increase exposure to palbociclib (NOTE: Oranges and orange juice are allowed.)
- Herbal or dietary supplements known as strong inhibitors or inducers of CYP3A4 (refer to Appendix 10 [Concomitant Medications]) are prohibited.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized 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 Phase

Participant Re-enrollment: This study permits the re-enrollment of a participant that 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 Safety Run-in Phase will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

7 TREATMENT

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

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- BMS-936558 (nivolumab)
- Abemaciclib
- Palbociclib
- Anastrozole

An IP, also known as an 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 than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Description and storage information for the 4 drugs used in this open-label study are provided in Table 7-1.

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

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations.

Table 7-1: Study Treatments for Study Number CA2097A8

Product Description/ Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Injection[a]	10 mg/mL; 100-mg fill volume and 10 mg/mL; 40-mg fill volume	IP	Open Label	Vials	Refer to the label or container and/or Pharmacy Manual
Abemaciclib Tablets[b]	150 mg, 100 mg, and 50 mg	IP	Open Label	Tablets	Refer to the label or container and/or Pharmacy Manual
Palbociclib Capsules[b]	125 mg, 100 mg, and 75 mg	IP	Open Label	Capsules	Refer to the label or container and/or Pharmacy Manual
Anastrozole Tablets[b]	1 mg	IP	Open Label	Tablets	Refer to the label or container and/or Pharmacy Manual

Abbreviations: IP = investigational product; IMP, investigational medicinal product; mg = milligram; mL = milliliter; SmPC = summary of product characteristics.

[a] May be labeled as either “BMS-936558-01” or “Nivolumab".

[b] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or SmPC or according to institutional standards.

7.1 Treatments Administered

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

Table 7.1-1: Selection and Timing of Dose - Safety Run-in Phase

Cohort	Study Treatment	Dosage Level[a]	Frequency of Administration	Start and Duration of Treatment	Route of Administration
1	Nivolumab	480 mg	Q4W	Cycle 1-5	IV
	Abemaciclib	150 mg	BID	Cycle 1-5	PO (with or without food)
	Anastrozole	1 mg	QD	Cycle 1-5[b]	PO (with or without food)
2	Nivolumab	480 mg	Q4W	Cycle 1-5	IV
	Palbociclib	125 mg	QD × 3 weeks on (1 week off)	Cycle 1-5	PO (with food)
	Anastrozole	1 mg	QD	Cycle 1-5[b]	PO (with or without food)

Abbreviations: BID = twice daily; EOT = end of treatment; IV = intravenous; mg = milligram; PO = per os (by mouth); Q4W = every 4 weeks; QD = once daily.

Note: At the time of Revised Protocol 03, 2 participants had been treated in Cohort 1 (nivolumab + abemaciclib + anastrozole), which was subsequently closed for enrollment.

[a] For abemaciclib and palbociclib, this is the starting dose level. Dose levels may be reduced per Section 7.4 (Dosage Modification).

[b] After 5 cycles or EOT, all participants should continue to receive anastrozole until breast surgery. Anastrozole is not considered study therapy beyond completion of Cycle 5 or EOT.

Table 7.1-2: Selection and Timing of Dose - Randomized Phase

Arm	Study Treatment	Dosage Level[a]	Frequency of Administration	Start and Duration of Treatment	Route of Administration
A	Nivolumab	480 mg	Q4W	Cycle 1-5	IV
	Palbociclib	125 mg	QD × 3 weeks on (1 week off)	Cycle 1-5	PO (with food)
	Anastrozole	1 mg	QD	Cycle 1-5[b]	PO (with or without food)
B	Palbociclib	125 mg	QD × 3 weeks on (1 week off)	Cycle 1-5	PO (with food)
	Anastrozole	1 mg	QD	Cycle 1-5[b]	PO (with or without food)
	Nivolumab	480 mg	Q4W	Cycle 2-5	IV

Table 7.1-2: Selection and Timing of Dose - Randomized Phase

Arm	Study Treatment	Dosage Level[a]	Frequency of Administration	Start and Duration of Treatment	Route of Administration
C	Palbociclib	125 mg	QD × 3 weeks on (1 week off)	Cycle 1-5	PO (with food)
	Anastrozole	1 mg	QD	Cycle 1-5[b]	PO (with or without food)

Abbreviations: BID = twice daily; EOT = end of treatment; IV = intravenous; mg = milligram; PO = per os (by mouth); Q4W = every 4 weeks; QD = once daily.

Note: As of Revised Protocol 03, the abemaciclib-containing combination arms have been removed from the Randomization Phase of the study.

[a] For palbociclib, the starting dose level will be the safe dose determined upon completion of the Safety Run-in Phase.

[b] After 5 cycles or EOT, all participants should continue to receive anastrozole until breast surgery. Anastrozole is not considered study therapy beyond completion of Cycle 5 or EOT.

Randomized participants should begin study treatment within 3 calendar days of randomization.

7.1.1 Nivolumab Dosing (Safety Run-in Cohorts and Randomized Phase Arms A and B)

Participants are to start nivolumab within 3 calendar days of randomization.Participants will receive nivolumab at a dose of 480 mg as a 30-minute IV infusion for a maximum of 5 cycles (maximum 4 cycles for Arm B).

Doses of nivolumab may be interrupted, omitted, or discontinued, depending on how well the participant tolerates the treatment. There will be no dose escalations or reductions of nivolumab allowed. For Q4W dosing cycles, participants may be dosed within a ± 3-day window.

If a participant cannot receive nivolumab within a ± 3-day window, nivolumab must be omitted (skipped) for that cycle. If nivolumab is omitted, the other study medications may continue. If a participant discontinues nivolumab, the entire study treatment (CDK4/6 inhibitor and anastrozole) must be discontinued.

When nivolumab is scheduled to be administered on the same day with palbociclib plus anastrozole, nivolumab dosing should be started > 1 hour after palbociclib plus anastrozole ingestion. If nivolumab can not be given within 3 days of palbociclib plus anastrozole administration for a given cycle, nivolumab must be omitted for that cycle.

Premedications are not recommended for the first dose of nivolumab.

Participants should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, participants should be managed according to Section 7.4.4.3 (Treatment of Nivolumab Infusion Reaction).

Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of

the prepared solution, as the product does not contain any antimicrobial preservative or bacteriostatic agent.

7.1.2 CDK4/6 Inhibitors and Anastrozole Dosing

Premedications are not recommended for the first dose.

In the Safety Run-in Phase, participant assignment to abemaciclib or palbociclib will be carefully managed by the study team with the Investigator. The selected CDK4/6 inhibitor cannot be changed or switched to another one once the study treatment has been initiated. At implementation of Revised Protocol 03, the study will only evaluate the combination of nivolumab with palbociclib plus anastrozole. Patients in screening and not yet treated were offered the option to join the nivolumab + palbociclib + anastrozole arm. Patients on treatment were to be re-consented and continue on anastrozole alone, OR taken off study.

Study treatment must be taken within 3 calendar days following randomization.

In the Randomized Phase, participants will be randomly assigned by an IRT system.

Palbociclib should be taken together with anastrozole as follows:

- Palbociclib is dosed QD PO for the first 3 weeks of the cycle (with the 4th week off). Anastrozole is dosed continuously, BID and QD PO, respectively.
- On scheduled visit days, participants must hold taking study treatments at home. They must take them in the clinic under the supervision of the Investigator or designee after all study procedures for the visit have been completed. On all other days, participants may take study treatments at home.
- Participants should be instructed to take palbociclib and anastrozole with a large glass of water (~250 mL or ~8 oz) at the same time each day.
- Palbociclib should be administered with food. Anastrozole can be administered either with or without food.
- Participants should be instructed to swallow the tablets whole and not to chew, crush, or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the participant is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the AEs section of the eCRF.
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Multivitamins, glucosamine, probiotics, and fish oil are permitted.
- After 5 cycles or EOT, all participants should continue to receive anastrozole until subsequent breast surgery. If anastrozole can no longer be administered after EOT (ie, due to related toxicities), breast surgery will be performed right away. Anastrozole is not considered study therapy beyond completion of Cycle 5 or EOT.

7.2 Method of Treatment Assignment

Before the study is initiated, each user will receive log-in information and directions on how to access the IRT. Each participant will be assigned a unique participant number after signing the ICF. Participant numbers will be used on all participants' study information. Participant numbers will not be reassigned. The Investigator or designee will register the participant for enrollment by following the enrollment procedures established by BMS.

The following information is required for enrollment in the IRT:

- Date that informed consent was obtained
- Year of birth
- Gender at birth

Safety Run-in participants who have met all eligibility criteria will be enrolled in the IRT. [redacted]

After the Safety Run-in Phase is complete (safety of the combination is confirmed), randomization of participants to Arms A, B, and C can begin.

The following information is required for participant randomization:

- Participant number
- Year of birth

[redacted]

- Tumor characteristics (involvement of lymph nodes, tumor size at baseline)

Participants meeting all eligibility criteria will be randomized in a 4:4:3 ratio and stratified by [redacted] 2) involvement of lymph node (cytologically positive vs radiologically or cytologically negative), and 3) tumor size (> 3 cm or ≤ 3 cm).

The exact procedures for using the IRT will be detailed in the IRT manual. Study treatment will be dispensed at the study visits as listed in Section 2 (Schedule of Activities).

7.3 Blinding

This is a randomized, non-comparative, open-label study; blinding procedures are not applicable.

7.4 Dosage Modification

When assessing AEs, the Investigator must assign drug causality to each study drug for each AE. If a reasonable determination cannot be made, then the AE should be considered related to each of the study drugs. IO agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. No dose re-escalation will be allowed.

Please refer to individual approved drug labels for recommendations on dose reduction, interruption or discontinuation of individual study drugs in the management of study drug-related

adverse reactions. Clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit-risk assessment. However, for events requiring a discontinuation, treatment must be discontinued. Any changes to the dose must be recorded on the appropriate eCRF.

7.4.1 Dose Modifications for Abemaciclib

At the implementation of Revised Protocol 03, abemaciclib dosing will be discontinued in all patients.

7.4.2 Dose Modifications for Palbociclib

Palbociclib can be interrupted, reduced, or discontinued both within a cycle and between cycles. The dose modifications permitted for palbociclib in combination with anastrozole are based on the dose level changes outlined in Table 7.4.2-1.

Table 7.4.2-1: Dose Levels for Palbociclib

Dose Level	Oral Dose	Frequency
Starting dose	125 mg	QD × 3 weeks on (1 week off)
First dose reduction	100 mg	QD × 3 weeks on (1 week off)
Second dose reduction	75 mg	QD × 3 weeks on (1 week off)
Third dose reduction	Discontinue	Not applicable

Abbreviations: mg = milligram; QD = once daily.

7.4.3 Dose Modification for Anastrozole

No dose modification for anastrozole is listed per full prescribing information.

7.4.4 Dose Modifications for Nivolumab

Participants who require a dose omission for nivolumab should be re-evaluated and resume treatment at the next cycle when re-treatment criteria are met. Drug-drug interaction between nivolumab and palbociclib are not expected. Nivolumab is a monoclonal antibody given IV, and is unlikely to cause any cytokine mediated changes in CYP isoenzymes.

7.4.4.1 Dose Omission Criteria for Nivolumab

Nivolumab administration should be omitted for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue.
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities.
- Grade 3 skin, drug-related AE.
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose omission.
  - Grade ≥ 3 AST, ALT, total bilirubin will require dose discontinuation (see Section 8.1.1 [Nivolumab Dose Discontinuation]).

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants an omission of the dose.

For the nivolumab omission criteria and criteria to resume treatment, please refer to the nivolumab dose delay criteria in Appendix 6.

7.4.4.2 Criteria to Resume Treatment with Nivolumab

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

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

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor (or designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

7.4.4.3 Treatment of Nivolumab Infusion Reaction

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study Medical Monitor and reported as a serious adverse event (SAE) if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE v5.0 guidelines.

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

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

- Remain at bedside and monitor participant until recovery from symptoms occurs. The following prophylactic pre-medications are recommended for future infusions:

diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before subsequent nivolumab administrations.

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

- Stop the 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 should be administered at least 30 minutes before nivolumab 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 [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 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. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. Investigators should follow their 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).

7.5 Preparation/Handling/Storage/Accountability

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

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

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

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

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 (Study Governance Considerations).

7.5.1 Retained Samples for Bioavailability/Bioequivalence/Biocomparability

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be periodically monitored by drug accountability, dosing diary cards, participant's medical records, and eCRF. On the day of a scheduled visit, study drug will be administered in the clinic by trained site personnel and drug accountability should be reviewed by the site study staff. Sites should discuss discrepancies with the participant at each scheduled visit.

7.7 Concomitant Therapy

Concomitant medications, all forms of premedications, and supportive care are recorded at baseline and throughout study treatment and safety follow-up in the appropriate section of the eCRF at each visit.

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant from Screening through the Safety Follow-up Period will be documented and recorded, including start and stop date, dose and route of administration, frequency, and indication. Medications taken for a procedure (eg, biopsy) should also be included.

Anastrozole administered after completion of 5 cycles of neoadjuvant treatment (or EOT) up to subsequent breast surgery must be collected as concomitant medication.

Any subsequent anti-cancer therapy (ie, adjuvant treatment, radiotherapy) will be recorded up to 100 days after last dose of nivolumab or 30 days after last dose of study treatment (Arm C), in the appropriate section of the eCRF.

7.7.1 Prohibited and/or Restricted Treatments for Nivolumab

The following medications are prohibited during the study (unless utilized to treat a drug-related AE):

- 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.
- Immunosuppressive agents.

- Supraphysiological doses of systemic corticosteroids.
- Any concurrent anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of ER-, HER+ BC).
- Any botanical preparation (eg, herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.

7.7.2 Prohibited and/or Restricted Treatments for Abemaciclib and Palbociclib

- **Anticancer agents:** No additional investigational or commercial anticancer agents (including specifically aromatase inhibitors, anti-estrogens other than fulvestrant, chemotherapy, and immunotherapy) other than those mentioned in this study will be permitted during the On-treatment Pre-surgery (neoadjuvant) Period. In general, any drugs containing "for the treatment of breast cancer" on the product insert are not permitted on the study. Additionally, use of megestrol acetate as an appetite stimulant is not permitted.
- **Strong CYP3A inhibitors/inducers and CYP substrates (refer to Appendix 10 [Concomitant Medications]):** The results from human disposition (I3Y-MC-JPBD) and in vitro human recombinant CYP phenotyping studies indicate that abemaciclib is extensively metabolized primarily via CYP3A. Co-administration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of abemaciclib in humans.
  - Co-administration with strong CYP3A inhibitors and strong inducers should be avoided while on treatment. Participants treated with those drugs within the last 5 days prior to randomization/study treatment cannot be included in the trial.
  - Co-administration with moderate CYP3A inhibitors and moderate inducers should also be avoided if possible, or otherwise be subject to caution (eg, increased frequency of safety monitoring).
  - **CYP substrates:** In vitro studies in cultured human hepatocytes indicate that abemaciclib and its major metabolites LSN2839567 and LSN3106726 downregulate messenger ribonucleic acid (mRNA) of CYPs at clinically relevant concentrations. The mechanism of downregulation and its clinical relevance are presently not understood. Therefore, care should be taken when co-administering substrate drugs of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A) with narrow therapeutic margin. Participants treated on CYP3A Substrates with Narrow Therapeutic Index (NTI) can only be included in the trial after discontinuation of the drug for longer than 5 half-lives prior to randomization/study treatment.
- **Herbal/alternative remedies:** Participants are to avoid Seville oranges and grapefruit and grapefruit juice, as they affect CYP and PgP activity.

- **Chronic immunosuppressive therapies:** Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics, or inhaled, as well as short courses of oral/topical steroids given for allergic reactions or asthma flares are allowed.
- **Erythropoietin:** Erythropoietin is not to be used. Any potential indication should be discussed with the Investigator and the Sponsor.

7.7.3 Other Restrictions and Precautions

Participants with a condition requiring systemic treatment with either corticosteroids at above physiological replacement dose or other immunosuppressive medications within 14 days of randomization/study treatment are excluded.

7.7.3.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, 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 magnetic resonance imaging (MRI), participants with severe renal insufficiency (ie, estimated glomerular filtration rate < 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.

Gentle hydration before and after IV contrast should follow local SOC. 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 IEC.

7.7.4 Permitted Therapy

Participants are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). 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.

7.8 Treatment After the End of the Study

At the end of the study, BMS will not continue to provide BMS-supplied study treatment to participants/Investigators unless BMS chooses to extend the study. The Investigator should ensure that the participant receives appropriate SOC to treat the condition under study.

BMS reserves the right to terminate access to BMS-supplied study treatment if any of the following occur:

1) The study is terminated due to safety concerns.
2) The development of the study treatment is terminated for other reasons, including but not limited to lack of efficacy and/or not meeting the study objectives.

3) The participant can obtain medication from a government-sponsored or private health program. In all cases BMS will follow local regulations.

8 DISCONTINUATION CRITERIA

Reasons for discontinuation (of treatment vs from study): Participants are expected to complete 5 cycles of neoadjuvant therapy except in the event of disease progression, death, unacceptable toxicity, symptomatic deterioration, Investigator's decision to discontinue treatment, the participant's decision to discontinue treatment or withdraw consent, the participant being lost to follow-up, or BMS decides to terminate the study.

8.1 Discontinuation from Study Treatment

Participants MUST discontinue IP (and non-IP at the discretion of the Investigator) for any of the following reasons:

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

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

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate eCRF page.

8.1.1 Nivolumab Dose Discontinuation

If a participant discontinues nivolumab, the entire study treatment (CDK4/6 inhibitor and anastrozole) must be discontinued.

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related AE lasting > 7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
    - Grade ≥ 3 drug-related AST, ALT, or total bilirubin requires discontinuation (see below).
    - Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN.

  NOTE: In most cases of Grade 3 AST or ALT elevation, 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.
- Any Grade 4 drug-related AE or laboratory abnormality (including, but not limited to, creatinine, AST, ALT, or total bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days.
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase elevation.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 drug-related endocrinopathy AEs, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor.

- Any event that leads to a dose omission lasting > 10 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dose omissions to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dose omissions lasting > 10 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor (or designee).
  - NOTE: Prior to re-initiating treatment in a participant with a dose omission lasting > 10 weeks, the Medical Monitor (or designee) must be consulted. Tumor assessments should continue per protocol, even if a dose is omitted. Periodic study visits to assess safety and laboratory studies should also continue Q4W or more frequently if clinically indicated during such dose omissions.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

8.1.2 Abemaciclib Dose Discontinuation

At the implementation of Revised Protocol 03, abemaciclib dosing will be discontinued in all patients.

8.1.3 Palbociclib Dose Discontinuation

Scenarios in which palbociclib should be discontinued are included in the dose modification details provided in Section 7.4.2 (Dose Modifications for Palbociclib). If palbociclib needs to be discontinued, the participant may continue nivolumab and anastrozole.

8.1.4 Anastrozole Dose Discontinuation

If anastrozole needs to be discontinued, the participant must also stop the other study treatments and subsequent breast surgery must be performed right away.

8.1.5 Post-study Treatment Study Follow-up

Participants who discontinue study treatment must continue to be followed per Table 2-3.

8.2 Discontinuation from the Study

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

- Participants should notify the Investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate eCRF page.

- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

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

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in Section 2 (Schedule of Activities).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in Section 2 (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. 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 Section 2 (Schedule of Activities).

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 Blinded Independent Pathology Review

Blinded independent pathology review will be established for central review and central assessment of RCB. Tumor and lymph node collection from definitive surgical resection [redacted] should be performed on the day of surgery. Processing of the remainder of the specimens for histopathologic analysis should be performed within 72 hours of the procedure. Sections will be used for central pathology review assessing pathologic response. All hematoxylin and eosin (H&E) slides prepared from the specimens that are reviewed locally must be sent for central pathology review, along with a copy of the completed pathology report. Diagnostic H&E slides are preferred, but recut sections from all the tissue blocks are acceptable. Pathology samples acquisition guidelines and submission process will be outlined in the laboratory manual.

9.1.2 Pathologic Assessment of Effect

9.1.2.1 RCB Determination

Central RCB will be assessed from routine pathologic sections of the primary breast tumor site and the regional lymph nodes right after surgery [redacted]. Five variables are included in a calculation formula, which includes the following:

1) The primary tumor bed area in its 2 dimensions. For multifocal tumors (defined as the presence of 2 or more foci of cancer within the same breast quadrant), the largest lesion must be ≥ 2 cm and designated as the "target" lesion for the RCB determination.
2) The overall cancer cellularity (percentage of area).
3) The percentage of cancer that is in situ disease (percentage of area).
4) The number of positive lymph nodes.
5) The diameter of the largest lymph node metastasis.

The calculated RCB index value can also be categorized as 1 of 4 RCB classes. The calculation formula and detailed description can be found at a dedicated website: http://www.mdanderson.org/breastcancer_RCB. The 4 RCB classes are the following:

1) RCB 0: no residual disease
2) RCB-I: minimal residual disease
3) RCB-II: moderate residual disease
4) RCB-III: extensive residual disease

Detailed procedures are provided in Appendix 7 (Detailed Pathology Methods For Using Residual Cancer Burden).

9.1.2.2 Pathological Complete Response Determination

The determination of pCR will be performed by the local pathologist following examination of tissue (breast and nodes) removed at the time of surgery.

Criteria for evaluation of pCR includes the following:

- pCR in breast and axillary lymph nodes as well as non-axillary sentinel node (pCR breast and nodes).
- No histologic evidence of invasive tumor cells in the surgical breast specimen or axillary nodes after neoadjuvant treatment.
- pCR in the breast (pCR breast). No histological evidence of invasive tumor cells in the surgical breast.

[redacted]

9.1.3 Clinical Response Assessments

For the purposes of this study, all clinical response assessments, including 1) clinical breast examination by palpation of breast and axilla, and 2) imaging assessment of breast and axilla via ultrasound (preferred) or mammography, will be assessed by the Investigator and performed locally. Every attempt should be made to image each participant using an identical imaging modality and acquisition protocol for all imaging time points. Tumor measurements should be

made by the same Investigator or Imager for each assessment, whenever possible. Tumor assessments for all participants should continue per protocol, even if dosing is delayed or discontinued. The longest diameter (LD) of the initial lesion(s) will be reported as the baseline measurement and used as reference to characterize the objective tumor response. The LD of the same lesion(s) will be measured during subsequent imaging studies.

A best overall response of stable disease requires a minimum of 49 days on study from the first dose of treatment.

Screening and on-study images should be acquired as outlined in Section 2 (Schedule of Activities). Tumor assessments at other time points may be performed if clinically indicated.

Bone scans and other SOC imaging, including pathologic examination of suspicious lesions, may be acquired per local standards, as clinically indicated.

At the Sponsor's discretion, images may be collected for review.

9.1.3.1 Objective Response Rate Assessed by Imaging

ORR will be assessed at the end of the neoadjuvant treatment prior to Surgery.

For the purposes of this study, tumor response assessments will be performed by bilateral breast and axilla ultrasound (preferred) or mammography. Changes in tumor measurements and tumor responses will be assessed by the same Investigator or designee. The timepoint of tumor assessments will be reported on the eCRF based on the Investigator's assessment.

Radiographic Response Assessments:

- Radiographic complete response: Disappearance of the target lesion.
- Radiographic partial response (PR): At least a 30% decrease in the LD of the target lesion taking as reference the baseline LD.
- Radiographic progression (PD): At least a 20% increase in the LD of target lesion taking as references the baseline LD or the appearance of one or more new lesions.
- Radiographic stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the baseline LD.

Note:

1) Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should lend themselves to reproducible repeated measurements. Up to 2 lesions in the breast may be identified as target lesions. Per this protocol, target lesion #1 must be ≥ 2 cm and, if selected, target lesion #2 must be ≥ 10 mm. A sum of the diameters of all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease. Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither target nor non-target) since

they are, by definition, simple cysts. Pathologic axillary lymph nodes are not to be designated at target lesions, and lymph node measurements are not to be included in the sum of diameters.

2) Target Lesions that become too small to measure: all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions that are recorded as target lesions at baseline become so faint on imaging 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 eCRF as follows:
   - 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 accurately measure, too small to measure should be indicated.
3) Assessments of partial response and complete response do not require confirmation. A best objective response of stable disease requires a minimum of 42 days on study from randomization to the date of the follow-up imaging assessment.

For further information please refer to Appendix 8 (RECIST v1.1).

9.1.4 Breast Conserving Surgery Rate

BCS rate is defined as the number of participants who undergo BCS after completing the study treatments divided by the number of randomized participants for each treatment group.

For this study, planned breast surgery (mastectomy or BCS) at the time of diagnosis or baseline and the actual surgery patient undergo after completion of the study treatment will be captured on the eCRF to assess BCS rate with palbociclib plus anastrozole with or without nivolumab in participants with untreated primary BC ≥ 2 cm (ER+, HER2-).

[redacted]

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, surrogate, or the participant's legally authorized representative).

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

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and for a minimum of 100 days of discontinuation of nivolumab dosing. For participants randomized in Arm C, SAEs should be collected for 30 days from the date of last dose. For participants randomized/assigned to treatment and never treated with study drug, SAEs should be collected for 30 days from the date of randomization/treatment assignment.

The Investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure (eg, a follow-up skin biopsy).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF module.
- All SAEs will be recorded and reported to the 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 treatment or study participation, the Investigator must promptly notify the Sponsor.

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

9.2.2 Method of Detecting AEs and SAEs

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.

All non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the On-treatment Pre-surgery (neoadjuvant) Period and for a minimum of 100 days following discontinuation of nivolumab. For participants randomized in Arm C, non-serious AEs should be collected for 30 days from the date of last dose.

Every AE must be assessed by the Investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's eCRF.

9.2.3 Follow-up of AEs and SAEs

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

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in

Section 9.2 [Adverse Events]) 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 [Lost to Follow-up]).

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

9.2.4 Regulatory Reporting Requirements for SAEs

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

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

9.2.5 Pregnancy

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

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

In cases where a study drug can be present in seminal fluid, at exposures sufficient to potentially cause fetal toxicity, and if any sexual activity (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant WOCBP partner(s), the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner(s) must sign an informed consent form for disclosure of this information. Information on the pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

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

- Any laboratory test result that is clinically significant or meets the definition of an SAE.

- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted.
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting Investigator (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 p-DILI event. All occurrences of p-DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 [Adverse Events] and Appendix 3 for reporting details).

p-DILI is defined as:

1) Aminotransaminase (AT; ALT or AST) elevation > 3 × ULN,

AND

2) Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP),

AND

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

9.2.8 Other Safety Considerations

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

9.2.9 Management Algorithms for Nivolumab

IO agents are associated with IMAEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab is considered an IO agent in this protocol. Early recognition and management of IMAEs associated with IO agents may mitigate severe toxicity. Management algorithms have been developed from extensive experience with nivolumab to assist Investigators in assessing and managing the following groups of IMAEs:

- GI
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies

- Skin
- Neurological
- Myocarditis

The algorithms recommended for the management of IMAEs in this protocol are in Appendix 6. Please note that for this protocol, nivolumab delay means nivolumab omission.

- Checkpoint inhibitor molecules have been uncommonly associated with ocular drug-related AEs. Inflammation of components within the eye (eg, episcleritis, uveitis) are uncommon events of nivolumab monotherapy (< 1% of cases). These events are usually of low or intermediate grade, reversible, detected early in the course of therapy, and manageable with topical or systemic steroids.
  - Routine eye examinations should be performed in participants receiving immune checkpoint inhibitors (Section 2 [Schedule of Activities]). Upon clinical suspicion of an ocular event consider ophthalmic consult, dose omission, or dose discontinuation.
  - Permanently discontinue for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids for severe immune-mediated adverse reactions.
  - Permanently discontinue for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.
  - Administer corticosteroid eye drops to participants who develop uveitis, iritis, or episcleritis.

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 (refer to Appendix 3).

All instances of accidental overdose and/or dosing errors should be reported on the Dosage Administration Record eCRF.

For this study, any dose of nivolumab, abemaciclib, palbociclib, or anastrozole that is greater than the scheduled dose within a 24-hour time period will be considered an overdose.

In the event of an overdose the Investigator should:

1) Contact the Medical Monitor immediately.
2) Closely monitor the participant for AEs/SAEs and laboratory abnormalities until study treatment can no longer be detected systemically (at least 5 days for abemaciclib or palbociclib, and at least 10 days for anastrozole).
3) Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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 Section 2 (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/ECHO (preferred) or MUGA

Refer to Schedule of Activities (Section 2).

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

Results of clinical laboratory tests (performed by local laboratory) must be available within 3 calendar days prior to dosing. Complete blood counts must be performed within 7 days prior to the first dose.

A list of the clinical laboratory analyses to be tested is provided below in Table 9.4.4-1.

Table 9.4.4-1: Clinical Safety Laboratory Assessments

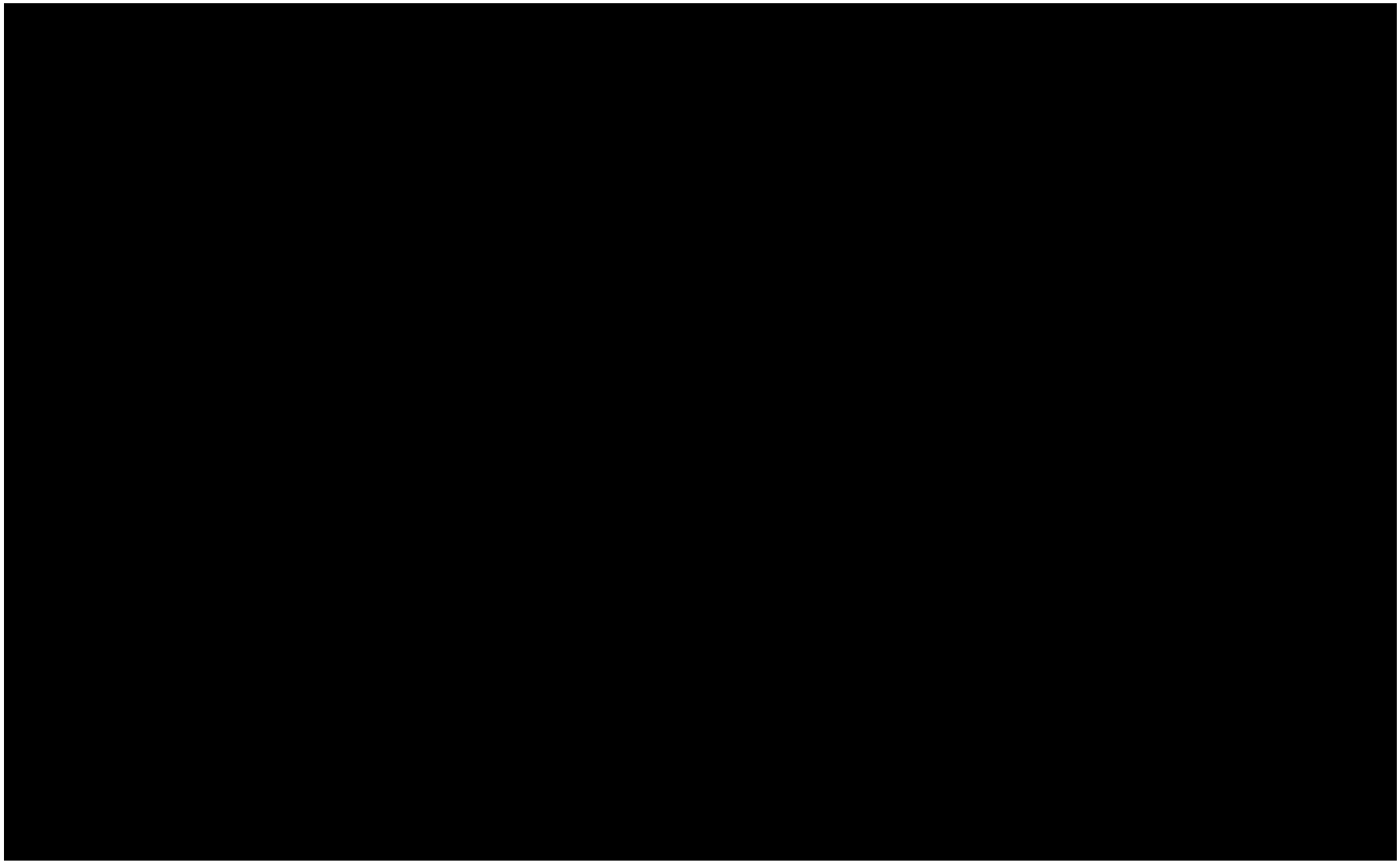
Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatinine or creatinine clearance (as calculated using the method standard for the institutions) Blood urea nitrogen (BUN) or serum urea glucose Lipase and amylase (if pancreatitis is suspected)	Albumin - screening only Sodium Potassium Chloride Calcium Phosphorus TSH, free T3 and free T4 - screening TSH, with reflexive fT3 and fT4 if TSH is abnormal - on-treatment and follow-up
Serology	
Hepatitis B/C, (HBVsAG, HCV antibody or HCV RNA) - screening only	
Other Analyses	
FSH screening - only required to confirm menopause in women ≤ age 55	

Table 9.4.4-1: Clinical Safety Laboratory Assessments

Estradiol level - only required to confirm menopause in women ≤ age 55
INR

Abbreviations: FSH = follicle stimulating hormone; HBV sAG = hepatitis B surface antigen; HCV = hepatitis C virus; INR = international normalized ratio; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone.

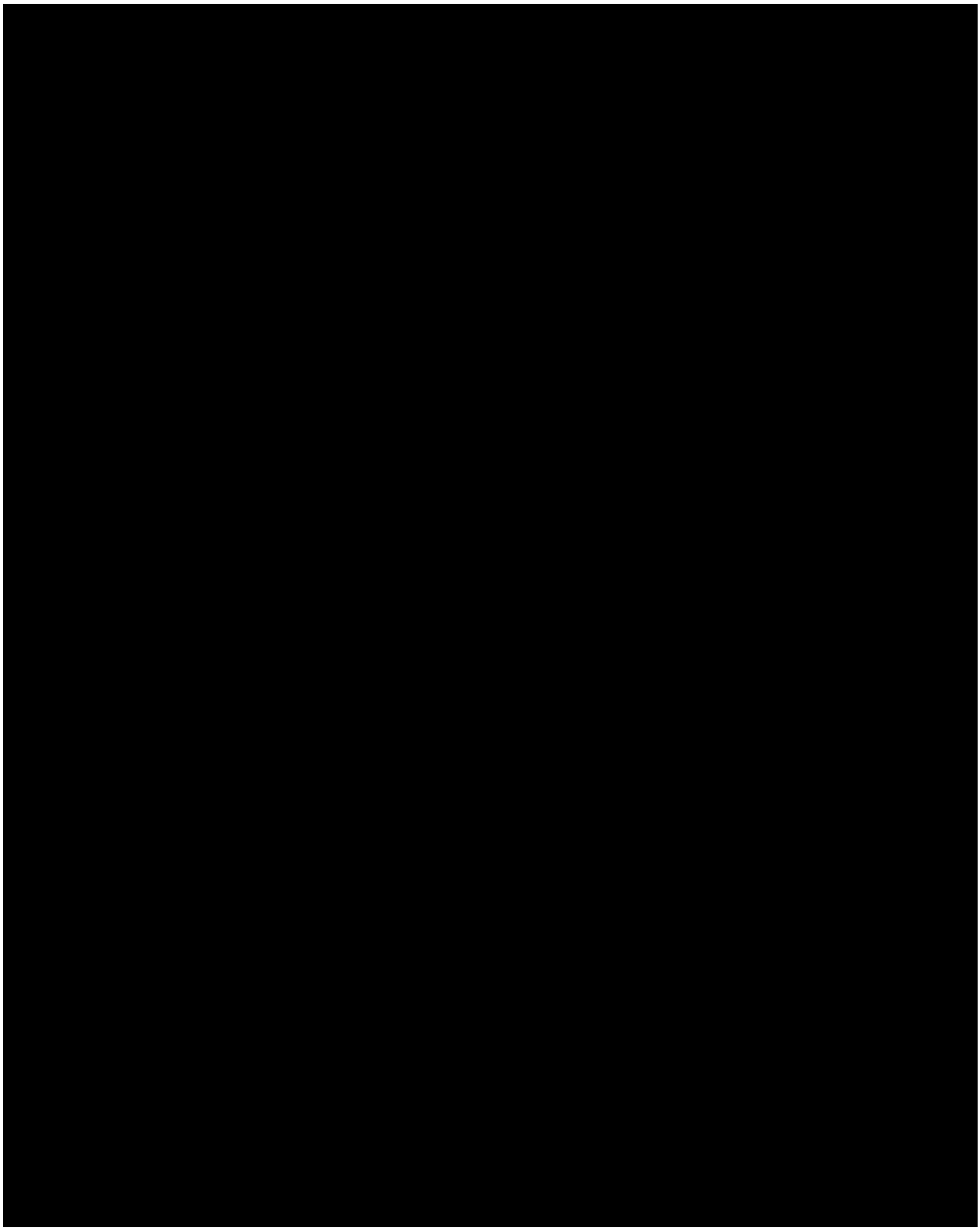
[redacted]



[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

9.9 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 Sample Size Determination

A total of approximately 115~136 participants will be treated in the study. Approximately 3~24 participants will be treated in the Safety Run-in Phase in each cohort (Cohort 1: nivolumab + abemaciclib + anastrozole for 5 cycles; n = 3~6 per dose level of abemaciclib; Cohort 2: nivolumab + palbociclib + anastrozole for 5 cycles; n = 3~6 per dose level of palbociclib). At the time of Revised Protocol 03, 2 participants had been treated in Cohort 1 (nivolumab + abemaciclib + anastrozole), which was subsequently closed for enrollment. Approximately 110 participants are planned to be randomized in this study at a 4:4:3 ratio into Arm A (nivolumab + palbociclib + anastrozole for 5 cycles; n = 40), Arm B (palbociclib + anastrozole for 1 cycle, followed by nivolumab + palbociclib + anastrozole for 4 cycles; n = 40), and Arm C (palbociclib + anatrozole for 5 cycles; n = 30), respectively. No stratification variables will be included for formal analysi [redacted].

[redacted]

[redacted]

10.2 Populations for Analyses

Populations for purposes of analysis are defined in Table 10.2-1 below.

Table 10.2-1: Populations for Analyses

Population	Description
All Enrolled	All participants who signed an ICF and were registered into the IRT.
All Randomized	All participants who were randomized to any treatment arm in the study. Participants are grouped within the All Randomized population by the treatment to which they were randomized. This is the primary analysis set for demography, protocol deviations, baseline characteristics, and primary efficacy analyses.
All Treated	All randomized participants who receive at least 1 dose of study drug. Participants are grouped within the All Treated population according to the treatment they actually received. This is the analysis set for all safety analyses and study drug administration.
All Treated from Safety Run-in Phase	All enrolled participants who received at least 1 dose of study drug in the Safety Run-in Phase. Participants are grouped within the All Treated from Safety Run-in Phase population according to the treatment and dose level they actually received. This is part of the analysis set for all safety analysis and study drug administration.
All RCB Evaluable	All Treated participants who have an RCB of 0, I, II, or III from both the Safety Run-in Phase and Randomized Phase. [redacted]

[redacted]

Abbreviations: ICF = informed consent form; IRT = Interactive Response Technology; [redacted] RCB = residual cancer burden.

10.3 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 a statistical output report, including subgroups of age, gender, and race.

10.3.1 Efficacy Analyses

Statistical analyses for efficacy are shown in Table 10.3.1-1.

Table 10.3.1-1: Efficacy - Statistical Analyses

Endpoint	Statistical Analysis Methods
Primary	
• RCB (0-I) rate per central assessment	Estimates of response rate and corresponding exact 90% and 95% CIs will be generated for each arm in the Randomized Phase. CIs will be constructed using the Clopper-Pearson method.
Secondary	
• pCR per local assessment • ORR by Investigator assessment • BCS	Estimates of response rate and corresponding exact 95% CIs will be generated for each arm. CIs will be constructed using the Clopper-Pearson method.
[redacted]	

Abbreviations: BCS = breast-conserving surgery; CI = confidence interval; [redacted] ORR = objective response rate; pCR = pathological complete response; [redacted] RCB = residual cancer burden.

After review of the efficacy data in each arm and upon agreement of the study team, efficacy endpoints might also be estimated based on pooled arms (eg, RCB [0-I] rate in Arm A and Arm B), when appropriate. Details of the analyses will be defined in the SAP.

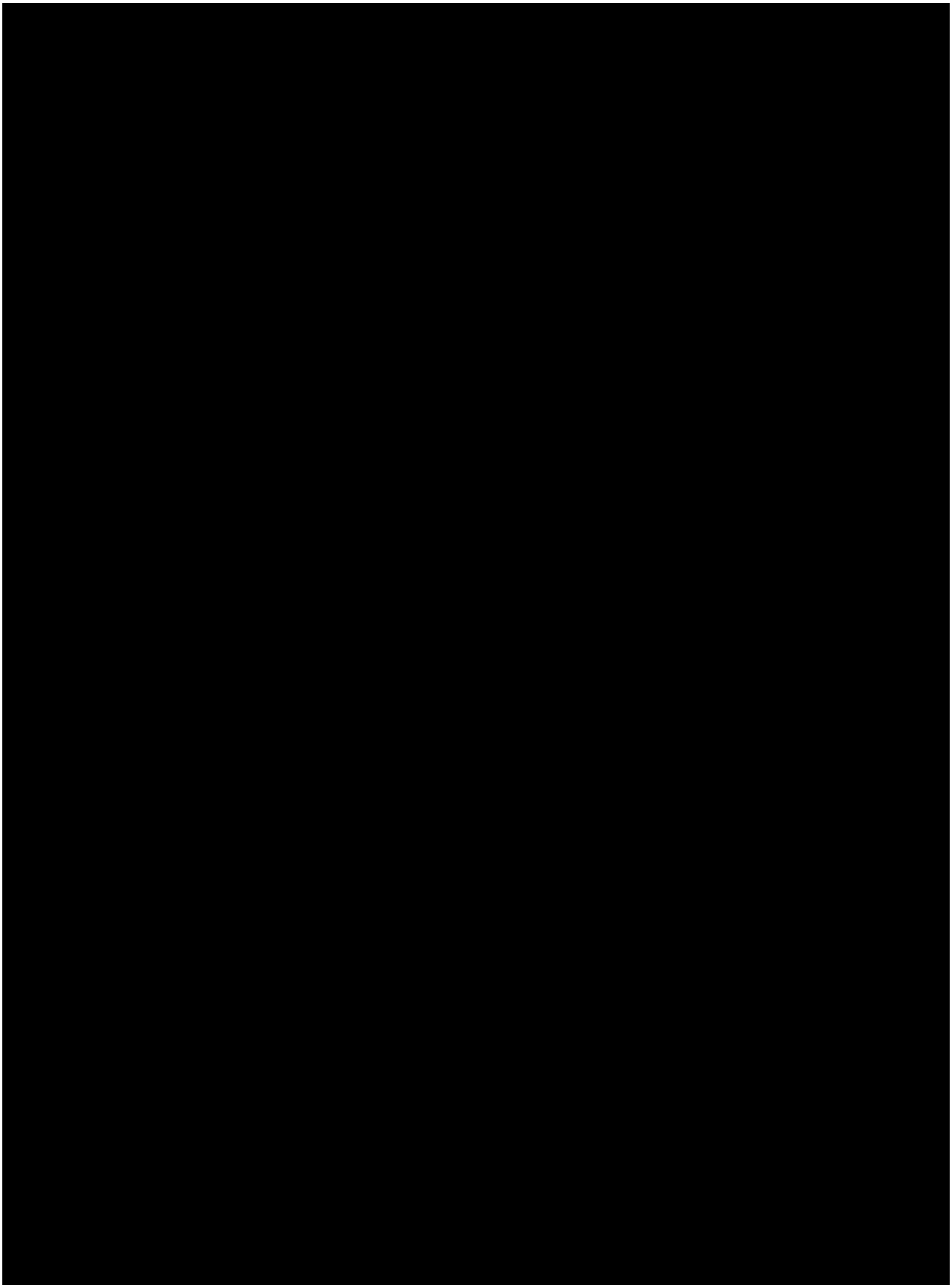
10.3.2 Safety Analyses

Statistical analyses for safety are shown in Table 10.3.2-1.

Table 10.3.2-1: Safety - Statistical Analyses

Endpoint	Statistical Analysis Methods
Primary	
• Number of participants with occurrence of DLT (Time frame: from start of study treatment up to 4 weeks).	• DLT rate by treatment and dose level in the Safety Run-in Phase.
Secondary	
• Incidence of AEs, SAEs, immune-related AEs, AEs leading to discontinuation, and death. • Laboratory abnormalities.	AEs will be graded according to NCI CTCAE v5.0.Frequency distribution of treated participants with AE using the worst CTC grade. Participants will only be counted (1) once at the PT level, (2) once at the system organ class level, and (3) once in the "total participant" row at their worst CTC grade, regardless of system organ class or PT. Laboratory values will be graded according to NCI CTCAE v5.0. Laboratory shift table using the worst CTC grade on treatment per participant.

Abbreviations: AE = adverse event; DLT = dose-limiting toxicity; CTC = Common Terminology Criteria; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; PT = preferred term; SAE = serious adverse event.



10.3.4 Interim Analysis

Not applicable.

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[redacted]

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
°C	degrees Celsius
µL	microliter
Abema	abemaciclib
ACOSOG	American College of Surgeons Oncology Group
[redacted]	[redacted]
ADL	activities of daily living
AE	adverse event
AI	aromatase inhibitor
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANZ	anastrazole
[redacted]	[redacted]
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AT	aminotransaminases
BC	breast cancer
Bcl-xL	B-cell lymphoma-extra large
BCS	breast-conserving surgery
BID	bis in die, twice daily
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BTLA	B- and T-lymphocyte attenuator
BUN	blood urea nitrogen
C	cycle
CAP	College of American Pathologists

Term	Definition
CBC	complete blood count
CCND1	cyclin D1
CD28	cluster of differentiation 28
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CI	confidence interval
CISH	chromogenic in situ hybridization
Cm	Centimeter
CMV	Cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CTAg	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
CYP	cytochrome p-450
D	Day
dL	deciliter
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DNMT	DNA methyltransferase 1
EC50	half-maximal effective concentration
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eg	exempli gratia (for example)

Term	Definition
[redacted]	[redacted]
EMA	European Medicines Agency
EOT	end of treatment
ER	estrogen receptor
ER+	estrogen receptor-positive
ET	endocrine therapy
etc	et cetera
EU	Europe
[redacted]	[redacted]
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
FU1	follow-up visit 1
FU2	follow-up visit 2
g	gram
GCP	Good Clinical Practice
[redacted]	[redacted]
GI	Gastrointestinal
H&E	hematoxylin and eosin
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HER2+	human epidermal growth factor receptor 2-positive
HER2-	human epidermal growth factor receptor 2-negative
HIV	Human Immunodeficiency Virus
HR	heart rate
HR+	hormone receptor-positive

Term	Definition
HRT	hormone replacement therapy
IB	Investigator Brochure
INR	international normalized ratio
IC50	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ICOS	inducible T cell co-stimulator
ie	id est (that is)
IEC	Independent Ethics Committee
IFN	interferon
IFN-γ	interferon-γ
IHC	Immunohistochemistry
IL	Interleukin
IMAE	immune-mediate adverse event
[redacted]	[redacted]
IMP	investigational medicinal product
IND	Investigational New Drug
IO	immuno-oncologic
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	Intravenous
kg	kilogram
LDH	lactate dehydrogenase
LH-RHa	luteinizing hormone-releasing hormone agonist
LLN	lower limit of normal
mAb	monoclonal antibody
MD	medical doctor
MDSC	myeloid-derived suppressor cells

Term	Definition
mg	Milligram
min	minute
[redacted]	[redacted]
mL	Milliliter
MLR	mixed lymphocyte reaction
m^2	meters squared
mm^3	cubic millimeters
MMR	measles, mumps, rubella
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
msec	milisecond
mTOR	mammalian target of rapamycin
MUGA	multiple gated acquisition
N	number of subjects or observations
NCI	National Cancer Institute
NET	neoadjuvant endocrine treatment
Nivo	Nivolumab
nM	Nanomolar
NSAI	nonsteroidal aromatase inhibitors
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
oz	ounce
Palbo	Palbociclib
[redacted]	[redacted]
pCR	pathological complete response
PD-1	programmed cell death-1
p-DILI	potential drug-induced liver injury
PD-L1	programmed death-ligand 1

Term	Definition
PD-L2	programmed death-ligand 2
PE	physical examination
[redacted]	[redacted]
PFS	progression-free survival
PgP	P-glycoprotein
PgR	progesterone receptor
PI3K	phosphoinositide-3 kinase
PK	Pharmacokinetics
PO	per os (by mouth route of administration)
PPK	population pharmacokinetics
PR	partial response
[redacted]	[redacted]
[redacted]	[redacted]
PS	performance status
PT	preferred term
Q4W	every 4 weeks
QD, qd	quaque die, once daily
[redacted]	[redacted]
QTc	corrected QT interval
QTcF	Fridericia's Correction Formula
Rand	Randomized
Rb	retinoblastoma
RCB	residual cancer burden
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	relapse-free survival
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan

Term	Definition
SCCHN	squamous cell carcinoma of the head and neck
SISH	silver in situ hybridization
SmPC	summary of product characteristics
SOC	standard of care
SOP	Standard Operating Procedures
SPOP	speckle-type POZ protein
SSC	Study Steering Committee
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocyte
[redacted]	[redacted]
TME	tumor microenvironment
TNBC	triple-negative breast cancer
Treg	regulatory T cell
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
vs	versus
WHO	World Health Organization
Wk	week
WOCBP	women of childbearing potential
WNOCBP	women **not** of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical GuidelinesGood Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree, one or more of the following: (1) the physical, safety, or mental integrity of one or more subjects/participants; or (2) the scientific value of the 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, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects/participants. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects/participants and any updates.

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

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

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects/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 subjects/participants prior to enrollment.

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

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

Investigators must:

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

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

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

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

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

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

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

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (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 SOPs/standards of the sourcing pharmacy.

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will

be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify subjects/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, 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 electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

MONITORING

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable Certain CRF pages and/or electronic files may serve as the source documents:

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

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

RECORDS RETENTION

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

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

If the investigator withdraws from the study (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 designee.

RETURN OF STUDY TREATMENT

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

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

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

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

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

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

CLINICAL STUDY REPORT

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

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

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Participant recruitment (eg, among the top quartile of enrollers)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the 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 subjects 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 preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study 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, ECG, 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/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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • 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; 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 potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see Section 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

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 (IB) 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 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 Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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 eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) 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 (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

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

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. The duration of the washout period below are suggested guidelines and the 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.

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of study treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment plus an additional 90 days.

COLLECTION OF PREGNANCY INFORMATION

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

APPENDIX 5 ECOG PERFORMANCE STATUS

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 6 NIVOLUMAB MANAGEMENT ALGORITHMS

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. Non-inflammatory etiologies should be considered and appropriately treated.

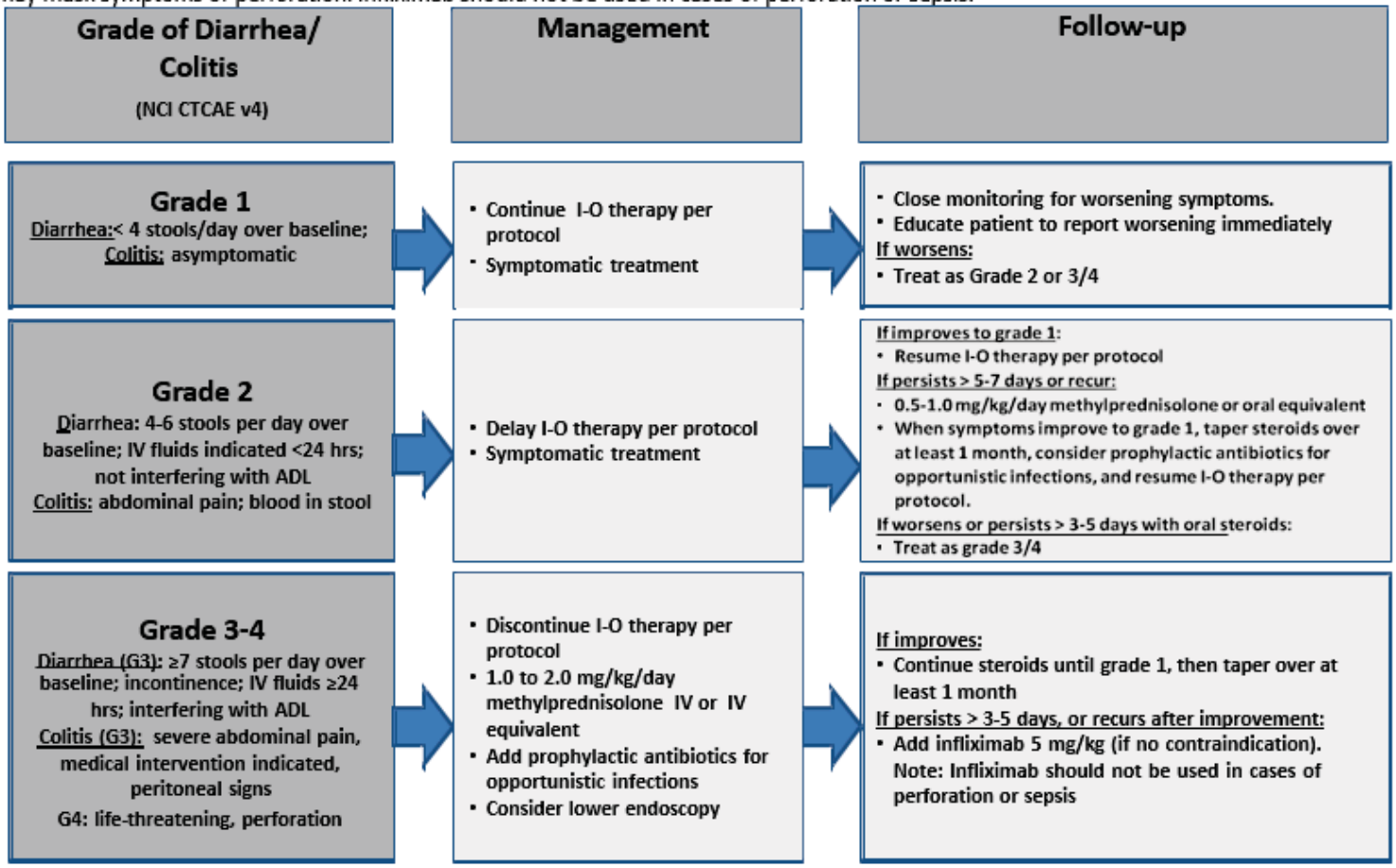
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic 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.

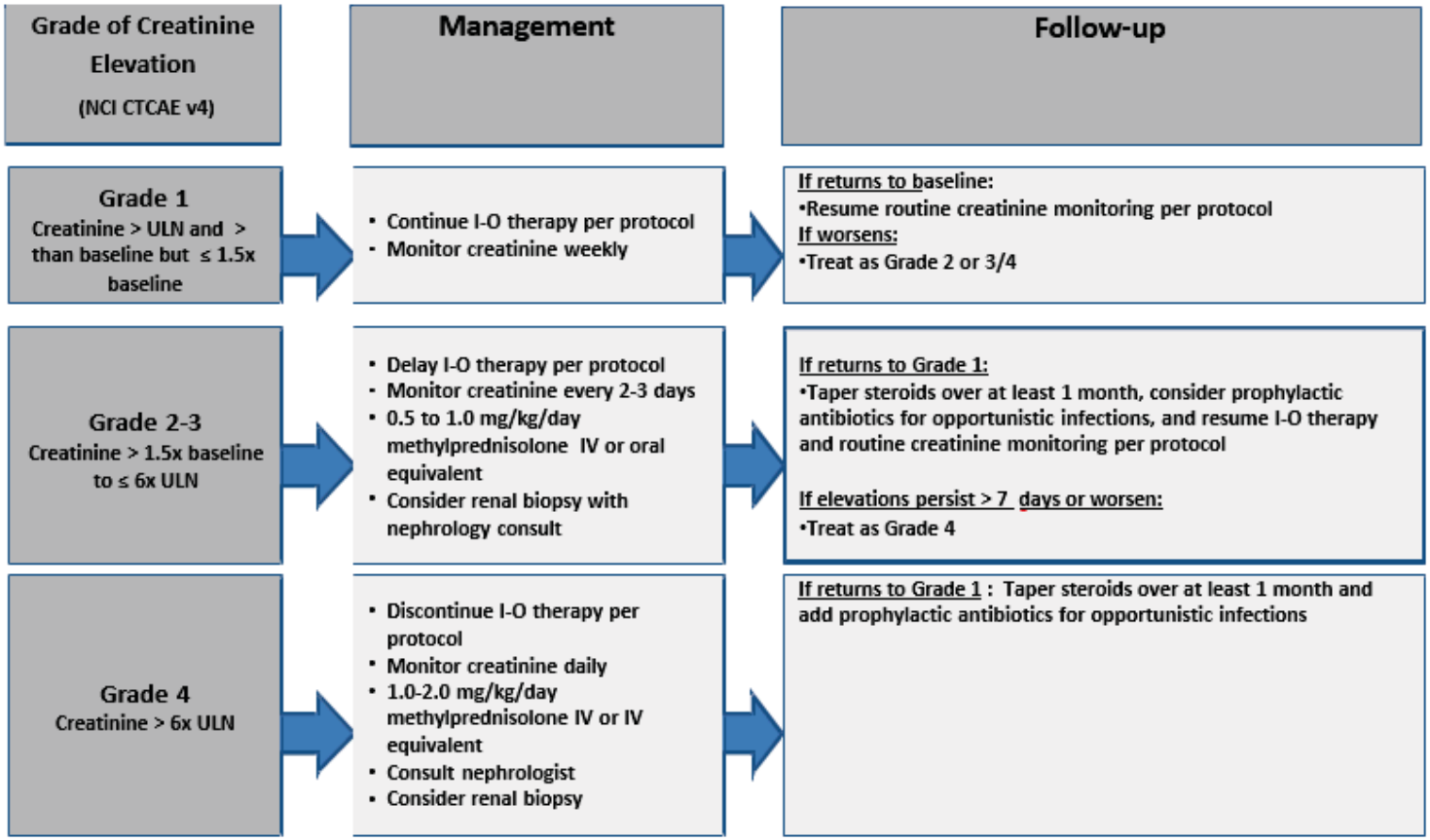


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

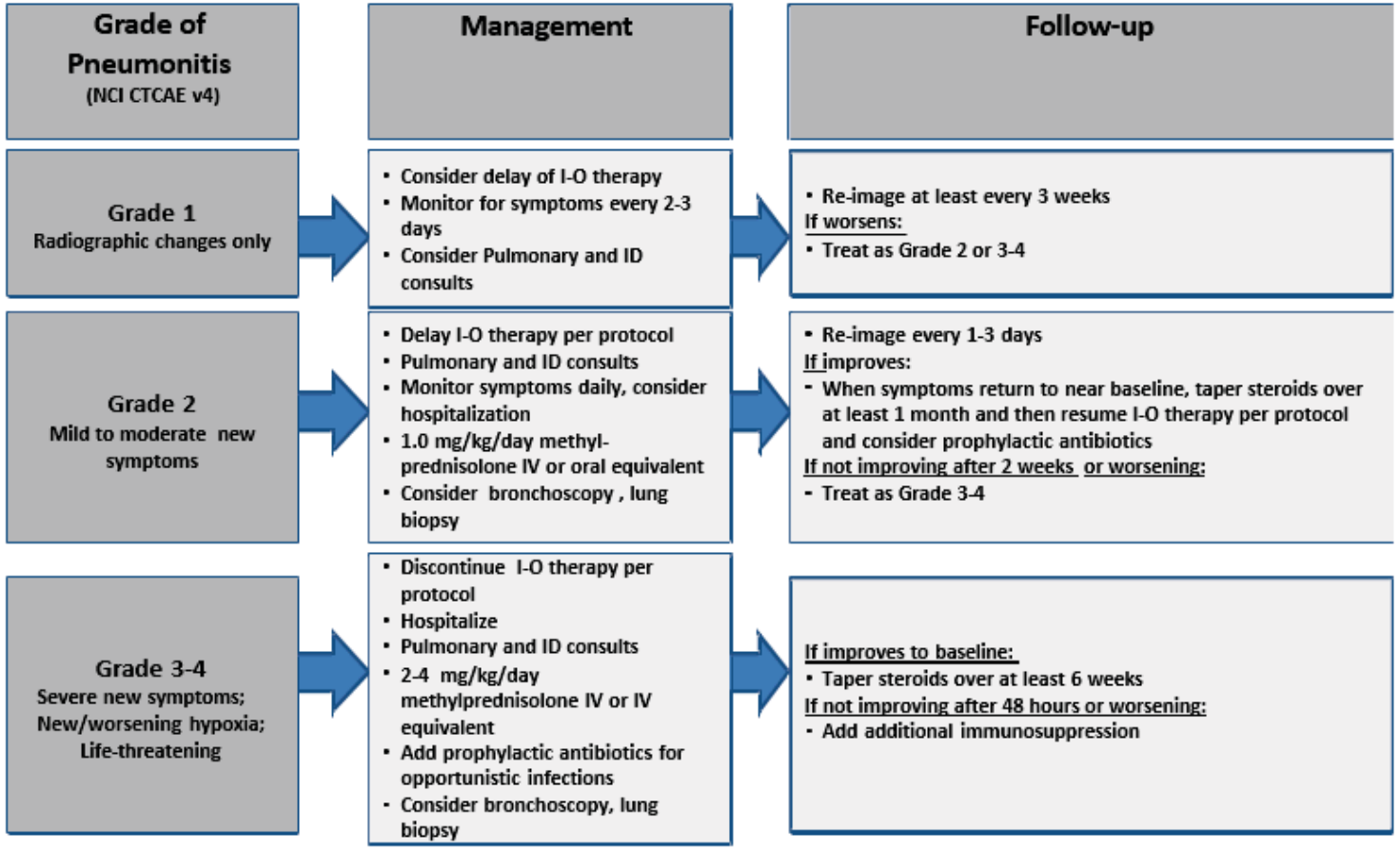


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

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.

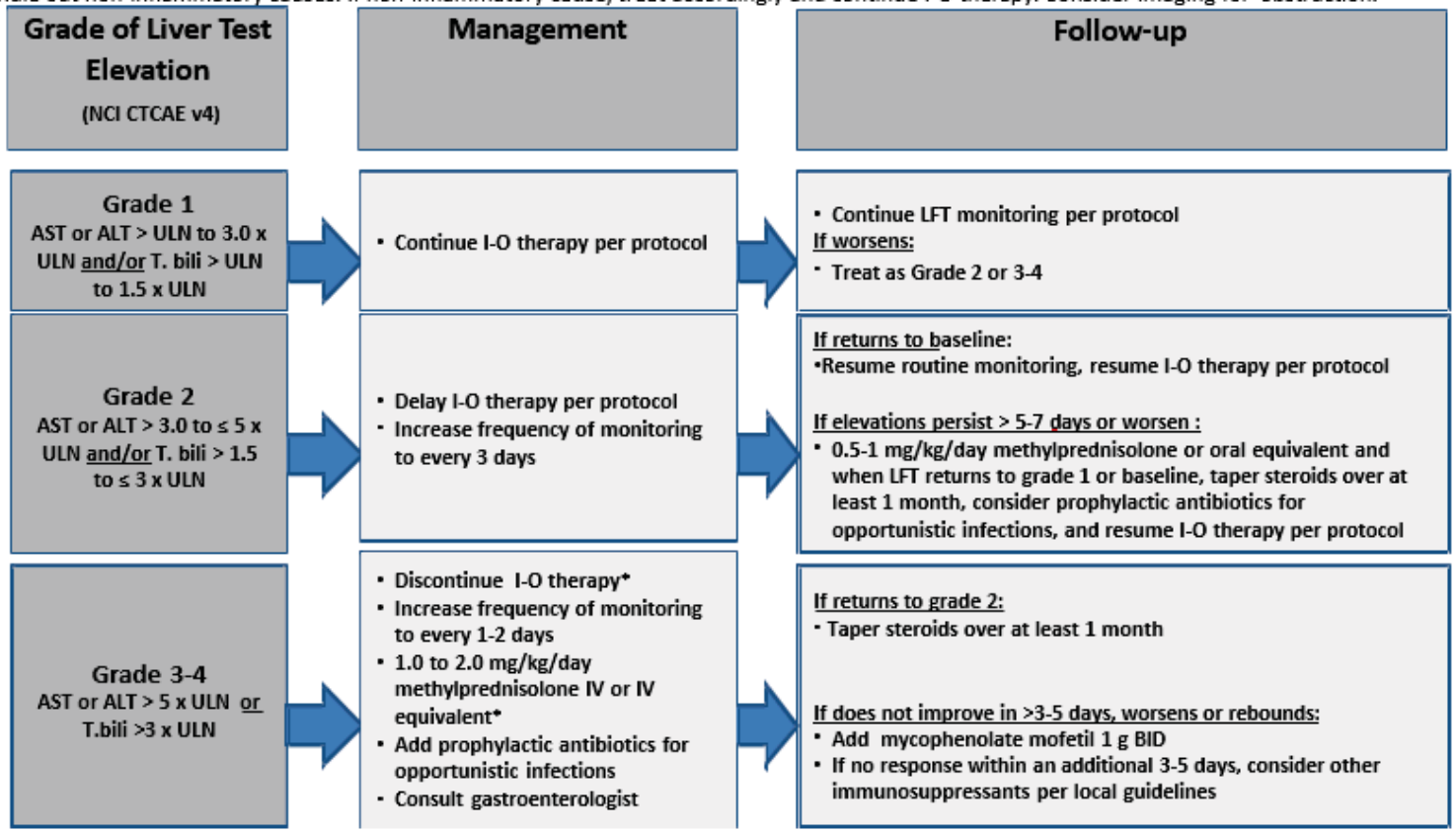


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

27-Jun-2019

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.



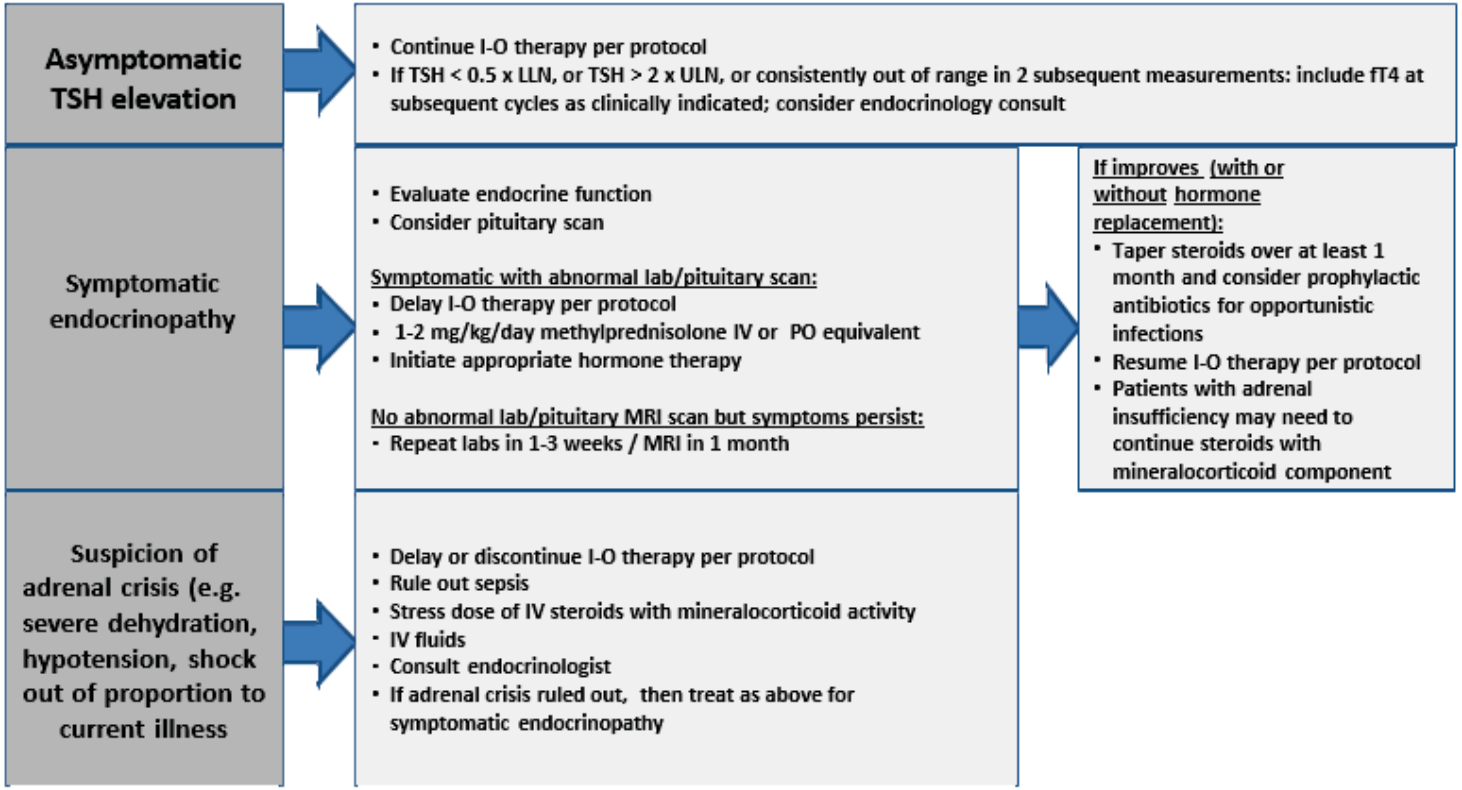
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

27-Jun-2019

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.

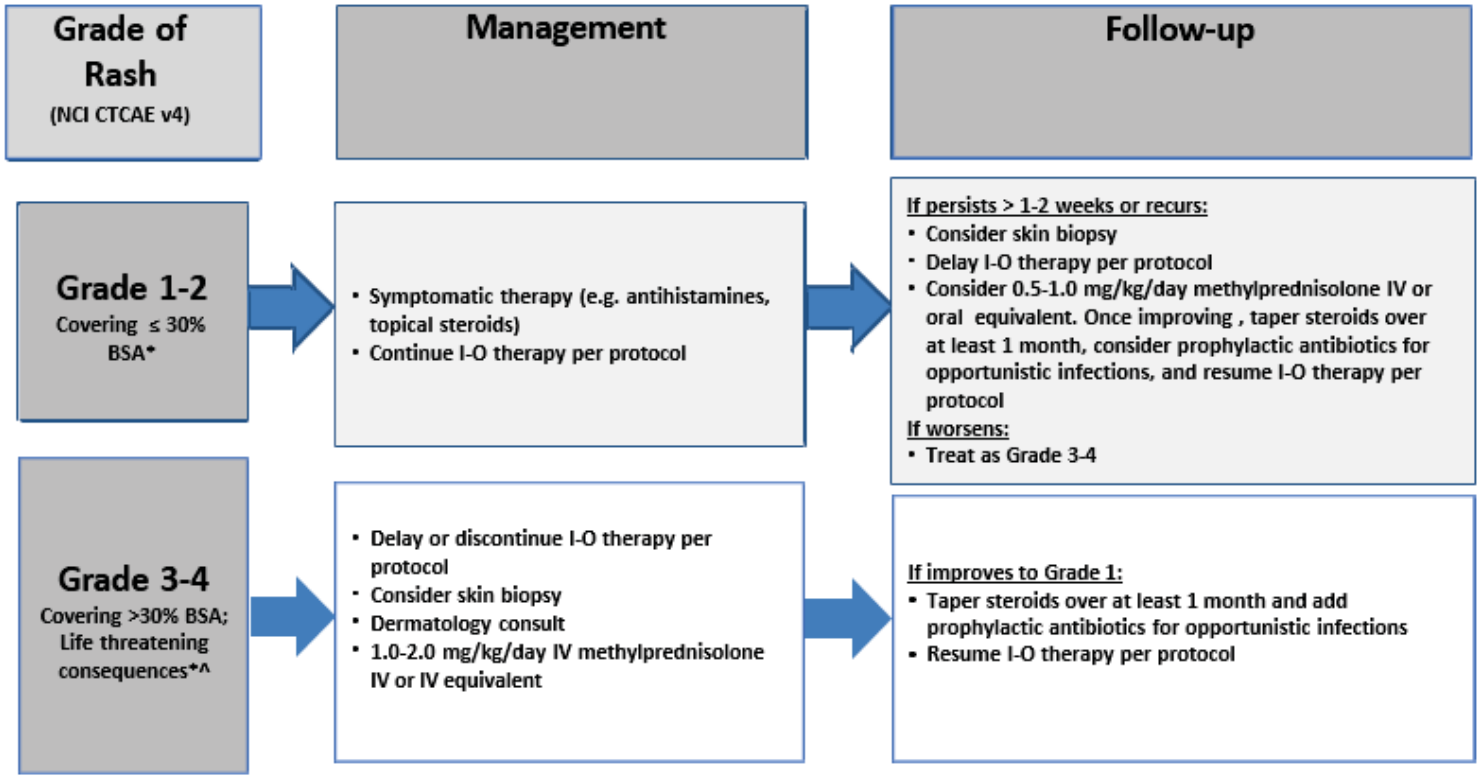


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

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, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

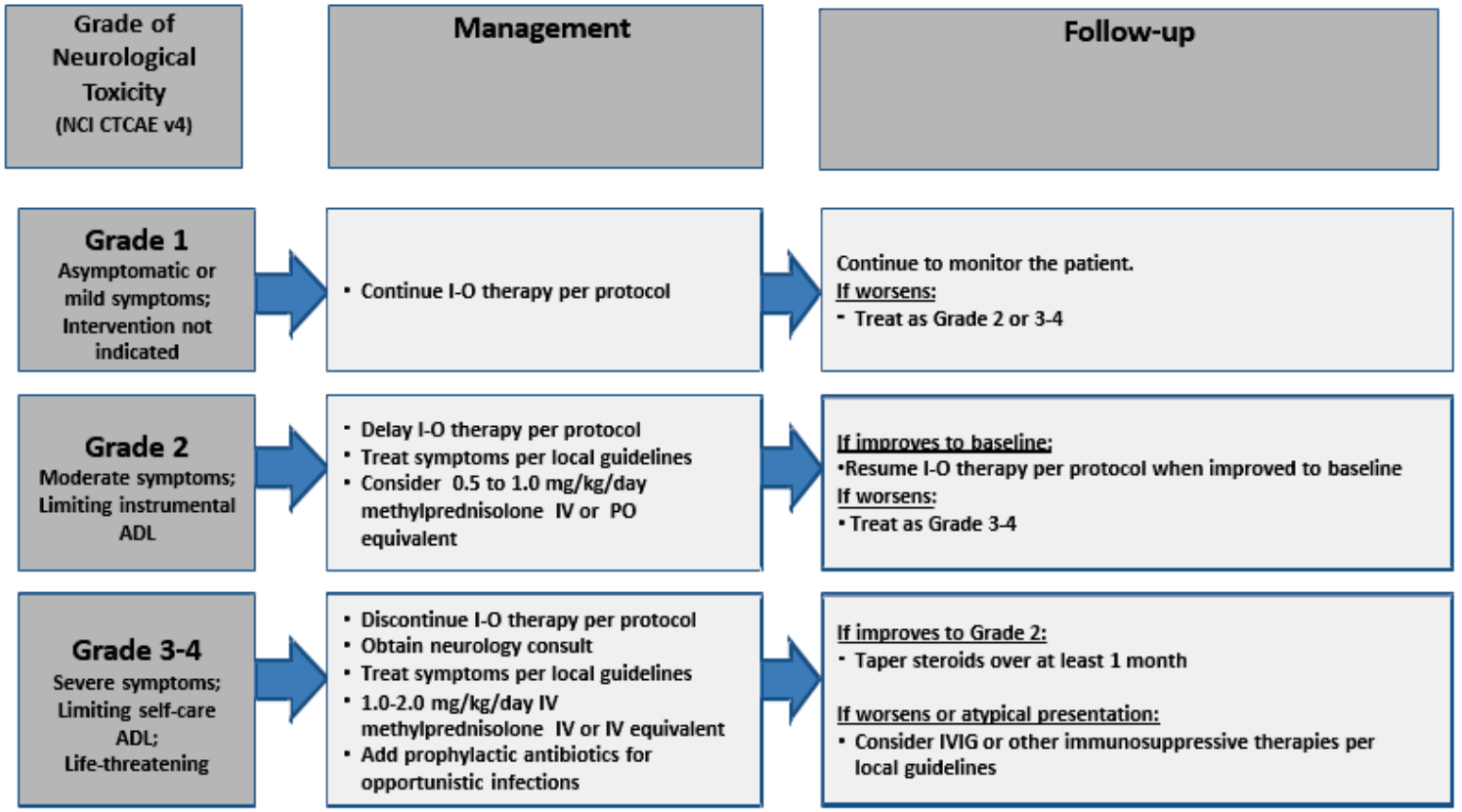
*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

27-Jun-2019

Neurological Adverse Event Management Algorithm

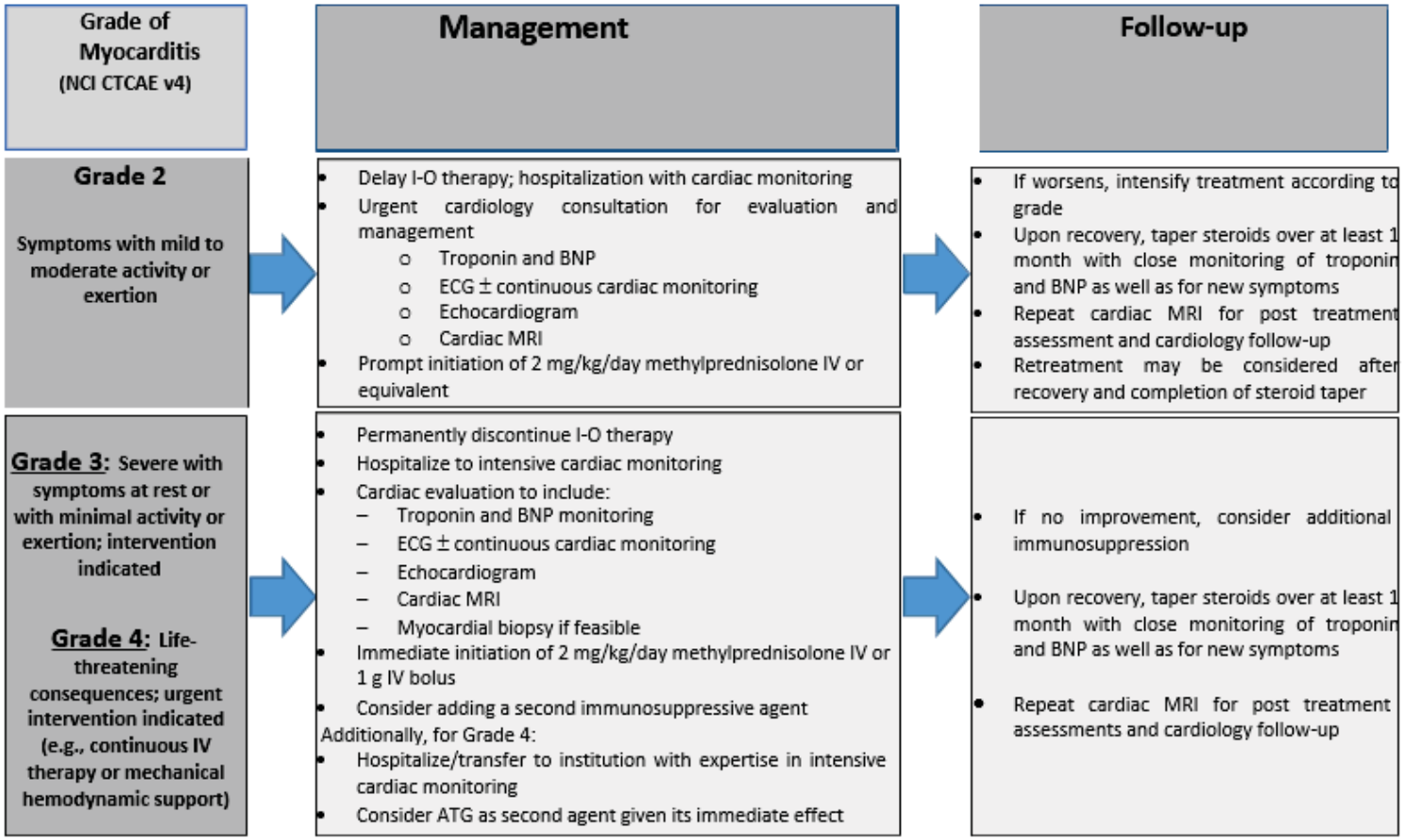
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

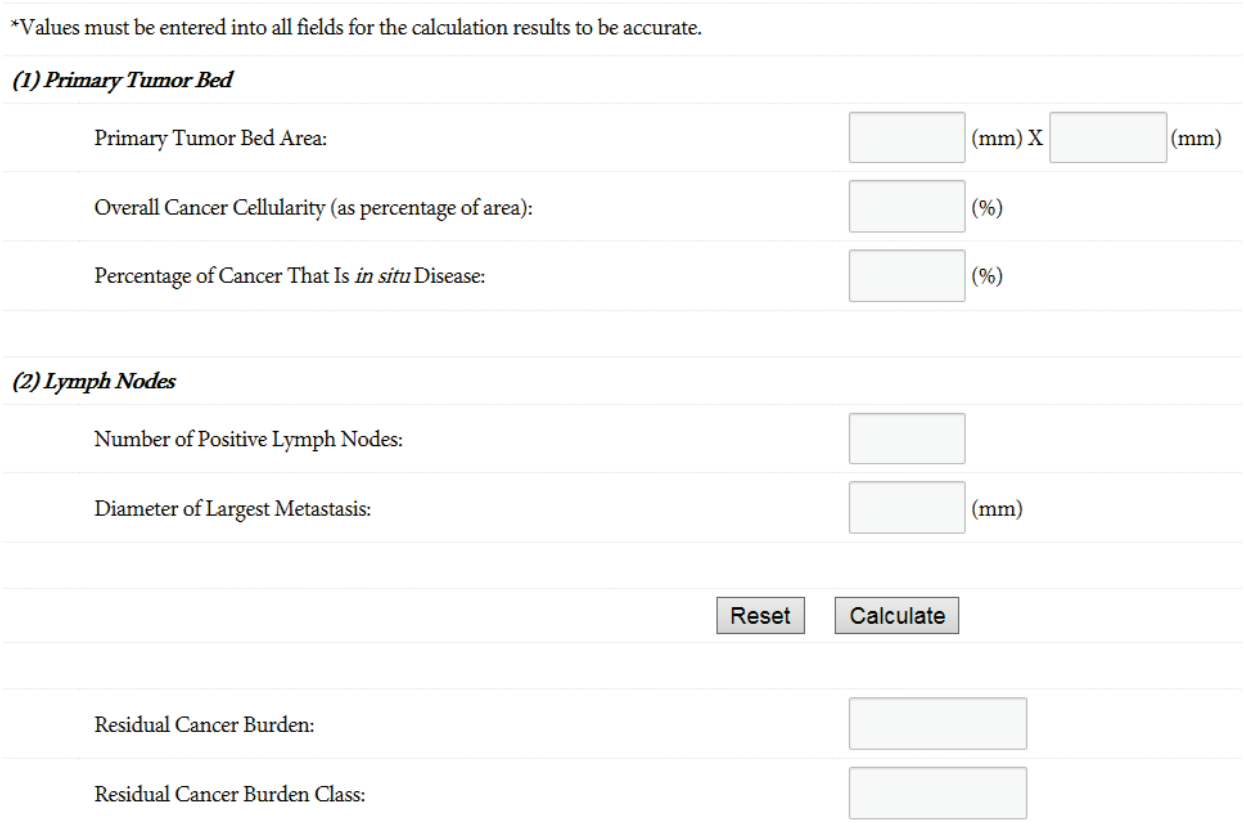
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

27-Jun-2019

APPENDIX 7 DETAILED PATHOLOGY METHODS FOR USING RESIDUAL CANCER BURDEN

Residual cancer burden (RCB) is estimated from routine pathologic sections of the primary breast tumor site and the regional lymph nodes (LNs) after the completion of neoadjuvant therapy. Six variables are included in a calculation formula. The calculated RCB index value can also be categorized as 1 of 4 RCB classes. The calculation formula (see image below) and detailed description can be found at a dedicated website: http://www.mdanderson.org/breastcancer_RCB.



Relevant information can be included within a pathology report (diagnoses or comment) without a need for reporting calculated RCB index results. An example of relevant information from a report would be:

- Residual invasive carcinoma with chemotherapy effect
- Residual carcinoma measures 2.4 × 1.8 cm (d1 × d2) and contains approximately 10% cancer cellularity (proportion of cancer; %CA)
- Residual intraductal carcinoma, solid type with necrosis, comprising 5% of the residual carcinoma (proportion of in situ component; %CIS)
- Metastatic carcinoma involving 3 of 14 axillary LNs (3/14)
- The largest metastasis measures 4 mm in greatest dimension (diameter of the largest nodal metastasis; dmet)

From the results above, one could calculate RCB using these results: d1 = 24 mm; d2 = 18 mm; %CA = 10%; %CIS = 5%; LN = 3; dmet = 4 mm.

Primary Tumor Bed

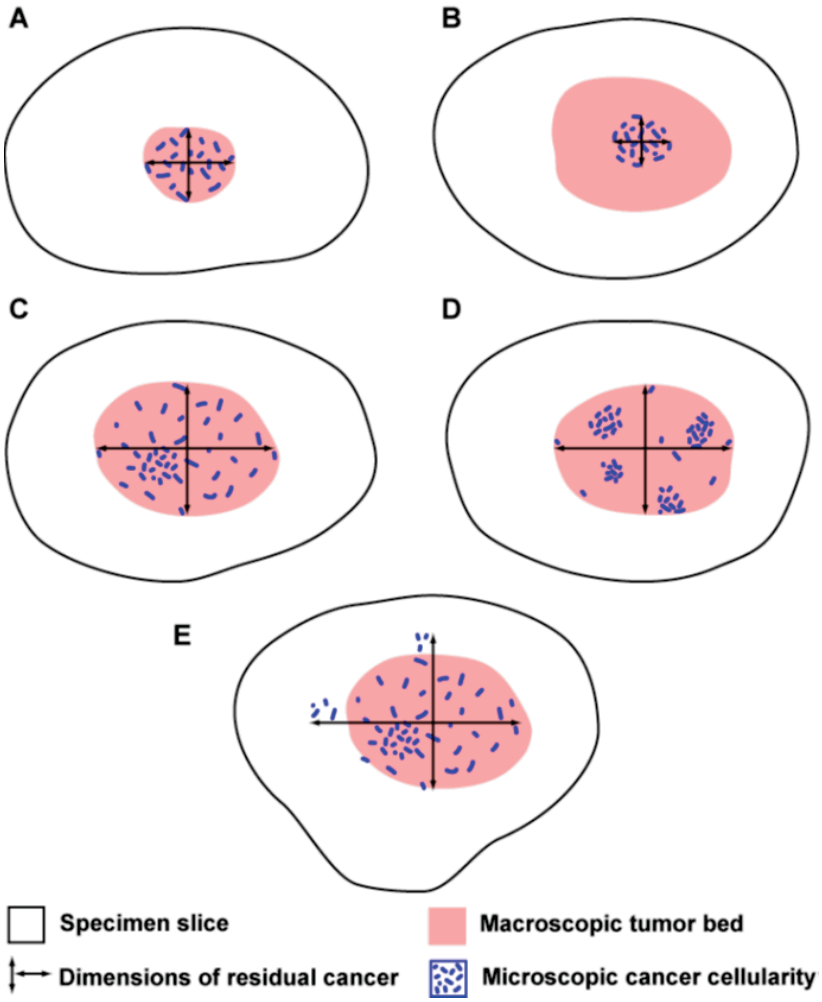
In general terms, pathologic evaluation of the primary tumor bed in the breast requires that the pathologist make 3 judgments about the primary tumor bed:

1) Identify the cross-sectional dimensions of the residual tumor bed (d1 and d2).
2) Estimate of the proportion of that residual tumor bed area that is involved by cancer (%CA).
3) Estimate the proportion of the cancer that is in situ component (%CIS).

Defining the Tumor Bed

In cases of multicentric disease, the RCB measurements are from the largest residual tumor bed. In cases where the extent of residual cancer under the microscope does not correlate with the gross measurement of the residual tumor bed, the tumor bed dimensions are to be revised according to the microscopic findings.

Schematic diagrams are shown below to illustrate how gross residual tumor bed dimensions are first estimated from the gross findings (pink area) but may be revised after review of the slides from the gross tumor bed area according to the extent of residual cancer (blue).



In the diagrams above, the macroscopic tumor bed dimensions in examples A, C, and D also define the final dimensions of the residual tumor bed after microscopic review. However, the macroscopic tumor bed dimensions in example B overestimate the extent of residual cancer, and so the dimensions of the residual tumor bed (d1 and d2) would be revised after microscopic evaluation of the extent of residual cancer in the corresponding slides from the gross tumor bed. In a different example (E), microscopic residual cancer extends beyond the confines of the macroscopic tumor bed. Again, the dimensions of the residual tumor bed (d1 and d2) would be revised after microscopic evaluation of the recognizable extent of residual cancer beyond the macroscopic tumor bed.

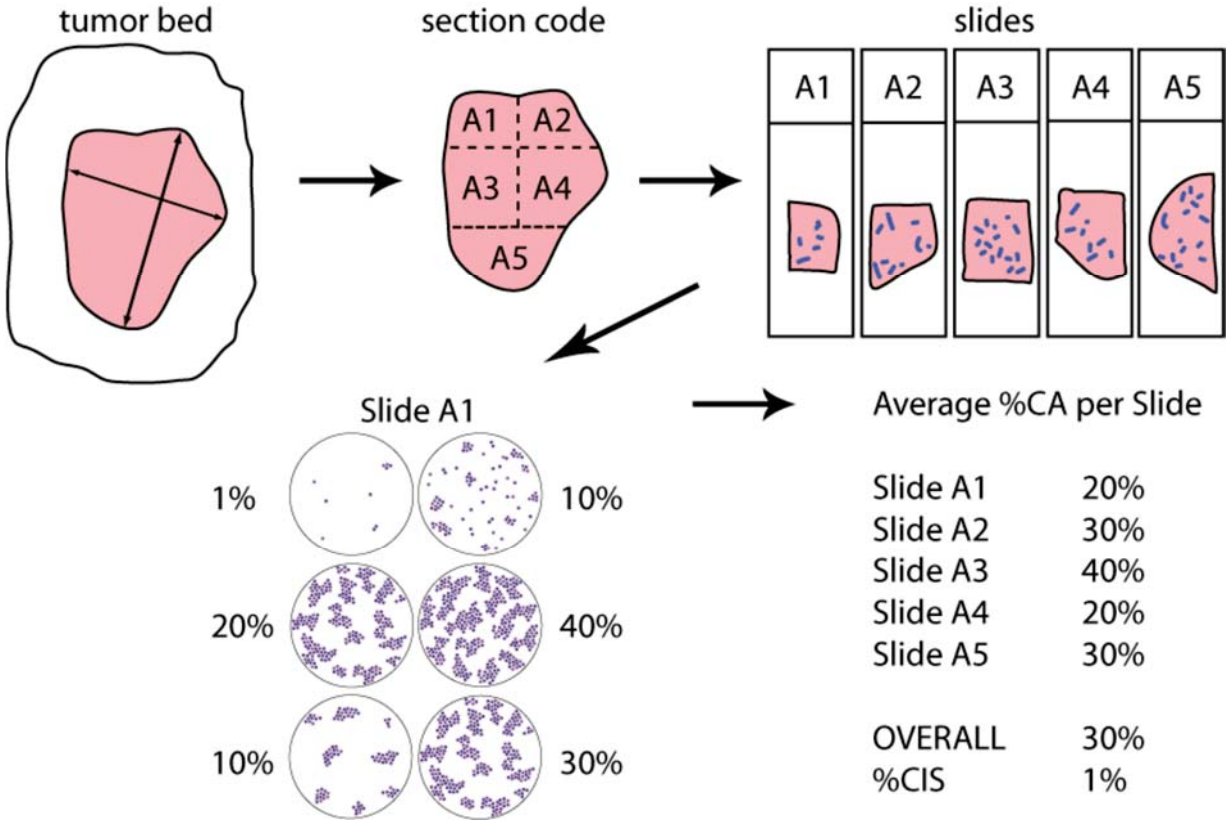
This approach accounts for differences in the concentration and distribution of residual cancer within a tumor bed. In the illustration above, the estimated %CA in example A would be high (in a small area), whereas the estimated %CA for examples C and D would be lower (in a larger area). In examples C and D, the estimated %CA would likely be similar, even though the distribution of cancer within the residual tumor bed is different in those 2 examples.

Estimating Cellularity within the Tumor Bed

The %CA and the %CIS are estimated from microscopic evaluation of the slides from the residual tumor bed area. The most effective way to obtain this information is to measure and submit for histology the largest cross-sectional area of residual tumor bed, and to designate in the report which slides represent the cross section of tumor bed. After reviewing those slides, the pathologist can estimate the average cellularity in the tumor bed on each slide in order to estimate the overall average cellularity of the tumor bed area, as illustrated below.

The key is to simply:

1) Define the gross tumor bed as the largest cross-sectional area.
2) Submit sections representing that tumor bed area as individual slides.
3) Review those slides to estimate the %CA and %CIS within the residual tumor bed.



A practical way to estimate %CA in a slide is to encircle with ink dots the tumor bed on each slide from the grossly defined residual tumor bed (eg, slides A1-A5 in the example above). Then use the microscope to estimate the cellularity in each microscopic field across the area of tumor bed. In each microscopic field, %CA can be estimated by comparing the proportion of residual tumor bed area containing cancer (invasive or in situ). Estimate an average of the readings for %CA in the cross-sectional area. The same can be done for %CIS. Estimates are to the nearest 10%, but include 0%, 1%, and 5% for areas with low cellularity. The average cellularity within the tumor

bed from each slide across the tumor bed can then be estimated, as illustrated above. The website provided above contains computer-generated diagrams of % cellularity per area to assist pathologists with accurately estimating the cellularity of a microscopic field. Those diagrams are provided at the end of this Appendix.

Regional Lymph Nodes: Pathologic evaluation of the primary tumor bed in the breast requires that the pathologist make 2 judgments:

1) Count the number of positive LNs.
2) Measure the dmet.

Footnotes

Inoperable or Progressive Disease

The RCB index cannot be accurately calculated for patients whose disease remains inoperable at the completion of the neoadjuvant treatment course (eg, requiring subsequent additional treatments before surgical resection is possible), or those who experience disease progression and so do not undergo surgical resection at the completion of the neoadjuvant treatment course. For those patients, RCB is assigned as extensive (ie, RCB-III).

Internal Mammary Lymph Node Metastasis

There were no examples of internal mammary nodal metastasis in the published study that evaluated the prognostic value of RCB. However, it is reasonable to include internal mammary nodes with the other regional (axillary) nodes in the assessment of RCB.

Pre-treatment Sentinel Lymph Node Biopsy

Surgical excision of a positive sentinel LN before the neoadjuvant treatment would invalidate the accuracy of measuring RCB after the treatment to assess response. If all sentinel LNs were negative before treatment began, this would not affect the assessment of RCB after treatment ended.

Summary of Key Points for Pathologic Assessment of the Primary Tumor Bed

Define the dimensions of residual tumor bed and estimate the percent of that area that is cancer.

3) **GROSS.** Identify the residual tumor bed and describe this macroscopic finding:
   a) Report the measurements of the largest gross dimensions (prefer 3 dimensions, but minimum is 2 dimensions).
   b) Submit the largest cross-sectional area for histology and specifically describe those blocks in the Section Code:
      i) Try to indicate how they are oriented by photography, or a scheme or intelligent description (eg, “blocks B1 – B7 cross section of tumor bed in rows from antero-superior to postero-inferior”).
      ii) If additional blocks are from surrounding tissues, then describe those as well.
      iii) Five representative sections from a big, obvious tumor bed should be sufficient.
4) **MICROSCOPY.** Review the slides that correspond to the tumor bed (± surrounding tissues):
   a) Estimate the extent of spread of residual cancer relative to the gross tumor bed:
      i) If similar to the gross description, then keep the original measurements.
      ii) If obviously different, then revise the dimensions of the tumor bed based on the microscopic review of the tumor bed.
      iii) Suggestion: Dotting the perimeter of cancer in each slide can be helpful to reconstruct the tumor extent across multiple slides (see point 1) b) i)).
   b) Using the microscope, make visual snapshots of cancer cellularity as you go from field to field across the defined tumor bed from one end to the opposite (eg, left to right, then top to bottom) to estimate the:

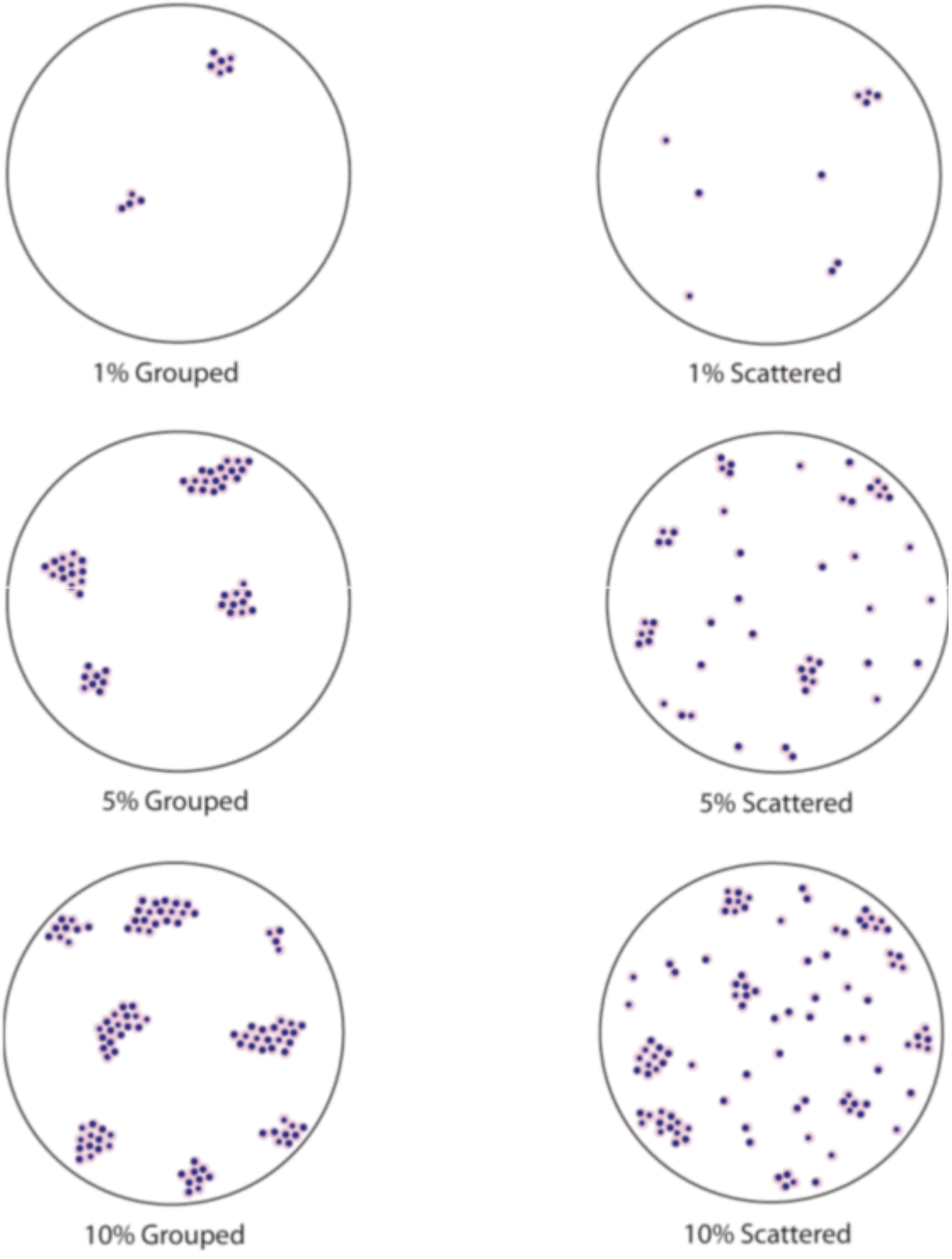
i) Average cancer cellularity (%) across the entire tumor bed. Considering both invasive and in situ components.

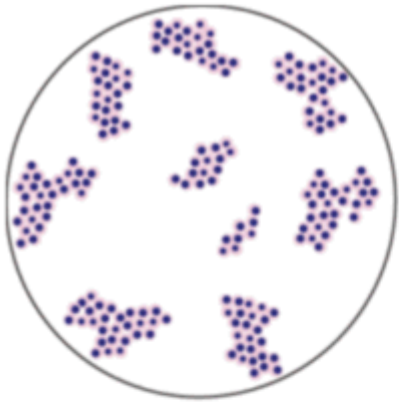
ii) Average percent of the cancer within the tumor bed that is in situ.

iii) Cellularity estimates are to the nearest 10%, with additional selections of 1% and 5% for very low cellularity. For reference, there are images of computer generated examples at the following website: http://www.mdanderson.org/breastcancer_RCB.

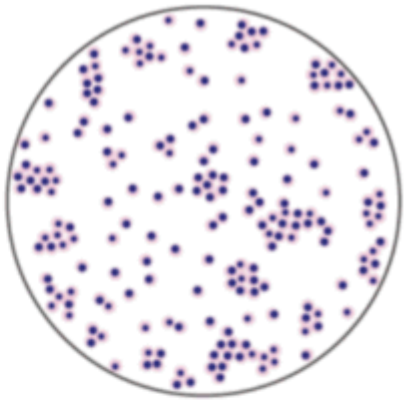
iv) The usual misunderstanding is to only make estimates in foci of the tumor bed that contain lots of cancer. The estimates are supposed to represent the average across the entire residual tumor bed area.

Graphical Illustrations of Percentage Cancer Cellularity

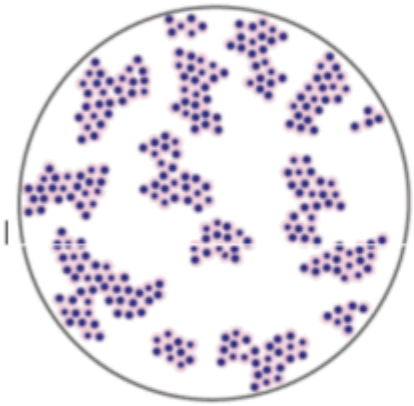




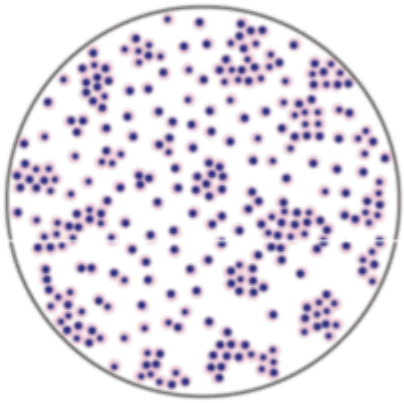
20% Grouped



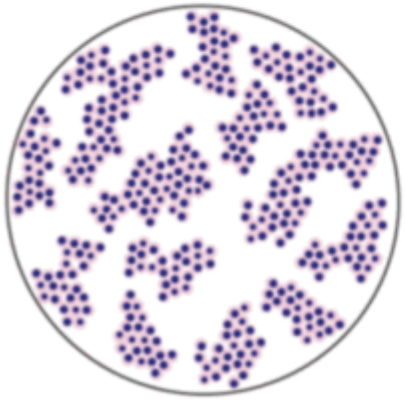
20% Scattered



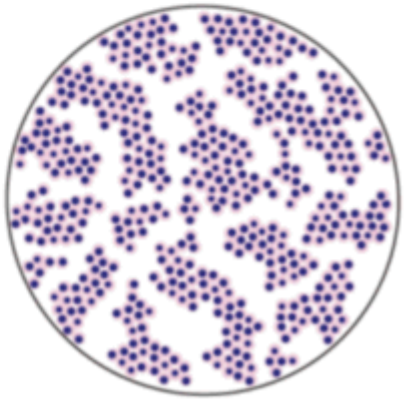
30% Grouped



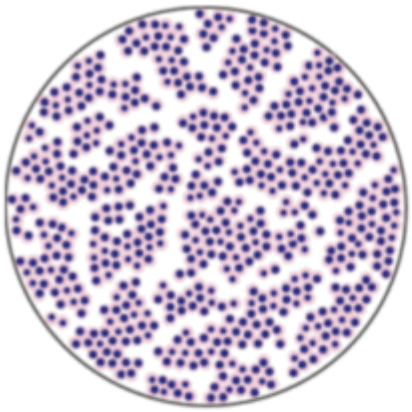
30% Scattered



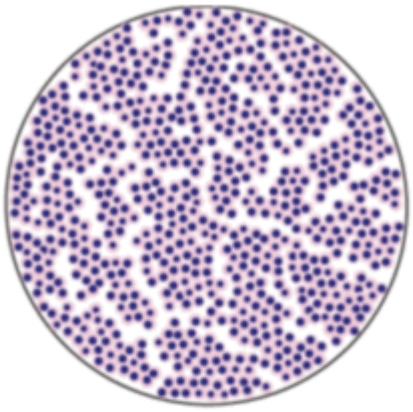
40%



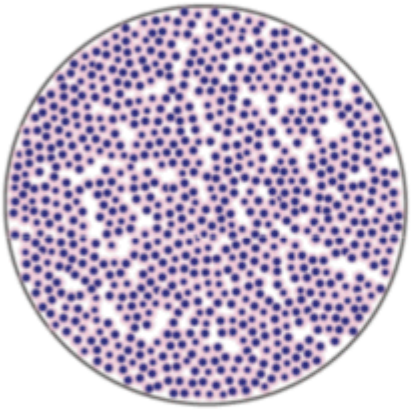
50%



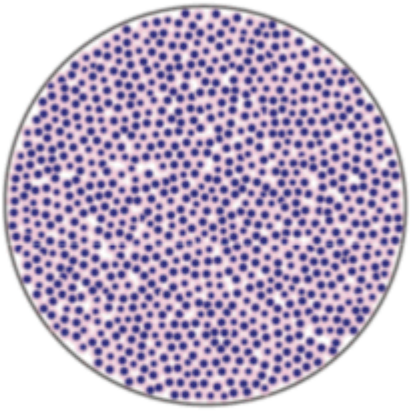
60%



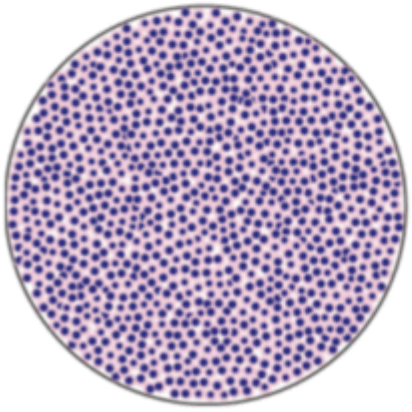
70%



80%



90%



95%

DETAILS OF THIS MODEL

Area of circle = 2,827.8 mm^2

Area of 1 cell = 2.8278 mm^2

1 cell = 0.1% of Area = 0.1% cellularity

10 cells = 1% cellularity

1000 cells = 100% cellularity

APPENDIX 8 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) [redacted]

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline [redacted].[1]

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

2 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.

3 NON-MEASURABLE

All other 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.

3.1 Special Considerations Regarding Lesion Measurability

3.1.1 Bone Lesions

- Bone scan, PET scan and plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

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 five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two 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. 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 (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

5 RESPONSE CRITERIA

5.1 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.

5.1.1 Special Notes on the Assessment of Target Lesions

5.1.1.1 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.

5.1.1.2 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 (eg, 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.

5.1.1.3 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'.

5.2 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 of existing non-target lesions.

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

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

5.2.1.1 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 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.

5.2.1.2 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: ie, 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.

5.2.2 New Lesions

The appearance of new malignant 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 (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). 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. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

2) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

5.3 Response Assessment

5.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression 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.

5.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 5.3.2-1 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 5.3.2-2 is to be used.

Table 5.3.2-1: 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 5.3.2-2: 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.

5.3.3 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 5.3.3-1. 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 5.3.3-1: Best Overall Response (Confirmation of CR and 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

Table 5.3.3-1: Best Overall Response (Confirmation of CR and PR Required)		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
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.

5.3.4 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. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.

APPENDIX 9 COUNTRY-SPECIFIC AMENDMENTS

Argentina, Czech Republic, Germany, Italy, Spain, and Any Other Countries Where Exclusion of HIV Positive Participants Is Locally Mandated

	Country-specific language
Section 2 Schedule of Activities, Table 2-1: Screening Assessments - Laboratory Tests	Add "HIV" to the list of laboratory tests
Section 6.2 Exclusion Criteria, Exclusion criterion 1) e)	"Known human immunodeficiency virus (HIV) positive with an AIDS defining opportunistic infection within the last year, or a current CD4 count <350 cells/uL." to be replaced with "Positive test for HIV".

APPENDIX 10 CONCOMITANT MEDICATIONS

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or CDK4/6 inhibitors.

The following lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction and Co-Medication Considerations (v06 release date: 2016), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/clinpharm/ddis/main-table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012; fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (druginteractioninfo.org/).

For current lists of medications that may cause QT prolongation and/or Torsades de Pointes (TdP), refer to the CredibleMeds® website (qtdrugs.org/).

The lists provided in the tables below are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions.

Table 1: List of Prohibited Medications During Study Drug Treatment

Category	Drug Name
Strong CYP3A4/5 Inhibitors	VIEKIRA PAK2, indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat (GS-9350), indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, elvitegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, saquinavir, idelalisib, boceprevir, darunavir/ritonavir
Strong CYP3A4/5 Inducers	Avasimibe,[a,b] carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)[b] St. John's wort (hypericum perforatum)[b]
CYP3A Substrates with Narrow Therapeutic Index (NTI)[c]	Alfentanil, apixaban (doses > 2.5 mg only), aprepitant, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine, lomitapide
Medications with a Known Risk for QT Prolongation[d]	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl, mesoridazine, methadone, moxifloxacin, ondansetron (i.v. only), oxaliplatin, papaverine HCl, pentamidine, pimozide, probucol, procainamide, propofol, quinidine, sevoflurane, sotalol, sparfloxacin, sulpiride, terfenadine, thioridazine, vandetanib, venlafaxine
Herbal Preparations/medications	Herbal preparations/medications known as string inducers or inhibitors of CYP3A/5 are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba,

Table 1: List of Prohibited Medications During Study Drug Treatment

Category	Drug Name
	dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Participants should stop using these herbal medications 7 days prior to first dose of study drug.
Other Investigational and Antineoplastic Therapies	Other investigational therapies must not be used while the participant is on the study. Antineoplastic therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to participants while the participant is on the study medication. If such agents are required for a participant, then the participant must discontinue study drug.

[a] Herbal product.

[b] Pg inducer.

[c] Drugs with exposure-response that indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

[d] Source: qtdrugs.org (as of 12-Dec-2016).

As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (eg, via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or TdP is available online at qtdrugs.org.

Table 2: List of Medications to be Used with Caution During Study Drug Treatment

Category	Drug Name
Moderate CYP3A4/5 Inhibitors	Amprenavir, atazanavir, casopitant, cimetidine, darunavir, diltiazem, fosamprenavir netupitant, tofisopam, verapamil, crizotinib, faldaprevir, imatinib, nilotinib
Moderate CYP3A4/5 Inducers	Bosentan, efavirenz, etravirine, genistein, lersivirine, modafinil, nafcillin, talviraline, semagacestat, lopinavir
Sensitive CYP3A4/5 Substrates[a]	Alpha-dihydroergocryptine, alisoporivir, almorexant, aplaviroc, apixaban (doses < 2.5 mg only), atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, danoprevir,darifenacin, darunavir, dasatinib, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, fluticasone, ibrutinib, ivacaftor, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, perospirone, quetiapine, ridaforolimus, sildenafil, simeprevir, ticagrelor, tilidine, tipranavir, tolvaptan, triazolam, ulipristal, vardenafil, vicriviroc, voclosporin
Strong BSEP Inhibitors	Alectinib, Atazanavir, bromocriptine, Bosentan, clofaziminie, cerivastatin, fusidate, glibenclamide, glyburide, nefazadone, paritaprevir, pioglitazone, reserpine, rosiglitazone, sulindac, troglitazone (TGZ-sulfate), valinomycin
Medications That Carry a Possible Risk for QT Prolongation[b]	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine, atazanavir, atomoxetine, asenapine, bedaquiline, bortezomib, buprenorphine, capecitabine, ceritinib, clomipramine, crizotinib, clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, eribulin, ezogabine, famotidine, felbamate, fingolimod, foscarnet, gatifloxacin, gemifloxacin, granisertron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, lapatinib, lenvatinib, leuprolide, lithium, mifepristone, mirabegron, mirtazapine, moexipril, norfloxacin, nortriptyline, ofloxacin, olanzapine, osimertinib, ondansetron (PO only at 4 mg or 8 mg), oxytocin, paliperidone, panabinostat, pasireotide, pazopanib, pipamperone, promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin, sertindole, sorafenib, sunitinib, telavancin, tetrabenazine, tizanidine, tolterodine, toremifene, trimipramine, vardenafil, vemurafenib, vorinostat, ziprasidone
MATE1 and OCT2 substrates[c]	Acyclovir, amantadine, amiloride, apricitabine, carboplatin, cisplatin, cephalexin, cephradine, cimetidine, dofetilde, famotidine, fexofenadine, furamidine, ganciclovir, glycopyrronium, Ipratropium, lamivudine, linagliptin, memantine, metformin (also a substrate for OCT1, MATE1, and MATE2K), oxyplatin, pindolol, plisicainide, pramsorafenib, ranitidine, topotecan, tropisetron, trospium, umeclidinium, varencicline and zidovudine
BCRP substrates	Daunorubicin, doxorubicin, ethinyl estradiol methotrexate, mitoxantrone, pitavastatin rosuvastatin, sulfasalazine, sofosbuvir, tenofovir

Table 2: List of Medications to be Used with Caution During Study Drug Treatment

Category	Drug Name
CYP2C9 substrates with NTI (for participants receiving tamoxifen)	Phenytoin, warfarin

[a] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.

[b] Source: qtdrugs.org (as of 12-Dec-2016).

[c] Source: FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and implications for Dosing and Labeling (February 2012) and Yonezawa and Inui (2011) Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics. Br J Pharmacology 164:1817-25; www.druginteractioninfo.org (May-2016).

Table 3: List of Cytochrome P450 Substrates with Narrow Therapeutic Range Cytochrome P450

Cytochrome P450 Substrates with Narrow Therapeutic Range Cytochrome P450	Substrate
CYP1A2	Theophylline Tizanidine
CYP2C8	Paclitaxel
CYP2C9	Warfarin Phenytoin
CYP2D6	Thioridazine Pimozide
CYP3A	Alfentanil Astemizole Cisapride Cyclosporine Dihydroergotamine Ergotamine Fentanyl Pimozide Quinidine Sirolimus Tacrolimus Terfenidine

APPENDIX 11 NYHA FUNCTIONAL CLASSIFICATION

Heart failure is usually classified according to the severity of the patient's symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) functional classification. It places patients in 1 of 4 categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

APPENDIX 12 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall rationale for Revised Protocol 02, 24-July-2019

The primary reasons for these changes [redacted] ensure that the protocol is consistent with internal BMS policies and operating procedures. Additional amendments, including to sections of the Synopsis, have been made to align the protocol with respect to these changes.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
2: Schedule of Activities	Modified Table 2-2 (screening procedural outline) to update inclusion criterion number in the notes for 'documentation of postmenopausal status.'	To align with updates made in Section 6.1, described below.
4: Objectives and Endpoints 5.1.2.1: Safety Run-in Phase	The following modifications were made: • Updated definition of DLT. • Added DLT criteria.	These changes were made to refine wording to facilitate Investigator interpretation.
5.1: Overall Study Design	Revised window to perform definitive breast cancer surgery to 4 weeks after last dose of neoadjuvant treatment. Modified Figure 5.1-1 to update key inclusion criteria to include men in addition to postmenopausal women.	Allow flexibility to plan the breast surgery and reflect updated study design in which men are now also eligible.
5.4: Early Study Termination Criteria	Added early study termination criteria.	These changes were made to refine wording to facilitate Investigator interpretation.
6.1: Inclusion Criteria	The following modifications were made: • Moved eligibility criteria for women to sub-criteria for criterion 3) b) • Added additional sub-criteria related to eligibility of men to criterion 3)	These changes were made to refine wording to facilitate Investigator understanding and include men in the study.
6.2: Exclusion Criteria 7.7.1: Prohibited and/or Restricted Treatments for Nivolumab 7.7.3: Other Restrictions and Precautions 7.7.4: Permitted Therapy	The following modifications were made: • Changed criteria 1) d) and 1) i) to exclude steroids above physiological replacement dose. • Changed from 'immunosuppressive' to 'supraphysiological' when describing other restrictions and precautions. • Deleted the prednisone permitted dose. • Changed '> 10 mg daily prednisone equivalent' to 'at above physiological replacement dose' when describing permitted therapy.	These changes were made to refine wording to facilitate Investigator understanding.
7.4.1: Dose Modifications for Abemaciclib 7.4.2: Dose Modifications for Palbociclib	The following modifications were made: • Aligned the section with the US prescribing information language for each medication.	These changes were made to refine wording to facilitate Investigator understanding.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
7.4.3: Dose Modification for Anastrozole		
9.2.5: Pregnancy Appendix 4: Women of Childbearing Potential Definitions and Methods of Contraception	Added language describing male contraception expectations.	Aligned methods of contraception with the update to the study design to now include men.
Appendix 6: Nivolumab Management Algorithms	Updated management algorithms and added myocarditis.	These changes were made to reflect updates made to the IB.
Appendix 9: Country-specific Amendments	Removed France from list of countries.	France does not mandate HIV testing.
All	The following global updates were made: • Added males. • Minor formatting and typographical corrections.	These changes were made to: • Clarify that men are eligible. • Incorporate corrections for clarity and consistency within the document. These changes were minor, and therefore have not been summarized.

Overall rationale for revised protocol 01, 12-June-2019

The primary reasons for these changes are to clarify and decrease the frequency of assessments and sample collections, clarify participant eligibility and stratification, and reduce the dose-limiting toxicity (DLT) period. These changes were made to reduce participant burden and increase overall feasibility of the study. Additional amendments, including to sections of the Synopsis, have been made to align the protocol with respect to these changes.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
2: Schedule of Activities	• The following modifications were made: • Table 2-1: – Added row describing Original Diagnosis IHC Tumor Slides Submission. – Updated number of unstained slides for tumor tissue sections from 25 to 22 and lowered minimum number of slides for participant eligibility from 20 to 15. – Added respiratory rate to safety assessments. – Updated "Tumor Assessment by PE" to "Clinical Breast Examination." – Added "axilla" to breast ultrasound (preferred) or mammogram. – Added Axillary Lymph Nodes Fine Needle Biopsy or Core Biopsy row. • Table 2-2: – Decreased the frequency of ocular exams and electrocardiograms. – Updated "Tumor Assessment by PE" to "Clinical Breast Examination." – Added "axilla" to breast ultrasound (preferred) or mammogram and aligned timing of this assessment with on-treatment biopsy (now on Cycle 2 Day 22). [redacted] • Table 2-3: – Updated ocular assessments to be as clinically indicated.	These changes were made to clarify assessment expectations and/or decrease the number of assessments to reduce participant burden.
4: Objectives and Endpoints	• Removed text describing timeframe of Safety Run-in Phase.	• Streamlined text to improve readability.
4: Objectives and Endpoints; 9.1.2.1: RCB Determination	• Removed local assessment of residual cancer burden (RCB) 0-1 rate as a secondary endpoint.	• Updated to improve study feasibility.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
4: Objectives and Endpoints; 5.1.2.1: Safety Run-in Phase; 10.3.2: Safety Analyses	Shortened the DLT period from 8 weeks to 4 weeks and redefined DLT-evaluable participants as those who receive 1 dose.	Aligned with clinical experience regarding safety feasibility of the study drugs.
[redacted]		
5.1: Overall Design; 5.1.2.2: Randomized Phase; 7.2: Method of Treatment Assignment	Specified axillary node status for stratification factor as "cytologically positive vs radiologically or cytologically negative."	Clarified expectations for node status stratification factor.
5.1.1: Screening Period	Added details related to documentation and tumor samples for central review.	Clarified expectations for central review.
5.1.1: Screening Period; 6.1: Inclusion Criteria; [redacted]	Modified number of unstained slides for tumor tissue sections from 25 to 22 and lowered minimum number of slides for participant eligibility from 20 to 15.	Updated to improve study feasibility.
5.1: Overall Design; 5.2: Number of Participants; 10.1: Sample Size Determination; [redacted]	Provided range of anticipated number of study participants for the Safety Run-in Phase within text and Study Design Schematic in Figure 5.1-1.	Clarified expectations for number of participants.
5.1.2.1: Safety Run-in Phase	Modified criteria for gastrointestinal and dermatologic DLTs.	Updated for participant safety.
6.1: Inclusion Criteria	The following modifications were made: • Updated sub-criteria for criterion 2) b) to remove staging requirement but specify primary tumor size per radiological assessment. • Incorporated details in previous criterion 2) e) related to measurable disease into sub-criteria for criterion 2) b) iii).	These changes were made to: • Clarify expectations for participant inclusion criteria and improve study feasibility. • Remove repetitive information per changes to 2) b) sub-criteria.
7.4.1: Dose Modifications for Abemaciclib	Added "Third dose reduction" row to Table 7.4.1-2.	Clarified dose levels for abemaciclib.
9.1.1: Blinded Independent Pathology Review	Changed "mandatory" sample collections to "should be performed" and removed statement on site training.	Aligned expectations for sample collections with update described above to remove local RCB assessment as a secondary endpoint.
9.1.2.1: RCB Determination	Slightly modified variables included in the RCB calculations.	Updated for clarity and consistency with RCB calculator referenced in this section.

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
9.1.3: Clinical Response Assessments	The following modifications were made: • Replaced "targeted PE" with "clinical breast examination by palpation of breast and axilla." • Added "axilla" to ultrasound (preferred) or mammogram. • Added "including pathologic examination of suspicious lesions." • Added statement: "At the Sponsor's discretion, scans may be collected for review."	These changes were made to: • Align description of clinical response assessments with changes made to the Schedule of Activities described above. • • • Clarify expectations for clinical response assessments.
[redacted]		

Summary of key changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
10.3.1: Efficacy Analyses	Updated Table 10.3.1-1 for consistency with changes to Table 4-1.	Aligned efficacy analyses with updates to objectives and endpoints described above.
[redacted]		
Appendix 8: Staging Criteria	Prior Appendix 8 containing American Joint Committee on Cancer (AJCC) criteria was removed.	AJCC criteria no longer relevant per updates made to Section 6.1.
All	The following global updates were made: • Replaced "Stage II-III" with "≥ 2 cm" in titles, text, and in Figure 5.1-1. • Minor formatting and typographical corrections.	These changes were made to: • Clarify breast cancer type throughout protocol. • Incorporate corrections for clarity and consistency within the document. These changes were minor, and therefore have not been summarized.